doi:10.1093/brain/awm121 *Brain* (2007), **130**, 2085–2096

Whole brain functional connectivity in the early blind

Yong Liu,[1*] Chunshui Yu,[2*] Meng Liang,[1] Jun Li,[1] Lixia Tian,[1] Yuan Zhou,[1] Wen Qin,[2] Kuncheng Li[2] and Tianzi Jiang[1]

[1]National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080 and [2]Department of Radiology, Xuanwu Hospital, Capital University of Medical Sciences, Beijing 100053, P.R. China

*The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

Correspondence to: Tianzi Jiang, PhD, National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, P.R. China
E-mail: jiangtz@nlpr.ia.ac.cn

Early visual deprivation can lead to changes in the brain, which may be explained by either of two hypotheses. The general loss hypothesis has been proposed to explain maladjustments, while the compensatory plasticity hypothesis may explain a superior ability in the use of the remaining senses. Most previous task-based functional MRI (fMRI) studies have supported the compensatory plasticity hypothesis, but it has been difficult to provide evidence to support the general loss hypothesis, since the blind cannot execute visual tasks. The study of resting state fMRI data may provide an opportunity to simultaneously detect the two aspects of changes in the blind. In this study, using a whole brain perspective, we investigated the decreased and increased functional connectivities in the early blind using resting state fMRI data. The altered functional connectivities were identified by comparing the correlation coefficients of each pair of brain regions of 16 early blind subjects (9 males; age range: 15.6–29.3 years, mean age: 22.1 years) with the corresponding coefficients of gender- and age-matched sighted volunteers. Compared with the sighted subjects, the blind demonstrated the decreased functional connectivities within the occipital visual cortices as well as between the occipital visual cortices and the parietal somatosensory, frontal motor and temporal multisensory cortices. Such differences may support the general loss hypothesis. However, we also found that the introduction of Braille earlier in life and for longer daily practice times produced stronger functional connectivities between these brain areas. These findings may support the compensatory plasticity hypothesis. Additionally, we found several increased functional connectivities between the occipital cortices and frontal language cortices in those with early onset of blindness, which indicate the predominance of compensatory plasticity. Our findings indicate that changes in the functional connectivities in the resting state may be an integrated reflection of general loss and compensatory plasticity when a single sensory modality is deprived.

Keywords: blind; resting state fMRI; functional connectivity; general loss; plasticity

Abbreviations: BOLD = blood oxygen level dependent; FDR = false discovery rate; LFF = low frequency fluctuations

Received September 25, 2006. Revised April 27, 2007. Accepted April 30, 2007. Advance Access publication May 28, 2007

Introduction

Object perception benefits from the coordinated interplay of vision, audition and touch. These different sensory modalities work together to provide full information about an object (Amedi *et al.*, 2005*a*). Single sensory modality deprivation provides a unique opportunity to investigate plastic changes in brain function. In terms of the early onset of blindness, the plasticity may be explained by two hypotheses. The general loss hypothesis refers to maladjustments due to blindness (Pascual-Leone *et al.*, 2005). For example, visual deprivation may lead to a decreased ability in processing sensory perception/spatial information (Zwiers *et al.*, 2001; Amedi *et al.*, 2005*b*). The compensatory hypothesis may explain a superior ability in the use of the remaining senses of the blind (Pascual-Leone *et al.*, 2005).

The compensatory plasticity of the brain has been well studied by many task-based studies. Functional MRI (fMRI) and positron emission tomography (PET) studies have demonstrated that visual areas of the blind were activated when performing Braille reading (Sadato *et al.*, 1996, 1998; Büchel *et al.*, 1998; Burton *et al.*, 2002*a*; Sadato *et al.*, 2002; Gizewski *et al.*, 2003; Burton *et al.*, 2004; Sadato, 2005; Burton *et al.*, 2006), auditory tasks

(Röder *et al.*, 1999; Leclerc *et al.*, 2000; Weeks *et al.*, 2000; Röder *et al.*, 2001; Amedi *et al.*, 2003; Gougoux *et al.*, 2004; 2005; Poirier *et al.*, 2006), as well as various complex cognitive tasks (De Volder *et al.*, 2001; Burton *et al.*, 2002*b*; Röder *et al.*, 2002; Amedi *et al.*, 2003; Vanlierde *et al.*, 2003; Lambert *et al.*, 2004; Raz *et al.*, 2005). In the early blind, the participation of the occipital visual cortex in higher-level cognitive function tasks was also confirmed by studies using transcranial magnetic stimulation (Cohen *et al.*, 1997; Amedi *et al.*, 2004). The general loss hypothesis, however, has not been studied extensively using fMRI due to a lack of appropriate tasks. The study of functional connectivity using resting state fMRI data may provide an opportunity to simultaneously detect the two aspects of plastic change.

Functional connectivity is a measurement of the spatiotemporal synchrony or correlations of the blood oxygen level-dependent (BOLD) fMRI signal between anatomically distinct brain regions of cerebral cortex (Friston *et al.*, 1993). In the resting state, low-frequency (<0.08 Hz) fluctuations (LFF) of the BOLD signal, which are considered to be related to neuronal spontaneous activity, have been used to identify the functional connectivities among different brain regions (Biswal *et al.*, 1995; Xiong *et al.*, 1999; Hampson *et al.*, 2002; Greicius *et al.*, 2003; Salvador *et al.*, 2005*a*). These previous studies showed that the functionally related brain regions, even those remotely located, have a high temporal coherent LFF, which implies the existence of neuronal coordinating activity between the cerebral cortices (Biswal *et al.*, 1995; Lowe *et al.*, 1998; Xiong *et al.*, 1999; Hampson *et al.*, 2002; Salvador *et al.*, 2005*a*). In addition, several previous resting state fMRI studies have further shown that the LFF correlation pattern was found to be altered in some diseases (Lowe *et al.*, 2002; Peltier *et al.*, 2005; Liang *et al.*, 2006). Recent fMRI studies have also revealed that the human brain is a complex, structured neurophysiological network, even if a person is lying in the scanner not performing any cognitive tasks (Greicius *et al.*, 2003; Fox *et al.*, 2005; Salvador *et al.*, 2005*a*). So Raichle and colleagues have suggested that the study of brain activity in the resting state is at least as important as the study of evoked activity, in terms of the entire brain function (Raichle and Gusnard, 2005; Raichle and Mintun, 2006). Therefore, it is important to investigate whether the functional connectivities of the entire brain were altered for subjects with early blindness.

We hypothesize that the alteration of each of the functional connectivities in early blind subjects will be an integrated reflection of the general loss and compensatory plasticity. Compared with the normal sighted, decreased functional connectivities in the blind could indicate that the general loss mechanism plays a dominant role; whereas increased functional connectivities could indicate the dominance of the compensatory plasticity mechanism. In this study, we explored the functional connectivity throughout the entire brain to investigate whether any alteration of the functional connectivities exists in people with early onset of blindness. We divided the brain into 116 regions (Tzourio-Mazoyer *et al.*, 2002; Salvador *et al.*, 2005*a*; Achard *et al.*, 2006; Liang *et al.*, 2006), and analysed the correlations between each pair of these regions in both blind and normally sighted subjects. Then we identified the significant differences in functional connectivities by comparing the correlation coefficients of each pair of brain regions between the two groups. We also evaluated the relationship between the altered functional connectivities and Braille practice to determine whether the compensatory plasticity exists.

Materials and methods

Subjects' recruitment

Eighteen early (loss of sight at birth or before 1 year of age) blind subjects were recruited from the Special Education College of Beijing Union University. One blind subject was discarded because of a lesion in the right cerebral hemisphere, and another blind individual was removed due to large head motions (>1.5 mm) in the *z* direction. The remaining 16 blind subjects (9 males, 7 females; age range: 15.6–29.3 years, mean age: 22.1 years) were involved in further analysis. Thirty-two gender- and age-matched ($P = 0.953$) healthy sighted individuals (18 males, 14 females; age range: 17.3–28.1 years, mean age: 22.1 years) were recruited by advertisement. All subjects were free of any neurological or psychiatric disorders, had normal brain MR scans (assessed from structural images by an experienced neuroradiologist). All of them were right-handed according to the Edinburgh handed inventory (Raczkowski *et al.*, 1974). Details of the blind subjects are shown in Table 1. All participants provided informed consent before the MRI examinations following guidelines approved by the Medical Research Ethics Committee of Xuanwu Hospital of Capital University of Medical Sciences.

Acquisition of biographical data on Braille practice

Each blind subject was asked to answer a detailed questionnaire on the self-estimated amount of Braille practice for different age periods (Bengtsson *et al.*, 2005). The subjects were asked to retrospectively identify key events in their Braille practice, such as when they started to learn Braille, and when they changed the amount of their Braille practice. They thereafter estimated the mean hours of Braille practice per week in the time periods between these key events. From this biographical information for each blind person we calculated the total number of practice hours for three different age periods: childhood (from the start of Braille practice to age 11 years), adolescence (age 12–16 years) and adulthood (from age 17 years to the time of the experiment). The details of Braille practice can be found in Table 1.

Data acquisition

The fMRI data were obtained using a 3.0-Tesla Siemens MRI system. We acquired 270 echo planar imaging (EPI) BOLD volumes with the following parameters: slice number = 32 (interleaved); matrix = 64 × 64; slice thickness = 3 mm; inter-slice gap = 1 mm; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view = 22 cm. Each

Table 1 Subjects' characteristics

	Sex	Age (years)	Onset Age (years)	Braille practice				
				Start age (years)	Childhood (h)	Adolescence (h)	Adulthood (h)	Causes of blindness
01	Female	22.8	0	7.2	11 388	11 863	7410	Retinitis pigmentosa
02	Male	20.9	0	8.3	8103	13 688	6406	Retinitis pigmentosa
03	Male	24.6	0	9	3285	10 038	8322	Optic nerve atrophy
04	Male	19.1	0	9.7	2938	5475	3066	Retinitis pigmentosa
05	Male	24.6	0	10	4745	13 688	11096	Retinitis pigmentosa and optic nerve atrophy
06	Female	23.6	0	7.8	6899	8213	3614	Optic nerve hypoplasia
07	Male	22.4	<1	11.7	274	8213	1971	Congenital glaucoma
08	Male	29.3	0	7.8	3833	4563	4490	Optic nerve hypoplasia
09	Male	23.4	<1	7	10 038	8213	12848	Congenital glaucoma
10	Female	26.6	0	9.8	6022	18 250	12264	Optic nerve atrophy
11	Female	15.6	0	7	13 688	16 790	–	Optic nerve atrophy
12	Female	18.4	0	10.1	4508	13 688	1788	Retinitis pigmentosa
13	Female	21.7	0	7.1	7154	14 600	6004	Congenital cataract
14	Female	21.7	0	7.1	6260	4563	6862	Congenital glaucoma and cataract
15	Male	18.7	0	6.1	15 075	15 513	3413	Optic nerve hypoplasia
16	Male	20.8	0	8.1	5694	11 863	7629	Retrolental fibroplasias

subject was instructed to keep their eyes closed, relax their minds and move as little as possible. Foam pads were used to reduce head motion during EPI data acquisition. Structural sagittal images were obtained using a magnetization prepared rapid acquisition gradient echo (MP-RAGE) three-dimensional T1-weighted sequence (voxel size $= 1 \times 1 \times 1\,mm^3$; TR $= 2000$ ms; TE $= 2.6$ ms; FA $= 9°$).

Data preprocessing

Unless specially stated, all the preprocessing were carried out using the statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm). Considering for the magnetization equilibrium, the first 10 images were discarded. The remaining 260 images were corrected for the acquisition time delay between different slices and realigned to the first volume. The head motions time course were computed by estimating the translations in each direction and the rotations in angular motion about each axis for each of the 260 consecutive volumes. The subjects we used had the maximum displacement <1 mm at each axis and the angular motion less than 1° for each axis. We also considered the influence of head motion (Jiang *et al.*, 1995; Lowe *et al.*, 1998) since the correlation analysis is sensitive to such factor. Our results showed that the two groups had no significant differences in head motion (blind: 0.41 ± 0.17 mm versus healthy subjects: 0.48 ± 0.24 mm; two sample two-tailed *t*-test, $P = 0.27$). We further spatially normalized the realigned images to the Montreal Neurological Institute (MNI) EPI template and re-sampled the normalized images to 3 mm cubic voxel. We also used a linear regression process for further reducing the effects of head motion and regressing out the constant elements and the linear drift (Fox *et al.*, 2005; Liang *et al.*, 2006). Finally, temporal band-pass filtering ($0.01 < f < 0.08$ Hz) was performed on the time series of each voxel using AFNI (http://www.afni.nimh.nih.gov/) 3D Fourier program so as to reduce the effects of low-frequency drift and high-frequency noises (Fox *et al.*, 2005; Liang *et al.*, 2006).

Anatomical parcellation

The registered fMRI data were segmented into 116 regions using the anatomically labelled template reported by Tzourio-Mazoyer *et al.* (2002), which was used in several previous studies (Salvador *et al.*, 2005*a*, *b*; Achard *et al.*, 2006; Liang *et al.*, 2006). This parcellation divided the cerebra into 90 regions (45 in each hemisphere) and the cerebella into 26 regions (nine in each cerebellar hemisphere and eight in the vermis). These are listed in Table 2 together with their abbreviations and the MNI coordinates of the centre of each region.

Estimation of inter-regional Pearson's correlations

Regional mean time series were estimated by averaging the time series of all voxels in this region (Salvador *et al.*, 2005*a*, *b*; Achard *et al.*, 2006; Liang *et al.*, 2006). The Pearson's correlation coefficients were computed between each pair of brain regions for each subject. For further statistical analysis, a Fisher's *r*-to-*z* transformation $z = 0.5 \times \log[(1+r)/(1-r)]$ was applied to improve the normality of the correlation coefficients. The individual *z* scores were entered into a one-sample two-tailed *t*-test to determine if the two brain regions show significant functional connectivity within each group. They were also entered into a two-sample two-tailed *t*-test to determine if the functional connectivities were significantly different between the two groups.

A *t*-test was performed for all the 6670 ($116 \times 115/2$) functional connectivities, so a correction for multiple comparisons was strictly necessary. The false discovery rate (FDR) approach was applied to find a threshold that would restrict the expected proportion of type I errors to lower than 0.05 (Benjamini and Yekutieli, 2001; Salvador *et al.*, 2005*a*). In this study, we identified the significant differences in functional connectivities between the blind and sighted subjects according to the following two criteria: (a) the *z* values were significantly different from zero at

Table 2 Cortical and subcortical regions defined in AAL template image in standard stereotaxic space

Index	Region	Abbreviation	MNI (L/R)	Index	Region	Abbreviation	MNI (L/R)
1,2	Superior frontal gyrus, dorsolateral	SFGdor	(−18,35,42)/(22,31,44)	63,64	Insula	INS	(−35,7,3)/(39,6,2)
3,4	Superior frontal gyrus, orbital	SFGorb	(−17,47,−13)/(18,48,−14)	65,66	Thalamus	THA	(−11,−18,8)/(13,−18,8)
5,6	Superior frontal gyrus, medial	SFGmed	(−5,49,31)/(9,51,30)				
7,8	Superior frontal gyrus, medial orbital	SFGmorb	(−5,54,−7)/(8,52,−7)	67,68	Superior temporal gyrus	STG	(−53,−21,7)/(58,−22,7)
9,10	Middle frontal gyrus	MFG	(−33,33,35)/(38,33,34)	69,70	Superior temporal gyrus, temporal pole	STGp	(−40,15,−20)/(48,15,−17)
11,12	Middle frontal gyrus, orbital	MFGorb	(−31,50,−10)/(33,53,−11)	71,72	Middle temporal gyrus	MTG	(−56,−34,−2)/(57,−37,−1)
13,14	Inferior frontal gyrus, opercular	IFGoper	(−48,13,19)/(50,15,21)	73,74	Middle temporal gyrus, temporal pole	MTGp	(−36,15,−34)/(44,15,−32)
15,16	Inferior frontal gyrus, triangular	IFGtri	(−46,30,14)/(50,30,14)	75,76	Inferior temporal gyrus	ITG	(−50,−28,−23)/(54,−31,−22)
17,18	Inferior frontal gyrus, orbital	IFGorb	(−36,31,−12)/(41,32,−12)	77,78	Heschl gyrus	HES	(−42,−19,10)/(46,−17,10)
19,20	Gyrus rectus	REG	(−5,37,−18)/(8,36,−18)	79,80	Hippocampus	HIP	(−25,−21,−10)/(29,−20,−10)
21,22	Anterior cingulate gyrus	ACC	(−4,35,14)/(8,37,16)	81,82	Parahippocampal gyrus	PHIP	(−21,−16,−21)/(25,−15,−20)
23,24	Olfactory cortex	OLF	(−8,15,−11)/(10,16,−11)	83,84	Amygdale	AMYG	(−23,−1,−17)/(27,1,−18)
25,26	Precentral gyrus	PreCG	(−39,−6,51)/(41,−8,52)	85,86	Caudate nucleus	CAU	(−11,11,9)/(15,12,9)
27,28	Supplementary motor area	SMA	(−5,5,61)/(9,0,62)	87,88	Lenticular nucleus, putamen	PUT	(−24,4,2)/(28,5,2)
29,30	Rolandic operculum	ROL	(−47,−8,14)/(53,−6,15)	89,90	Lenticular nucleus, pallidum	PAL	(−18,0,0)/(21,0,0)
31,32	Median- and para-cingulate gyrus	MCC	(−5,−15,42)/(8,−9,40)				
				91,92	Cerebelum_Crus1	CERcr1	(−35,−67,−29)/(38,−67,−30)
33,34	Calcarine fissure and surrounding cortex	CAL	(−7,−79,6)/(16,−73,9)	93,94	Cerebelum_Crus2	CERcr2	(−28,−73,−38)/(33,−69,−40)
35,36	Cuneus	CUN	(−6,−80,27)/(14,−79,28)	95,96	Cerebelum_3	CER3	(−8,−37,−19)/(13,−34,−19)
37,38	Lingual gyrus	LING	(−15,−68,−5)/(16,−67,−4)	97,98	Cerebelum_4_5	CER4_5	(−14,−43,−17)/(18,−43,−18)
39,40	Superior occipital gyrus	SOG	(−17,−84,28)/(24,−81,31)	99,100	Cerebelum_6	CER6	(−22,−59,−22)/(26,−58,−24)
41,42	Middle occipital gyrus	MOG	(−32,−81,16)/(37,−80,19)	101,102	Cerebelum_7b	CER7	(−31,−60,−45)/(34,−63,−48)
43,44	Inferior occipital gyrus	IOG	(−36,−78,−8)/(38,−82,−8)	103,104	Cerebelum_8	CER8	(−25,−55,−48)/(26,−56,−49)
45,46	Fusiform gyrus	FG	(−31,−40,−20)/(34,−39,−20)	105,106	Cerebelum_9	CER9	(−10,−49,−46)/(10,−49,−46)
				107,108	Cerebelum_10	CER10	(−22,−34,−42)/(27,−34,−41)
47,48	Superior parietal gyrus	SPG	(−23,−60,59)/(26,−59,62)	109	Vermis_1_2	Ver1_2	(2,−39,−20)
49,50	Paracentral lobule	PCL	(−7,−56,48)/(10,−56,44)	110	Vermis_3	Ver3	(2,−40,−11)
51,52	Postcentral gyrus	PoCG	(−42,−23,49)/(41,−25,53)	111	Vermis_4_5	Ver4_5	(2,−52,−6)
53,54	Inferior parietal gyrus	IPG	(−43,−46,47)/(46,−46,50)	112	Vermis_6	Ver6	(2,−67,−15)
55,56	Supramarginal gyrus	SMG	(−56,−34,30)/(58,−32,34)	113	Vermis_7	Ver7	(2,−72,−25)
57,58	Angular gyrus	ANG	(−44,−61,36)/(46,−60,39)	114	Vermis_8	Ver8	(2,−64,−34)
59,60	Precuneus	PCNU	(−8,−25,70)/(7,−32,68)	115	Vermis_9	Ver9	(2,−55,−35)
61,62	Posterior cingulate gyrus	PCC	(−5,−43,25)/(7,−42,22)	116	Vermis_10	Ver10	(1,−46,−32)

MNI (L/R) = The Montreal Neurological Institute (MNI) coordinates of the centroids of the left/right region; AAL = Automated Anatomical Labeling.

least in one group at $P<0.05$ (one-sample two-tailed t-test; FDR corrected); (b) the z scores were significantly different between the two groups at $P<0.05$ (two-sample two-tailed t-test; FDR corrected).

Relationship between altered functional connectivities and Braille practice

We used Pearson's correlation coefficient to evaluate the relationship between altered functional connectivities and Braille practice in the early blind. For each of the altered functional connectivity, we calculated the Pearson's correlation coefficient between the z-score and the initial age of Braille practice, and between the z-score and the total practice hours in different age periods (Table 1). Because these analyses were exploratory in nature, we used a statistical significance level of $P<0.05$ (uncorrected).

Results

Functional connectivity within group

The normal sighted and blind groups showed a rather similar functional connectivity pattern. Most of the strong functional connectivities (large z-scores) were found between inter-hemispheric symmetric regions (the node near the diagonal), and within a lobe or anatomically adjacent brain areas (Fig. 1). The functional connectivity pattern within the sighted group was consistent with many previous studies of the whole brain functional connectivity in the resting state (Salvador *et al.*, 2005*a*, *b*; Achard *et al.*, 2006).

We also noticed that some regions (coloured rectangles in Fig. 1) demonstrated visible differences in the strength of functional connectivities between groups. We found that the functional connectivities between the visual and language areas were increased in the early blind; whereas the functional connectivities of the visual area with the motor, visual, somatosensory and multisensory regions were decreased in these subjects.

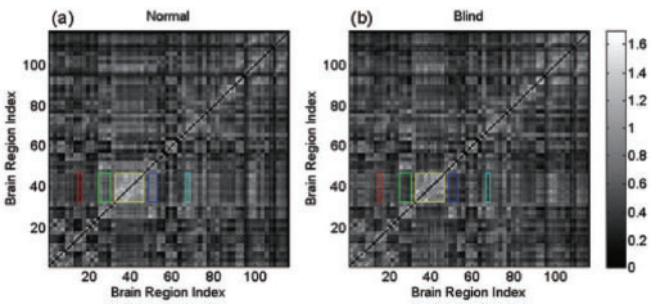

Fig. 1 Mean absolute z-score matrices for normal sighted (**a**) and early blind subjects (**b**). Each figure shows a 116 × 116 square matrix, where the x and y axes correspond to the regions listed in Table 2, and where each entry indicates the mean strength of the functional connectivity between each pair of brain regions. The diagonal running from the lower left to the upper right is intentionally set in black. The z-score of the functional connectivity is indicated with a coloured bar. The coloured rectangles indicate regions that show visual differences between the early blind and sighted groups. The red, green, yellow, blue and cyan rectangles represent the functional connectivity between the visual and language, motor, visual, somatosensory and multisensory regions, respectively.

Altered functional connectivities between early blind and normal sighted

In total, 71 functional connectivities were identified to be significantly different between the blind and the sighted group at the threshold of $P<0.05$ (FDR corrected). We noted that all the altered functional connectivities are related to the occipital cortex (Figs. 1 and 2*a*). Of the 71 altered connectivities, the blind group showed 66 decreased functional connectivities (Fig. 2b and c blue line; Table 3) and 5 increased functional connectivities (Fig. 2b and c red line; Table 4).

Functional connectivities within the occipital cortex (visual area)

Compared with the sighted group, 11 decreased functional connectivities were found within the occipital cortices in the blind group (Fig. 2b and c, Table 3). These decreased functional connectivities were all between the right and left hemispheres.

Functional connectivities between the occipital cortex and frontal cortex (motor area)

We found 15 decreased functional connectivities between the occipital regions and the motor-related regions in the right frontal cortex [including the precentral gyrus (part of

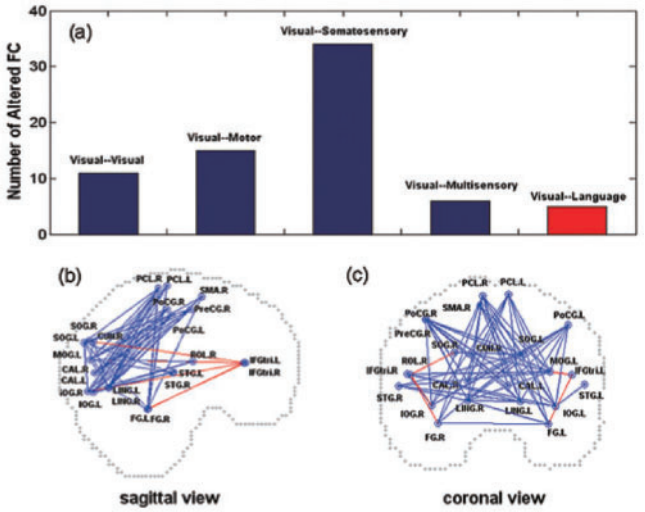

Fig. 2 Altered functional connectivity in the early blind (**a**) shown on sagittal (**b**) and coronal (**c**) views. In (**a**), the y axis indicates the number of the pairs with altered functional connectivity. In (**b**) and (**c**), the dots represent the centroids of each brain region. The blue colour represents decreased functional connectivity and the red colour denotes increased functional connectivity in the early blind. FC = functional connectivity.

Table 3 Decreased functional connectivities in the early blind

Region	Region	*P*-value	Region	Region	*P*-value
Visual – Visual			Visual – Somatosensory		
CUN.R	LING.L	6.34e−06	CAL.L	PoCG.L	9.82e−06
CUN.R	SOG.L	5.37e−06	CAL.L	PoCG.R	9.09e−06
CUN.R	MOG.L	3.47e−05	CAL.L	PCL.R	1.85e−05
FG.L	FG.R	3.56e−05	CAL.R	PoCG.L	1.46e−05
LING.L	LING.R	7.90e−07	CAL.R	PoCG.R	3.72e−05
LING.R	SOG.L	2.39e−08	CAL.R	PCL.L	3.70e−05
LING.R	MOG.L	4.32e−06	CAL.R	PCL.R	1.08e−05
LING.R	FG.L	3.16e−05	FG.L	PCL.L	7.37e−06
SOG.L	SOG.R	3.32e−06	FG.L	PCL.R	2.60e−06
SOG.L	IOG.R	3.13e−05	FG.R	PCL.L	1.28e−05
SOG.L	FG.R	1.61e−05	FG.R	PCL.R	7.28e−06
Visual – Motor			LING.L	PoCG.L	1.14e−07
CAL.L	PreCG.R	1.08e−05	LING.L	PoCG.R	1.14e−08
CAL.R	PreCG.R	1.73e−05	LING.L	PCL.L	2.56e−07
LING.L	PreCG.R	2.99e−07	LING.L	PCL.R	1.14e−07
LING.R	PreCG.R	1.75e−05	LING.R	PoCG.L	2.47e−06
SOG.L	PreCG.R	2.03e−05	LING.R	PoCG.R	5.03e−06
MOG.L	PreCG.R	2.02e−07	LING.R	PCL.L	1.07e−06
IOG.L	PreCG.R	1.19e−05	LING.R	PCL.R	2.61e−07
LING.L	ROL.R	2.28e−05	IOG.L	PoCG.L	2.64e−06
MOG.L	ROL.R	1.55e−06	IOG.L	PoCG.R	1.46e−06
IOG.L	ROL.R	1.81e−06	IOG.L	PCL.L	2.99e−07
IOG.R	ROL.R	1.37e−05	IOG.L	PCL.R	8.67e−08
LING.L	SMA.R	1.02e−06	IOG.R	PoCG.L	1.96e−05
MOG.L	SMA.R	1.11e−05	IOG.R	PoCG.R	2.35e−05
IOG.L	SMA.R	8.13e−07	IOG.R	PCL.L	1.12e−07
FG.L	SMA.R	1.29e−05	IOG.R	PCL.R	5.43e−07
Visual–Multisensory			MOG.L	PoCG.L	2.30e−07
LING.L	STG.R	2.91e−06	MOG.L	PoCG.R	7.83e−08
LING.R	STG.R	4.23e−05	MOG.L	PCL.L	1.15e−07
IOG.L	STG.L	1.59e−05	MOG.L	PCL.R	4.76e−08
IOG.L	STG.R	6.62e−07	SOG.L	PoCG.L	5.05e−05
MOG.L	STG.R	8.35e−06	SOG.L	PoCG.R	2.80e−05
SOG.L	STG.R	3.54e−05	SOG.L	PCL.R	1.31e−05

L = left, R = right.

BA4, 6), Rolandic operculum (part of BA4, 8) and supplementary motor area (part of BA 4, 6, 8)] in the blind group (Fig. 2b and c, Table 3).

Functional connectivities between the occipital cortex and the parietal cortex (somatosensory area)

Our results showed 34 decreased functional connectivities between the occipital areas and the parietal somatosensory areas [postcentral gyrus (part of BA3, 4), paracentral lobule (part of BA 4, 5)] in the blind (Fig. 2b and c, Table 3).

Functional connectivities between occipital cortex and the temporal cortex (multisensory area)

The statistical analyses showed six decreased functional connectivities between the visual brain areas and superior temporal gyrus (part of BA 21, 22, 48) in the blind (Fig. 2b and c, Table 3).

Functional connectivities between the occipital cortex and the frontal cortex (language area)

Compared with the sighted individuals, the blind subjects showed five increased functional connectivities between the inferior frontal triangular gyrus (part of BA44, 45, 47) and certain occipital visual areas in the same hemisphere (Fig. 2b and c red line, Table 4).

Relationship between the altered functional connectivities and Braille practice

We found that the strength (*z*-score) of the altered functional connectivities was negatively correlated with the initial age of learning Braille and positively correlated with the total Braille practice time in childhood (Table 5). No significant correlation was found between the strength of the altered functional connectivities and Braille practice in adolescence and adulthood (Table 5).

Table 4 Increased functional connectivities in the early blind

Region	Region	*P*-value
MOG.L	IFGtri.L	6.76e−06
FG.L	IFGtri.L	9.46e−06
SOG.R	IFGtri.R	9.86e−06
IOG.R	IFGtri.R	6.15e−07
FG.R	IFGtri.R	3.11e−07

L = left, R = right.

Table 5 Relationship between altered functional connectivities and Braille practice

Region	Region	Braille practice			
		Start age (years)	Childhood (h)	Adolescence (h)	Adulthood (h)
CAL.L	PreCG.R	−0.55*			
CAL.R	PreCG.R	−0.53*			
LING.L	PreCG.R	−0.62*			
LING.R	PreCG.R	−0.62*	0.51*		
MOG.L	PreCG.R	−0.61*	0.53*		
IOG.L	PreCG.R	−0.63**	0.69***		
LING.L	ROL.R	−0.53*			
MOG.L	ROL.R	−0.62*			
IOG.L	ROL.R	−0.68***	0.61*		
IOG.R	ROL.R	−0.6*			
LING.L	SMA.R	−0.59*			
IOG.L	SMA.R	−0.58*			
FG.L	SMA.R	−0.52*			
CUN.R	LING.L		0.62**		
LING.R	SOG.L		0.67***		
SOG.L	IOG.R		0.53*		
SOG.L	FG.R				
LING.L	PoCG.L	−0.51*			
LING.R	PoCG.L	−0.56*	0.52*		
MOG.L	PoCG.L		0.58*		
IOG.L	PoCG.L	−0.55*	0.76***		
IOG.R	PoCG.L	−0.59*	0.55*		
LING.R	PoCG.R		0.5*		
MOG.L	PoCG.R		0.59*		
IOG.L	PoCG.R		0.69***		
IOG.R	PoCG.R	−0.54*	0.55*		
IOG.L	PCL.L		0.60*		
IOG.R	PCL.L	−0.5*			
IOG.L	STG.L	−0.65**	0.65**		
IOG.L	STG.R	−0.56*	0.52*		

L = left; R = right.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$.

Discussion

Unlike most previous studies of the blind, we investigated the presence of altered functional connectivities in the resting state, and we focused on the distribution of altered functional connectivities throughout the entire brain.

The BOLD signal of the resting state fMRI has been confirmed to reflect neuronal activity, and the LFF of the BOLD signal in the resting state have been attributed to spontaneous neuronal activities (Xiong *et al.*, 1999; Salvador *et al.*, 2005*a*). Such synchronous neuronal fluctuations may facilitate the coordination and organization of information processing across several spatial and temporal ranges (Raichle and Mintun, 2006). Highly synchronous LFF in healthy adults were reported within the primary motor (Biswal *et al.*, 1995; Lowe *et al.*, 1998; Cordes *et al.*, 2001; Jiang *et al.*, 2004), auditory (Cordes *et al.*, 2001), visual cortices (Lowe *et al.*, 1998) and some non-primary brain regions such as language (Hampson *et al.*, 2002) and the default brain network (Greicius *et al.*, 2003; Fox *et al.*, 2005). Several previous studies on healthy subjects also indicated that different brain regions work together to form a complex, structured network in the resting state (Greicius *et al.*, 2003; Fox *et al.*, 2005; Salvador *et al.*, 2005*a*, *b*; Achard *et al.*, 2006). All of these studies suggest that resting state functional connectivities can be reliably measured by the temporal correlations of LFF.

Hypotheses of general loss and compensatory plasticity in the early blind

In those with early onset of blindness, the general loss hypothesis refers to maladjustments resulting from blindness (Pascual-Leone *et al.*, 2005). In sighted people, the visual system and the motor, somatosensory systems work in coordination to carry out many routine activities. This coordination indicates the existence of functional connectivities between these systems. However, in the early blind, these functional systems cannot work in coordination due to early visual deprivation (Pascual-Leone and Hamilton, 2001; Amedi *et al.*, 2005*b*); such lack of coordination may lead to the blind being unable to fulfill some tasks, such as spatial information processing, as well as sighted subjects (Zwiers *et al.*, 2001). Thus, the general loss mechanism may induce a decrease in the functional connectivities between visual areas and associated brain regions. In contrast, compensatory plasticity, which has been studied by many previous studies (Röder *et al.*, 2001; Amedi *et al.*, 2003, 2004; Gougoux *et al.*, 2004, 2005; Sadato, 2005; Burton *et al.*, 2006), may lead to an increase in functional connectivities between visual areas and associated brain regions due to the establishment of new functional connectivities or reinforcement of the existing functional connectivities in order to complete certain specific tasks. Therefore, we speculate that changes in brain functional connectivities in the resting state may be an integrated reflection of general loss and compensatory plasticity in the early blind. In support of this we were able to demonstrate that the correlation coefficients between the visual and somatosensory areas were found to increase when the blind subject started Braille earlier or spent more time on Braille practice, especially in childhood. This finding supports the existence of compensatory plasticity. However, the functional connectivities between these two systems

were found to be decreased in the early blind. This decrease may indicate that the general loss mechanism plays a dominant role.

Decreased functional connectivities in the early blind

In our study, all the altered functional connectivities were related to the occipital visual cortices in the early blind subjects (Figs. 1 and 2). Compared with the sighted subjects, most of the altered functional connectivities (66/71) were decreased in the blind. Many previous studies have indicated that the density of synapses in the visual cortex undergoes dramatic changes during normal development (O'Kusky *et al.*, 1980; Rakic *et al.*, 1986; Huttenlocher *et al.*, 1987). In the newborn human visual cortex, synaptic density is similar to adult levels. There is a modest increase during the early postnatal period, followed by a rapid increase of synaptic density between 2.5 and 8 months of age, after which the density declines gradually to reach adult levels at 11 years of age. This decline in synaptic density (referring to synaptic revision) corresponds to the elimination of redundant connections, through which effective functional connectivities are established (Herschkowitz *et al.*, 1997; Herschkowitz, 2000; Lewis and Maurer, 2005). The increasing phase of synaptogenesis in the visual cortex appears to be relatively independent of visual experience (Winfield, 1981). In contrast, synaptic revision is critically dependent on the activity of visual afferent inputs (Strycker *et al.*, 1986). In the early blind, visual input is interrupted prior to the stage of synaptic revision and thus may interfere with the establishment of effective functional connectivities between the visual cortices and other related regions. It has also been suggested that early sensory input plays an important role in setting up the infrastructure for later tuning of the visual cortex (Maurer *et al.*, 2005), and that visual input can affect later development of the brain by (a) preventing deterioration of existing neural structures; (b) reserving neural networks for later refinement; (c) allowing a developmental trajectory to start from an optimal state and (d) refining previously established structures (Lewis and Maurer, 2005). Thus the absence of visual input in the early years may lead to generalized loss by preventing the development of the associated occipital cortex and by preventing the establishment of effective functional connectivities between visual regions and other brain regions. The prevention of these normal functions may account for the decreased functional connectivities between the visual cortices and the motor and somatosensory areas in the early blind, although compensatory plasticity was reported in many task-based fMRI studies (Röder *et al.*, 2001; Amedi *et al.*, 2003, 2004; Gougoux *et al.*, 2004, 2005; Sadato, 2005; Burton *et al.*, 2006).

Decreased functional connectivities within the occipital cortices

In this study, we found that the functional connectivities within the occipital cortex were decreased in the blind group and we also noted that these decreased functional connectivities were all between the two hemispheres. In sighted people, left and right occipital visual regions are connected by the fibres of the splenium of the corpus callosum, and work coordinately to process visual information. However, the early blind subjects lost the practice of processing visual information during a critical development stage, which may result in hypogenesis of the splenium fibres of the corpus callosum. This inference was supported by a study that used diffusion tensor imaging, in which a decrease in the anisotropy of the splenium of the corpus callosum was demonstrated (Shimony *et al.*, 2006). The above finding may partially explain the decreased functional connectivities between the visual cortices of the two hemispheres.

Decreased functional connectivities between the occipital visual and frontal motor areas

From the results, we noted that the functional connectivities between the frontal motor areas and the visual areas were decreased in the blind (Figs. 1 and 2). The coordination between visual and motor areas is very important for normal life. Eye–hand coordination is critical for carrying out many routine human activities, such as tool use, eating, sports and work. It involves the synergistic function of several sensory-motor and visual systems. These systems work in coordination to optimize the accuracy of the hand motion (Christensen *et al.*, 2006). A previous PET study also showed that the visual cortex and motor systems were synchronously activated when performing certain difficult goal-directed reciprocal aiming tasks (Winstein *et al.*, 1997). The aforementioned studies may indicate the presence of functional connectivities between the prefrontal motor regions and the visual areas in healthy individuals. Therefore, it is reasonable to suppose that the resting state functional connectivities between these two regions were decreased due to visual deprivation in the blind subjects.

Our results also demonstrated that the decreased functional connectivities were located in the right hemisphere. Several previous studies reported that left motor cortex activity was more significant than its right counterpart when the blind performed a Braille-reading task even when using the left hand to read (Burton *et al.*, 2002*a*). This finding may indicate that the functional connectivities between the left motor regions and the visual cortex are stronger than those of the right side in the blind, which may explain why we only found significantly decreased functional connectivities between the visual regions and the right motor cortices under our threshold.

Decreased functional connectivities between the occipital visual and parietal somatosensory cortices

In sighted subjects, the visual areas have been reported as being involved in the tactile discrimination of orientation (Zangaladze *et al*., 1999; Sathian and Zangaladze, 2001) and in vibrotactile discrimination tasks (Burton *et al*., 2004) although simple tactile stimuli could not produce the activation of visual areas (Sadato *et al*., 1996). Using a special visuo-haptic task, Amedi *et al*. (2001) found robust and consistent somatosensory activation in the occipital–temporal region in normal sighted subjects. The visual cortices were found to be associated with somatosensory areas in sighted subjects by analysing the effective connectivity when performing a discrimination of a haptic shape or a texture task (Peltier *et al*., 2007). All these findings indicate the presence of functional connectivities between visual areas and somatosensory areas, and these two brain regions serving both visual and sensory modalities work in coordination to process certain complex cognitive tasks in normal sighted people. In the early blind, due to the absence of visual input, general loss may play a predominant role in interactions between these two functionally related brain areas. Hence these functional connectivities were weakened in early blind people, although functional reorganization has been found between these two regions in the blind when performing many different tasks (De Volder *et al*., 1997; Büchel *et al*., 1998; Burton *et al*., 2002*a*).

Decreased functional connectivities between the occipital visual and temporal multisensory cortices

We noted that the functional connectivities between the occipital cortex and superior temporal gyrus (STG) were decreased in the blind. This was consistent with the study by Burton and colleagues which indicated that the response pattern of the STG was significantly different between that of blind and of sighted subjects when using different embossed-capital-letter-reading tasks (Burton *et al*., 2006). The STG is considered to be an important multisensory functional brain region, which integrates visual, auditory and language information (Wright *et al*., 2003; Beauchamp, 2004*a*, *b*). The activity of the STG was enhanced when auditory-visual animated characters speaking single words were used as a stimulus compared with the activity level when a single auditory or visual stimulus was presented to healthy subjects (Wright *et al*., 2003; Beauchamp, 2004*a*). The above studies may indicate the existence of functional connectivities between the occipital cortices and the STG in sighted subjects. In the early blind, however, the STG and visual areas have no opportunity to work together to process visual information, due to visual deprivation, so the effective functional connectivities could not be established, which may explain why the functional connectivities between the occipital visual cortices and STG were decreased in these subjects.

Increased functional connectivities in the blind

We found that the functional connectivities between the inferior frontal triangular areas (part of BA 44, 45, 47) and the occipital areas were increased in the early blind. The inferior frontal triangular area is classically considered as a motor speech-production area, and is also involved in action understanding and imitation (Binder *et al*., 1997; Bookheimer *et al*., 2002; Nishitani *et al*., 2005). Beyond its classical language functions, this area also participates in language-related working memory during online sentence comprehension (Novick *et al*., 2005; Fiebach *et al*., 2005). In the blind, the occipital visual and frontal language areas are activated simultaneously when performing a Braille-reading task (Burton *et al*., 2002*b*; Burton, 2003) or reading embossed capital letters (Burton *et al*., 2006). These findings indicate that both these areas are important nodes in the brain language network of the blind (Amedi *et al*., 2004). Additionally, when comparing with the sighted subjects, the early blind showed simultaneous activations in the visual areas and frontal language areas when performing a verbal memory task (Amedi *et al*., 2003), which may account for the superior performance of the early blind in variety of verbal-memory tasks (Hull and Mason, 1995; Röder *et al*., 2001; Raz *et al*., 2005). All of the above evidences may explain why the functional connectivities between the two regions were increased in the early blind. Our result was also supported by an earlier finding of increased effective connectivity between the prefrontal cortices and occipital regions when the blind performed semantic processing tasks (Noppeney *et al*., 2003).

Possible mechanisms for complementary plasticity of visual cortices in the early blind

The recruitment of the visual cortex for tactile processing may be through two alternative routes: thalamo-cortical connections from the thalamus to the visual cortices and cortico-cortical connections from the somatosensory cortex to the visual cortices (Hamilton and Pascual-Leone, 1998; Pascual-Leone *et al*., 2005). Based on functional and structural evidence, other researchers have suggested that cortico-cortical connections could play a key role in cross-modal plasticity (Hamilton and Pascual-Leone, 1998; Sadato *et al*., 1998, 2002; Bavelier and Neville, 2002). We found that the correlation coefficients between the altered functional connectivities and Braille practice were increased when the blind subject started Braille earlier or spent more time on Braille practice, especially in childhood. This finding indicates the existence of compensatory plasticity in the early blind and supports the perspective that cortico-cortical connections are important in cross-modal plasticity. In this study, we also investigated the functional connectivities between the thalamus and all the other brain regions in a voxel-wise manner, and found

increased functional connectivities between the thalamus and visual areas ($P < 0.001$, uncorrected). These increased connectivities indicate that thalamo-cortical connections may also contribute to compensatory plasticity in the early blind. We suggest that both the thalamo-cortical connections and the cortico-cortical connections participate in complementary plasticity in the early blind. The details can be found in the first part of the supplemental material.

The effect of morphometric changes on functional connectivity analysis

Evidence from non-human primate studies has showed structural changes in the visual cortex at a microscopic level due to early visual deprivation (Dehay *et al.*, 1989; Bourgeois and Rakic, 1996). Structural alterations in the visual, somatosensory and motor systems have also been demonstrated in the early blind (Noppeney *et al.*, 2005; Shimony *et al.*, 2006). To reduce the influence of structural changes on the BOLD signals and to further test the reliability of our results, we regressed out the confounding factor of grey matter atrophy when performing the statistical analysis in order to identify differences of functional connectivities between the two groups. Similar results were obtained after eliminating the possible influences of grey matter atrophy. Extended details can be found in the second part of the supplemental material.

Limitations

It should be noted that, like most functional connectivity studies based on resting state fMRI, we can reduce to some degree, but cannot completely eliminate the effects of physiological noise because we used a relatively low sampling rate (TR = 2 s) for multi-slice acquisitions, and thus cardiac effects would be aliased into the low-frequency fluctuations. In future studies, these physiological effects may be estimated and removed by simultaneously recording the respiratory and cardiac cycles during data acquisition. It should also be noted that it is possible that, although the blind have fewer anatomical connections, they may use them more effectively when reading Braille or touching an object. Such effective use could be underestimated in this current, relatively large, inter-regional functional connectivity study. Future study based on voxel-level statistical analysis or investigating effective connectivities using a specifically designed task may be able to solve this issue.

Conclusion

In this study, we directly investigated the distribution of altered functional connectivities throughout the entire brain in the early blind using resting state fMRI. We found decreased functional connectivities within the occipital visual cortices, between the occipital visual areas and frontal motor, parietal somatosensory and temporal multisensory areas. The correlation coefficients between most of the decreased functional connectivities and Braille practice increased if the blind subject started Braille practice earlier or spent more time on it, especially in childhood. These findings may indicate that the general loss and the compensatory plasticity mechanisms coexist in the early blind. Therefore, we speculate that changes in functional connectivities in the resting state may be an integrated reflection of general loss and compensatory plasticity in such single sensory modality deprivations.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

The authors are grateful to the anonymous referees for their significant and constructive comments and suggestions, which greatly improved the paper. The authors also thank Kun Wang, Keith J. Worsley and Ming Song for their comments and suggestions. The authors also express appreciation to Drs Rhoda E. and Edmund F. Perozzi for English language and editing assistance. This work was partially supported by the Natural Science Foundation of China, Grant Nos. 30425004, 60675033 and 60121302, and the National Key Basic Research and Development Program (973), Grant No. 2004CB318107.

References

Amedi A, Malach R, Hendler T, Peled S, Zohary Z. Visuo-haptic object-related activation in the ventral visual pathway. Nat Neurosci 2001; 4: 324–30.

Amedi A, Raz N, Pianka P, Malach R, Zohary E. Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci 2003; 6: 758–66.

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci 2004; 7: 1266–70.

Amedi A, Kriegstein K, Atteveldt NM, Beauchamp MS, Naumer MJ. Functional imaging of human crossmodal identification and object recognition. Exp Brain Res 2005*a;* 66: 559–71.

Amedi A, Merabet L, Bermpohl F, Pascual-Leone A. The occipital cortex in the blind: lessons about plasticity and vision. Curr Direct Psychological Sci 2005*b*; 14: 306–11.

Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J Neurosci 2006; 26: 63–72.

Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci 2005; 8: 1148–50.

Beauchamp MS, Argall BD, Bodurka J, Duyn JH, Martin A. Unraveling multisensory integration: patchy organization within human STS multisensory cortex. Nat Neurosci 2004*a;* 7: 1190–2.

Beauchamp MS, Lee KE, Argall BD, Martin A. Integration of auditory and visual information about objects in superior temporal sulcus. Neuron 2004*b*; 41: 809–23.

Bavelier D, Neville HJ. Cross-modal plasticity: where and how? Nat Rev Neurosci 2002; 3: 443–52.

Benjamini Y, Yekutieli Y. The control of false discovery rate in multiple testing under dependency. Ann Stat 2001; 29: 1165–88.

Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997; 17: 353–62.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34: 537–41.

Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. Annu Rev Neurosci 2002; 25: 151–88.

Bourgeois JP, Rakic P. Synaptogenesis in the occipital cortex of macaque monkey devoid of retinal input from early embryonic stages. Eur J Neurosci 1996; 8: 942–50.

Büchel C, Price C, Frackowiak RS, Friston KJ. Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 1998; 121: 409–19.

Burton H, Snyder AZ, Conturo T, Akbudak E, Ollinger JM, Raichle ME. Adaptive changes in early and late blind: an fMRI study of Braille reading. J Neurophysiol 2002*a;* 87: 589–607.

Burton H, Snyder AZ, Diamond JB, Raichle ME. Adaptive changes in early and late blind: an fMRI study of verb generation to heard nouns. J Neurophysiol 2002*b*; 88: 3359–71.

Burton H. Visual cortex activity in early and late blind people. J Neurosci 2003; 23: 4005–11.

Burton H, Sinclair RJ, McLaren DG. Cortical activity to vibrotactile stimulation: an fMRI study in blind and sighted individuals. Hum Brain Mapp 2004; 23: 210–28.

Burton H, McLaren DG, Sinclair RJ. Reading embossed capital letters: an fMRI study in blind and sighted individuals. Hum Brain Mapp 2006; 27: 325–39.

Christensen MS, Ramsoy TZ, Lund TE, Madsen KH, Rowe JB. An fMRI study of the neural correlates of graded visual perception. Neuroimage 2006; 31: 1711–25.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, et al. Functional relevance of cross-modal plasticity in blind humans. Nature 1997; 389: 180–3.

Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in 'resting-state' data. Am J Neuroradiol 2001; 22: 1326–33.

Dehay C, Horsburgh G, Berland M, Killackey H, Kennedy H. Maturation and connectivity of the visual cortex in monkey is altered by prenatal removal of retinal input. Nature 1989; 337: 265–7.

De Volder AG, Bol A, Blin J, Robert A, Arno P, Grandin C, et al. Brain energy metabolism in early blind subjects: neural activity in the visual cortex. Brain Res 1997; 750: 235–44.

De Volder AG, Toyama H, Kimura Y, Kiyosawa M, Nakano H, Vanlierde A, et al. Auditory triggered mental imagery of shape involves visual association areas in early blind humans. Neuroimage 2001; 14: 129–39.

Fiebach CJ, Schlesewsky M, Lohmann G, von Cramon DY, Friederici AD. Revisiting the role of Broca's area in sentence processing: syntactic integration versus syntactic working memory. Hum Brain Mapp 2005; 24: 79–91.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993; 13: 5–14.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102: 9673–8.

Gizewski ER, Gasser T, Greiff A, Boehm A, Forsting M. Cross-modal plasticity for sensory and motor activation patterns in blind subjects. Neuroimage 2003; 19: 968–75.

Gougoux F, Lepore F, Lassonde M, Voss P, Zatorre RJ, Belin P. Neuropsychology: Pitch discrimination in the early blind. Nature 2004; 430: 309.

Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F. A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. PLoS Biol 2005; 3: e27.

Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100: 253–8.

Hamilton R, Pascual-Leone A. Cortical plasticity associated with Braille learning. Trends Cogn Sci 1998; 2: 168–74.

Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp 2002; 15: 247–62.

Herschkowitz N, Kagan J, Zilles K. Neurobiological bases of behavioral development in the first year. Neuropediatrics 1997; 28: 296–306.

Herschkowitz N. Neurological bases of behavioral development in infancy. Brain Dev 2000; 22: 411–6.

Huttenlocher PR, De Courten C. The development of synapses in striate cortex of man. Hum Neurobiol 1987; 6: 1–9.

Hull T, Mason H. Performance of blind children on digit-span tests. J Vis Impairm Blindn 1995; 89: 166–9.

Jiang A, Kennedy DN, Baker JR, Weisskoff RM, Tootell BH, Woods RP, et al. Motion detection and correction in functional MR imaging. Hum Brain Mapp 1995; 3: 224–35.

Jiang T, He Y, Zang Y, Weng X. Modulation of functional connectivity during the resting state and the motor task. Hum Brain Mapp 2004; 22: 63–71.

Lambert S, Sampaio E, Mauss Y, Scheiber C. Blindness and brain plasticity: contribution of mental imagery? An fMRI study. Cogn Brain Res 2004; 20: 1–11.

Leclerc C, Saint-Amour D, Lavoie ME, Lassonde M, Lepore F. Brain functional reorganization in early blind humans revealed by auditory event-related potentials. Neuroreport 2000; 11: 545–50.

Lewis TL, Maurer D. Multiple sensitive periods in human visual development: evidence from visually deprived children. Dev Psychobiol 2005; 46: 163–83.

Liang M, Zhou Y, Jiang T, Liu Z, Tian L, Liu H, et al. Widespread functional disconnectivity in schizophrenia with resting-state fMRI. Neuroreport 2006; 17: 209–13.

Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echo planar imaging using resting state fluctuations. Neuroimage 1998; 7: 119–32.

Lowe MJ, Phillips MD, Lurito JT, Mattson D, Dzemidzic M, Mathews VP. Multiple sclerosis: low-frequency temporal blood oxygen level dependent fluctuations indicate reduced functional connectivity initial results. Radiology 2002; 224: 184–92.

Maurer D, Lewis TL, Mondloch CJ. Missing sights: consequences for visual cognitive development. Trends Cogn Sci 2005; 19: 144–51.

Novick JM, Trueswell JC, Thompson-Schill SL. Cognitive control and parsing: reexamining the role of Broca's area in sentence comprehension. Cogn Affect Behav Neurosci 2005; 5: 263–81.

Nishitani N, Schurmann M, Amunts K, Hari R. Broca's region: from action to language. Physiology (Bethesda) 2005; 20: 60–9.

Noppeney U, Friston KJ, Price CJ. Effects of visual deprivation on the organization of the semantic system. Brain 2003; 126: 1620–7.

Noppeney U, Friston KJ, Ashburner J, Frackowiak R, Price CJ. Early visual deprivation induces structural plasticity in gray and white matter. Curr Biol 2005; 15: 488–90.

O'Kusky J, Colonnier M. Postnatal changes in the number of neurons and synapses in the visual cortex (areal7) of the macaque monkey: a stereological analysis in normal and monocularly deprived animals. J Comp Neurol 1980; 210: 291–306.

Pascual-Leone A, Hamilton R. The metamodal organization of the brain. Prog Brain Res 2001; 134: 427–45.

Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci 2005; 28: 377–401.

Peltier SJ, Kerssens C, Hamann SB, Sebel PS, Byas-Smith M, Hu X. Functional connectivity changes with concentration of sevoflurane anesthesia. Neuroreport 2005; 16: 285–8.

Peltier S, Stilla R, Mariola E, Laconte S, Hu X, Sathian K. Activity and effective connectivity of parietal and occipital cortical regions during haptic shape perception. Neuropsychologia 2007; 45: 476–83.

Poirier C, Collignon O, Scheiber C, Renier L, Vanlierde A, Tranduy D, et al. Auditory motion perception activates visual motion areas in early blind subjects. Neuroimage 2006; 31: 279–85.

Raczkowski D, Kalat JW, Nebes R. Reliablity and validity of some handedness questionnaire items. Neuropsychologia 1974; 2: 43–7.

Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 1986; 232: 232–5.

Raichle ME, Gusnard DA. Intrinsic brain activity sets the stage for expression of motivated behavior. J Comp Neurol 2005; 493: 167–76.

Raichle ME, Mintun MA. Brain work and brain imaging. Annu Rev Neurosci 2006; 29: 449–76.

Raz N, Amedi A, Zohary E. V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb Cortex 2005; 15: 1459–68.

Röder B, Teder-Salejarvi W, Sterr A, Rosler F, Hillyard SA, Neville HJ. Improved auditory spatial tuning in blind humans. Nature 1999; 400: 162–6.

Röder B, Rosler F, Neville HJ. Auditory memory in congenitally blind adults: a behavioral electrophysiological investigation. Cogn Brain Res 2001; 11: 289–303.

Röder B, Stock O, Bien S, Neville H, Rosler F. Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci 2002; 16: 930–6.

Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, et al. Activation of the primary visual cortex by Braille reading in blind subjects. Nature 1996; 380: 526–8.

Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M. Neural networks for Braille reading by the blind. Brain 1998; 121: 1213–29.

Sadato N, Okada T, Honda M, Yonekura Y. Critical period for cross-modal plasticity in blind humans: a functional MRI study. Neuroimage 2002; 16: 389–400.

Sadato N. How the blind ''see'' Braille: lessons from functional magnetic resonance imaging. Neuroscientist 2005; 11: 577–82.

Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb Cortex 2005*a;* 15: 1332–42.

Salvador R, Suckling J, Schwarzbauer C, Bullmore E. Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philos Trans R Soc Lond B Biol Sci 2005*b*; 360: 937–46.

Shimony JS, Burton H, Epstein AA, McLaren DG, Sun SW, Snyder AZ. Diffusion tensor imaging reveals white matter reorganization in early blind humans. Cereb Cortex 2006; 16: 1653–61.

Strycker MP, Harris WA. Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. J Neurosci 1986; 6: 2117–26.

Sathian K, Zangaladze A. Feeling with the mind's eye: the role of visual imagery in tactile perception. Optom Vis Sci 2001; 78: 276–81.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002; 15: 273–89.

Vanlierde A, De Volder AG, Wanet-Defalque MC, Veraart C. Occipito-parietal cortex activation during visuo-spatial imagery in early blind humans. Neuroimage 2003; 19: 698–709.

Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, et al. A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci 2000; 20: 2664–72.

Winfield DA. The postnatal development of synapses in the visual cortex of the cat and the effects of eyelid closure. Brain Res 1981; 206: 166–71.

Winstein CJ, Grafton ST, Pohl PS. Motor task difficulty and brain activity: investigation of goal-directed reciprocal aiming using positron emission tomography. J Neurophysiol 1997; 77: 1581–94.

Wright TM, Pelphrey KA, Allison T, McKeown MJ, McCarthy G. Polysensory interactions along lateral temporal regions evoked by audiovisual speech. Cereb Cortex 2003; 13: 1034–43.

Xiong J, Parsons LM, Gao JH, Fox PT. Interregional connectivity to primary motor cortex revealed using MRI resting state images. Hum Brain Mapp 1999; 8: 151–6.

Zangaladze A, Epstein CM, Grafton ST, Sathian K. Involvement of visual cortex in tactile discrimination of orientation. Nature 1999; 401: 587–90.

Zwiers MP, Van Opstal AJ, Cruysberg JR. A spatial hearing deficit in early-blind humans. J Neurosci 2001; 21: 1–5.