Age of Onset of Blindness Affects Brain Anatomical Networks Constructed Using Diffusion Tensor Tractography

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Studying blindness with various onset ages may elucidate the ways that unimodal sensory deprivation at different periods of development shape the human brain. In order to determine the effect of the onset age on brain anatomical networks, we extended a previous study of 17 early blind (EB) subjects with an additional 97 subjects with various onset ages. We constructed binary anatomical networks of these subjects and sighted controls (SC) using diffusion tensor tractography and calculated the topological properties of the network. Based on onset age, the subjects were divided into congenitally blind (CB), EB, adolescent-blind (AB), and late-blind (LB) subgroups. The LB subjects demonstrated a greater connectivity density and a higher global efficiency, similar to the SC. The CB and EB subgroups showed large group differences from the other groups in their topological networks, specifically, a reduced connectivity density and a decreased global efficiency compared with the SC, especially in the frontal and occipital cortices. Additionally, significant correlations were found between age of onset and the topological properties of the anatomical network in the blind. Our results suggest that visual experience during an early period of development is critical for establishing an intact efficient anatomical network in the human brain.

Keywords: age of onset, anatomical network, blindness, diffusion tensor imaging, tractography

Introduction

Studying visual deprivation may elucidate the ways that natural sensory impairment can affect experience-dependent plasticity in the human brain. The brain structure and function of subjects with congenital or early onset blindness are shaped by interactions between typical development, and plastic and disuse changes. However, the brains of late-onset blind subjects are primarily affected by degenerative and plastic factors. Additionally, the plasticity of the brain shows evidence of being lower in late-blind (LB) subjects than in early blind (EB) subjects (Jiang et al. 2009; Park et al. 2009; Lepore 2010).

In blind subjects, the lack of vision inevitably results in structural and functional changes in the brain, especially in the visual areas. Some of these changes, including decreased brain tissue volume (Noppeney et al. 2005; Pan et al. 2007; Pinto et al. 2008; Bridge et al. 2009; Lepore et al. 2010), white matter integrity (Shimony et al. 2006; Shu, Li, et al. 2009), functional connectivity (Liu et al. 2007; Yu et al. 2008), and increased cortical thickness (Bridge et al. 2009; Jiang et al. 2009; Park et al. 2009) in visual-related brain areas, are disruptive, but others are compensatory or plastic. In blind subjects, the occipital cortex has been repeatedly shown to shift from processing visual information to processing information from tactile and auditory modalities and to be involved in auditory or tactile discrimination, language or memory tasks (Bavelier and Neville 2002; Amedi et al. 2003, 2004; Gouguyp et al. 2005; Raz et al. 2005; Sadato 2006; Merabet et al. 2007; Cignolin et al. 2009; Fischler and Rosler 2010; Bedny et al. 2011; Chan et al. 2011). Other plastic evidence comes from structural magnetic resonance imaging (MRI), revealing increased anterior right hippocampal volume (Lepore 2009); diffusion MRI (dMRI), indicating increased integrity of the corticospinal tract (Yu et al. 2007); and resting-state functional MRI (fMRI), reporting increased spontaneous brain activity (Liu et al. 2011) and several functional connectivities (Liu et al. 2007; Yu et al. 2008) in the occipital cortex in blind subjects.

Although blind subjects have shown disruptive or plastic changes due to the lack of vision, increasing evidence has suggested that the functional organization of most of the visual areas can develop independently in the presence of visual experience (for review, see Kupers et al. 2010, 2011; Matteau et al. 2010; Reich et al. 2011; Striem-Amit et al. 2011). Moreover, other brain areas whose functions are mainly dependent on visual inputs, such as the mirror system for actions (Ricciardi et al. 2009), the left parietal cortex for representation of tools (Mahon et al. 2010), and the medial prefrontal cortex for self-referential processing (Ma and Han 2011), also preserve their functional organization in the congenitally blind (CB). Thus, studying blind subjects with different ages of onset provides an opportunity to investigate the dependence and independence of the brain’s structural and functional architecture on visual experience.

The human brain is a complex but efficient network. Recently, many researchers have used graph theory based on network topological measures to show that the human brain has small-world attributes (Watts and Strogatz 1998; Sporns and Zwi 2004; Bassett and Bullmore 2006; Hagmann et al. 2007; He et al. 2007; Gong et al. 2009) and modular structure (Chen et al. 2008; Hagmann et al. 2008; Meunier et al. 2009). These organizational aspects can ensure that different functional brain regions work together to interact with the world in an extremely short time (Sporns and Zwi 2004; Achard and Bullmore 2007; Bullmore and Sporns 2009; Sporns 2010, 2011). In blind subjects, only one recent dMRI study has focused on alterations in the topological properties of the brain anatomical network and found significant changes in the network...
properties, especially in the occipital cortex in 17 EB subjects (Shu, Liu, et al. 2009). However, we do not know how the age of onset of blindness affects brain network properties, although a previous dMRI study did not find any significant changes in the optic radiation and the corticospinal tract in LB subjects (Schoth et al. 2006).

Do LB subjects also show significant changes in the organizational architecture of the brain anatomical network? How does the age of onset of blindness affect the topological properties of the network? Based on previous studies, we hypothesized that the age of onset of blindness will affect the topological properties of the brain anatomical network. In the current study, we recruited a group of blind subjects who lost sight from 0 to 3+ years old and a group of age- and gender-matched sighted controls (SC). We first constructed binary anatomical networks of the individual brains with 90 brain regions as nodes extracted by automated anatomical labeling (AAL) (Tzourio-Mazoyer et al. 2002) and interregional fibers as connections identified by diffusion tensor tractography (Gong et al. 2009; Li et al. 2009; Shu, Liu, et al. 2009; Wang et al. 2012). Next, we computed the topological properties of the individual brain networks. Third, we analyzed the statistical differences between the CB, EB, adolescent blind (AB), and LB and SC groups. Finally, we evaluated the correlation between the age of onset of blindness and the topological properties of the anatomical network in the blind group.

Materials and Methods

Subjects
Blind subjects were recruited from the Special Education College of Beijing Union University or by advertisement in local blind communities, and normal SCs were recruited by advertisement. All aspects of the study were approved by the Ethics Committee of Tianjin Medical University, and all the participants signed an informed consent before being included in the study. One hundred and thirteen blind subjects participated in our experiment. After excluding those subjects not suitable for the study (left handed, different ages of onset of the left and right eyes, lack of diffusion MRI data, and low data quality as checked by 2 radiologists), 97 right-handed blind subjects (68 males, 29 females; mean age = 29.9 years, range 16–50 years; mean age of onset = 11.6 years, range 0–34 years) and 73 handedness-, age-, and gender-matched normal SCs (55 males, 18 females; mean age = 28.6 years, range 20–54 years) were included in this study. The blind subjects were further divided into 19 congenital-onset blind (CB, age of onset = 0), 28 early onset blind (EB, age of onset = 1–11 years), 18 adolescent-onset blind (AB, age of onset = 12–15 years), and 32 late-onset blind (LB, age of onset > 16 years) based on the various ages of onset of blindness (Huttenlocher and de Courten 1987; Bengtsson et al. 2005). Analysis of variance (ANOVA) tests did not reveal any significant differences in age (P = 0.10) and gender (P = 0.70) among the 5 groups (Table 1). For more detailed information about the blind subjects, please see Supplementary Part I.

Table 1

<table>
<thead>
<tr>
<th>Subjects information</th>
<th>CB</th>
<th>EB</th>
<th>AB</th>
<th>LB</th>
<th>SC</th>
<th>P value of ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males/females)</td>
<td>12/7</td>
<td>21/7</td>
<td>14/4</td>
<td>21/11</td>
<td>55/18</td>
<td>0.70</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.8 (±5.1)</td>
<td>29.0 (±7.7)</td>
<td>31.8 (±8.7)</td>
<td>31.5 (±7.0)</td>
<td>29.8 (±6.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Onset age (years)</td>
<td>0</td>
<td>7.1 (±3.2)</td>
<td>13.8 (±1.0)</td>
<td>21.0 (±5.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Chi-square was used for gender comparisons. One-way ANOVA with Bonferroni post hoc tests was used for age comparisons. For more detailed information of blind subjects, please see Supplementary Part I.

Data Acquisition and Preprocessing
Scans were obtained using a 3.0 T Siemens MR scanner (Magnetom Trio, Siemens, Erlangen, Germany). The Integral Parallel Acquisition Technique was used with an acceleration factor of 2, which can reduce acquisition time and image distortion from susceptibility artifacts. Diffusion sensitizing gradients were applied along 30 nonlinear directions (b = 1000 s/mm²) together with an acquisition without diffusion weighting (b = 0 s/mm²). The imaging parameters were 45 continuous axial slices with a slice thickness of 3 mm and no gap, repetition time/echo time (TR/TE) = 6000/90 ms, field of view (FOV) = 256 mm × 256 mm, matrix size = 128 × 128. The reconstruction matrix was 256 × 256, resulting in a voxel dimension of 1 mm × 1 mm × 3 mm. The acquisitions were repeated 2 times to improve the signal-to-noise ratio. A set of sagittal T₁-weighted 3D structural images was obtained for each individual using a magnetization prepared rapid gradient echo sequence. The imaging parameters for this were FOV = 224 mm × 256 mm, TR/TE = 2000/2.19 ms, flip angle = 9°, and 176 continuous sagittal slices with voxel dimensions = 1 mm × 1 mm × 1 mm.

All diffusion tensor imaging (DTI) data were corrected for distortions caused by eddy currents and head motions by applying an affine alignment of each diffusion-weighted image to the non-diffusion-weighted image (b = 0 s/mm²), using FMRI’s Diffusion Toolbox (http://www.fmrib.ox.ac.uk/fsl). After the above correction, the tensor diffusion and fractional anisotropy (FA) were calculated using in-house DTI Tracking software (http://www.fslion.uc.lac.uk/spm).

Construction of Anatomical Networks

Definition of Networks Nodes
The registered dMRI data were segmented into 90 regions (45 for each hemisphere, Supplementary Table S5) using the AAL reported by Tzourio-Mazoyer et al. (2002), which has been used in several previous studies (Salvador et al. 2005; Achard et al. 2006; Liang et al. 2006; Liu et al. 2007, 2008; Gong et al. 2009; He et al. 2009). Our parcellation process for each individual was performed in DTI native space (Gong et al. 2009; Li et al. 2009; Wang et al. 2012). In detail, we normalized each individually co-registered T₁ image to the T₁ template in Montreal Neurological Institute (MNI) space, and then used the resulting inverse transformation to warp the AAL template in MNI space to DTI native space (Gong et al. 2009; Li et al. 2009; Shu, Liu, et al. 2009). The normalization and inverse transformation were performed by nonlinear registration methods using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm). After defining the node, we connected each pair of nodes with edges in order to construct a network. The streamline fiber tracking method was employed to compute the fibers of the entire brain of each subject (Mori et al. 1999). Only voxels with FA value greater than 0.3 were chosen as seeds in each region (Thottakara et al. 2006; Li et al. 2009). This helped to ensure that the obtained tracts started from the white matter underlying the cortical region or around the subcortical structures, as the AAL template contains not only gray matter but also subcortical white matter (Tzourio-Mazoyer et al. 2002). Tractography...
was terminated at voxels with an FA < 0.15 or when the turning angle between adjacent voxels was greater than 45° (Thottakara et al. 2006; Li et al. 2009; Wang et al. 2012). The fiber tracking process was performed using in-house DTI Tracking software.

If a fiber tract started from an AAL region and ended in another AAL region, the 2 regions are considered to be connected with a fiber (Gong et al. 2009). For each subject, the number of fibers connecting each pair of nodes was counted. Combining the connection of the networks with the results of our previous studies (Li et al. 2009; Shu, Liu, et al. 2009), an edge was considered to exist only when 2 nodes were connected with at least 3 fibers in our study. The threshold of 3 fibers can ensure that the largest connected component was 90 nodes for most subjects, except for one normal-sighted individual whose 90 nodes were not all connected and thus had a threshold of only one fiber. The number of fibers between 2 nodes represented only the existence or absence of an edge. Finally, an anatomical network was constructed for each subject by binarizing the number of fibers between nodes and was represented by a symmetric 90 × 90 matrix.

**Analysis of the Anatomical Network**

**Graph Theoretical Analysis of the Network Topological Properties** In this study, the anatomical network topological properties both at the global and nodal levels were calculated using an in-house network analysis toolkit (http://www.ccm.org.cn/brat), with the degree ($D_i$), shortest path length ($L_p$), global efficiency ($E_{glob}$), clustering coefficient ($C_i$), and local efficiency ($E_{loc}$) of the entire brain describing the global properties, and the degree ($D_i$), shortest path length ($L_i$), global efficiency ($E_{glob}$), clustering coefficient ($C_i$), local efficiency ($E_{loc}$), and betweenness centrality ($b_i$) of each node $i$ quantifying the nodal properties. The definition of each property is as follows (here, $N$ is the node number):

**Degree** The degree of each node $D_{i,n=1,2,...,90}$ is defined as the number of direct connections to that node. The degree of the graph is the average of the degrees across all nodes in the network:

$$D_p = \frac{1}{N} \sum_{i \in G} D_i,$$

where $G$ represents the anatomical network.

**Clustering coefficient** The clustering coefficient of a node is:

$$C_i = \frac{E_i}{D_i(D_i-1)/2},$$

which is the number of existing edges among the node’s direct neighbors divided by all the neighbors’ possible edges. $E_i$ is the number of edges among the node’s direct neighbors. The clustering coefficient of the network is the average of the cluster coefficients across all nodes:

$$C_p = \frac{1}{N} \sum_{i \in G} C_i,$$

which quantifies the extent of local cliquishness or local efficiency of the network (Watts and Strogatz 1999; Latora and Marchiori 2001).

**Shortest path length** The mean shortest path of a node is:

$$L_i = \frac{1}{N-1} \sum_{j \in G, j \neq i} l_{ij},$$

in which $l_{ij}$ is the minimum number of edges which must be passed to connect the $i$th node with the $j$th node. The mean shortest path length of the network is the average of the shortest path lengths across all nodes:

$$L_p = \frac{1}{N} \sum_{j \in G} L_j,$$

which quantifies the ability to transform parallel information or global efficiency of the network (Latora and Marchiori 2001).

**Network efficiency** The global efficiency of a node is:

$$E_{glob} = \frac{1}{N-1} \sum_{j \in G, j \neq i} \frac{1}{l_{ij}}$$

The global efficiency of the network is:

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i,j \in G, i \neq j} \frac{1}{l_{ij}},$$

which is the inverse of the harmonic mean of the shortest path lengths of each pair of nodes, demonstrating the global efficiency of parallel information transfer in the network (Latora and Marchiori 2001).

The local efficiency of a node is:

$$E_{loc} = E_{glob}(G_i),$$

in which subgraph $G_i$ is defined as the set of nodes that are the direct neighbors of the node $i$, demonstrating how efficient the information transfer in $G_i$ is when node $i$ is eliminated (Achard and Bullmore 2007). The local efficiency of the network is:

$$E_{loc} = \frac{1}{N} \sum_{i \in G} E_{loc}(G_i),$$

which is the mean local efficiency across all nodes in the network.

**Betweenness centrality** The betweenness centrality $b_i$ of a node can be calculated as follows: 1) for each pair of nodes in the network ($b_i, j$), compute all the shortest paths between them $\phi_{b_i,j}$, 2) for each pair of nodes in the network ($b_i, j$), compute all the shortest paths between them that pass through the node $i$, $\phi_{b_i,j}(i, 3)$ summarize the fraction $\phi_{b_i,j}(i)/\phi_{b_i,j}$ over all pairs of nodes in the network (Freeman 1978; Girvan and Newman 2002). The normalized betweenness centrality $b_i$ is defined as:

$$b_i = \frac{B_i}{(N-1)(N-2)} = \frac{B_i}{(N-1)(N-2)} \sum_{b_i,j \in G} \frac{\phi_{b_i,j}(i)}{\phi_{b_i,j}},$$

which captures the influence of a node over the information flow between other nodes in the network (He et al. 2008).

**Statistical Analysis**

Statistical analyses were performed based on the constructed binary network and the network properties of each subject. First, a one-way ANOVA was employed to assess the effect of group (5 groups; for the detail, see the Subjects section) on the $D_p$, $L_p$, $E_{glob}$, $C_p$, and $E_{loc}$ values with age and gender being controlled at a threshold of $P < 0.05$ (uncorrected). If the group effect was significant, we further did post hoc comparisons to assess the differences between each possible pair of groups. Second, the network properties of each node were investigated to demonstrate the distributions of the regions, which showed significant differences between the five groups in the same way, at $P < 0.01$ (uncorrected). Third, the Pearson correlations between the age of onset of blindness and the network properties at both the global and nodal levels were evaluated in the blind groups after regressing out age and gender effects. Because these analyses were exploratory in nature, we used a statistical significance level of $P < 0.05$ (uncorrected).

**Results**

Considering the 90 AAL regions (Supplementary Table S5) as nodes and the fiber connections between nodes as edges, we successfully constructed binary anatomical networks and calculated the topological properties for each subject.
Altered Topological Properties of Anatomical Networks in Blind Subjects

We first investigated the topological properties at the global level, including the degree ($D_p$), shortest path length ($L_p$), global efficiency ($E_{glob}$), clustering coefficient ($C_p$), and local efficiency ($E_{loc}$) for each group (details can be found in the Subjects section). A one-way ANOVA showed significant differences in the $D_p$ ($P = 0.0020$), $L_p$ ($P = 0.0019$), $E_{glob}$ ($P = 0.0017$), $C_p$ ($P = 0.0278$), and $E_{loc}$ ($P = 0.0460$) among the 5 groups. Post hoc comparisons demonstrated that the CB group showed significant decreases in $D_p$, $E_{glob}$, and an increase in $L_p$ compared with the LB and SC groups; the EB group showed significant decreases in $D_p$, $E_{glob}$, and an increase in $L_p$ compared with the SC group. Both the AB and LB groups showed significantly decreased $C_p$ and $E_{loc}$ compared with the SCs (Fig. 1 and Table 2). In addition, our permutation test result demonstrated that our results are significant and logical (for details please see Supplementary Part VI).

Distribution of Brain Regions with Altered Network Properties in Blind Subjects

A one-way ANOVA was performed for each node to further localize the nodes that demonstrated significant differences in their network topological properties between the 5 groups. The $D_p$, $L_p$, and $E_{glob}$ parameters were significantly different in several brain regions, especially in the inferior frontal and occipital areas (Fig. 2 and Table 3). $C_p$ and $E_{loc}$ were also altered, especially in the right orbitofrontal cortex (IFGorb_R), left supplementary motor area (SMA_L), and right rectus ($P < 0.005$). An abnormal $b_i$ was found in the SMA_L, the left parahippocampal gyrus (PHIP_L), and the left putamen (PUT_L).

We found an increasing tendency of the mean $D_p$ and $E_{glob}$ and a decreasing tendency of the mean $L_p$ from the CB to the SC in most of the brain regions (Fig. 2 and Supplementary Tables S6–S10 in Supplementary Part III). Post hoc comparisons revealed significant changes in $D_i$, $L_i$, or $E_{glob}$ in the PUT_L and the left anterior cingulate cortex (ACC_L). Significant decreases in $D_i$ or $E_{glob}$ or increases in $L_i$ were mainly found between the CB and SC groups and between the EB and SC groups (Fig. 2 and Supplementary Tables S6–S9). In the PUT_L, the LB group also showed significant decreases in the $D_i$ and $E_{glob}$ when compared with those of the EB and SC groups.

In the SMA_L, the $b_i$ differed between the CB and SC, CB and LB, EB and LB, and the EB and SC groups. In the PHIP_L, the $b_i$ of the CB group was found to be significantly higher than those of AB and LB groups, and slightly higher than those of the EB and SC groups. In the PUT_L, $b_i$ was significantly lower in the LB group than in the 4 other groups (Fig. 2 and Supplementary Table S11).

Relationship between Network Properties and Onset Age of Blindness

The above group comparisons, at both the global and nodal levels, demonstrated that the age of the onset of blindness had a significant influence on brain network properties. In order to investigate the relationship between network properties and the age of onset of blindness, we used Pearson correlation tests between the age of the onset of blindness and the network properties after regressing out the effects of age and gender. $D_p$ and $E_{glob}$ were found to be positively correlated with the age of onset, whereas the $L_p$, $C_p$, and $E_{loc}$ were negatively correlated.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Statistical tests on the topological properties of the networks for all the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$ value of statistic test</td>
<td>$D_p$</td>
</tr>
<tr>
<td>ANOVA</td>
<td>CB versus EB</td>
</tr>
<tr>
<td></td>
<td>CB versus AB</td>
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<tr>
<td></td>
<td>CB versus LB</td>
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<tr>
<td></td>
<td>CB versus SC</td>
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<tr>
<td>Post hoc t test</td>
<td>EB versus AB</td>
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<td></td>
<td>EB versus LB</td>
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<tr>
<td></td>
<td>EB versus SC</td>
</tr>
<tr>
<td></td>
<td>AB versus LB</td>
</tr>
<tr>
<td></td>
<td>AB versus SC</td>
</tr>
<tr>
<td></td>
<td>LB versus SC</td>
</tr>
</tbody>
</table>

Note: significant group differences at $P < 0.05$.

Figure 1. Mean network properties of each group. The $D_p$, $L_p$, $E_{glob}$, $C_p$, and $E_{loc}$ denote the mean number of connections, average shortest path length, global efficiency, mean clustering coefficient, and local efficiency of the network, respectively. Detailed definitions can be found in the Materials and Methods section. The value of each property in each group was obtained by averaging the property across all the subjects in that group.
with this variable (Fig. 3). Further simulation analysis demonstrated that our results were robust and were not affected by outliers (for details, please see Supplementary Part VI).

To further localize brain regions whose network properties correlated with the age of onset of blindness, correlation analyses were performed across all 90 nodes in the blind group, while controlling for the effects of age and gender. Nodes with a significant correlation were widely distributed across the brain at a statistical threshold of $P < 0.01$ (Table 4). Generally, the $D_i$ or $E_{i,\text{glob}}$ were positively correlated with the age of onset of blindness, the $L_i$ was negatively correlated with the age of onset mostly in the frontal areas and visual pathway (right superior occipital gyrus, left superior and middle temporal gyrus). $C_i$ in the orbital part of the superior frontal gyrus (SFGorb_R), the IFGorb_R, and the ACC_R were negatively correlated with the age of onset of blindness, but the $C_i$ of SMA_L and PUT_L were positively correlated with the age of onset. Note that $b_i$ was positively correlated with the age of onset at the node of the IFGorb_R, but it was negatively correlated with the age of onset at the nodes of SMA_L, PHIP_L, and PUT_L (Table 4).

### Table 3

Alteration of network properties of each node between the 5 groups

<table>
<thead>
<tr>
<th>AAL region</th>
<th>$P$ value of ANOVA</th>
<th>$D_i$</th>
<th>$L_i$</th>
<th>$E_{i,\text{glob}}$</th>
<th>$C_i$</th>
<th>$E_{i,\text{loc}}$</th>
<th>$b_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreCG_R</td>
<td>0.0021, 0.0035</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IFGoper_L</td>
<td>0.0020, 0.0001, 0.0001</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>IFGtri_L</td>
<td>0.0019, 0.0040, 0.0024</td>
<td></td>
<td></td>
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<tr>
<td>SMA_L</td>
<td>0.0016, 0.0014, 0.0013</td>
<td></td>
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<tr>
<td>RGZT_R</td>
<td>0.0011, 0.0020</td>
<td></td>
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<tr>
<td>ACC_R</td>
<td>0.0083</td>
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<tr>
<td>PCC_R</td>
<td>0.0087</td>
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<tr>
<td>PHIP_L</td>
<td>0.0043, 0.0068, 0.0046</td>
<td></td>
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<tr>
<td>CUN_R</td>
<td>0.0086</td>
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<tr>
<td>LING_R</td>
<td>0.0022, 0.0046, 0.0089, 0.0090</td>
<td></td>
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<tr>
<td>SOG_L</td>
<td>0.0009, 0.0013, 0.0031</td>
<td></td>
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</tr>
<tr>
<td>SOG_R</td>
<td>0.0017, 0.0056, 0.0026</td>
<td></td>
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<tr>
<td>IOG_R</td>
<td>0.0027, 0.0086, 0.0077</td>
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<tr>
<td>CAU_L</td>
<td>0.0021, 0.0040, 0.0071</td>
<td></td>
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<tr>
<td>THA_R</td>
<td>0.0040</td>
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</tr>
</tbody>
</table>

Note: the result only showed the $P$ value of the network properties with significant differences between the 5 groups ($P < 0.01$).
Discussion

As stated in the introduction, CB or EB subjects have shown both altered and preserved structural and functional organization of the brain, especially the visual areas (for reviews, see Pascual-Leone et al. 2005; Kupers et al. 2011; Striem-Amit et al. 2011). However, only a few studies have investigated brain structural or functional alterations in LB subjects (Buchel et al. 1998; Sadato et al. 1998; Burton et al. 2004; Schoth et al. 2006; Jiang et al. 2009; Park et al. 2009; Lepore et al. 2010) and inconsistent results have been obtained. Studying blindness at different ages of onset provides an exceptional opportunity to investigate how unimodal sensory deprivation at various development periods affects the structural and functional organization of the human brain. In this study, we recruited a large sample of blind individuals with different ages of onset of blindness to investigate the relationship between the age of onset of blindness and the topological properties of the anatomical networks. We found significant differences in the topological properties of brain anatomical network between the 5 groups (especially between the CB and SC groups and between the EB and SC groups) and demonstrated that most of the network properties significantly correlated with the age of onset (years), while the $L_p$, $C_p$, and $E_{loc}$ were found to be negatively correlated to age of onset.

Network Properties at the Global Level in Blind Subjects

The degree of a graph is the average of the degrees across all the nodes in a network. The individual values of the degree, therefore, reflect the importance of the nodes in the network (Rubinov and Sporns 2010). The reduced average degree in the blind suggests a decreased connection between different

Table 4
Correlations between the age of onset of blindness and network properties in all blind subjects at the nodal level

<table>
<thead>
<tr>
<th>AAL region</th>
<th>$D_p$</th>
<th>$L_p$</th>
<th>$E_{glob}$</th>
<th>$C_p$</th>
<th>$E_{loc}$</th>
<th>$b_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreCG_R</td>
<td>0.2730</td>
<td>0.0068</td>
<td>0.2701</td>
<td>0.00075</td>
<td>-0.2732</td>
<td>0.0068</td>
</tr>
<tr>
<td>IFGop_L</td>
<td>0.3002</td>
<td>0.0028</td>
<td>-0.3312</td>
<td>0.0009</td>
<td>0.3272</td>
<td>0.0011</td>
</tr>
<tr>
<td>IFGop_R</td>
<td>-0.2821</td>
<td>0.0051</td>
<td>0.2674</td>
<td>0.0081</td>
<td>-0.3516</td>
<td>0.0004</td>
</tr>
<tr>
<td>ROL_L</td>
<td>-0.3085</td>
<td>0.0021</td>
<td>0.2995</td>
<td>0.0076</td>
<td>-0.3010</td>
<td>0.0027</td>
</tr>
<tr>
<td>ACC_R</td>
<td>-0.2863</td>
<td>0.0005</td>
<td>-0.2760</td>
<td>0.0062</td>
<td>-0.2775</td>
<td>0.0059</td>
</tr>
<tr>
<td>PHIP_L</td>
<td>-0.2741</td>
<td>0.0066</td>
<td>0.2893</td>
<td>0.0041</td>
<td>-0.3099</td>
<td>0.0020</td>
</tr>
<tr>
<td>STG_L</td>
<td>-0.2683</td>
<td>0.0079</td>
<td>-0.3217</td>
<td>0.0013</td>
<td>0.2920</td>
<td>0.0037</td>
</tr>
</tbody>
</table>

Note: for each property, the table shows the related coefficients and P values of the regions at $P < 0.01$. Abbreviations: PCC, partial correlation coefficient.

Figure 3. Relationship between network properties and the age of onset of blindness. The $D_p$, $L_p$, $E_{glob}$, $C_p$, and $E_{loc}$ denote the mean number of connections, average shortest path length, global efficiency, mean clustering coefficient, and local efficiency of the network, respectively. $D_p$, $L_p$, and $E_{glob}$ were found to be positively correlated to the age of onset (years), while the $C_p$, $E_{loc}$ were found to be negatively correlated to age of onset.
functional regions. The relatively lower degree in the CB and EB groups indicates sparse connections in these 2 groups. A shortest path length quantifies the ability to transform parallel information or the global efficiency of the network (Latora and Marchiori 2001). Global efficiency and local efficiency can measure the global/local efficiency of transferring parallel information in the network (Latora and Marchiori 2001). As the path length gets longer and the global efficiency gets lower in the whole brain network, the information transferred between nodes will get slower. This means that more nodes have to participate in the transfer of the neural information. Our findings in the CB and EB groups are consistent with a previous network study (Shu, Liu, et al. 2009), which also revealed decreases in $D_p$ and $E_{glob}$, an increase in $L_p$, and relatively unchanged $C_p$ and $E_{loc}$ in EB subjects. Previous findings of decreased white matter volumes in the optic tract and optic radiation (Noppeney et al. 2005) and decreased white matter integrity in the geniculocalcarine tracts (Shimony et al. 2006; Yu et al. 2007; Shu, Liu, et al. 2009) in EB subjects may suggest reduced connections in the brain. Furthermore, it supports our findings of reduced connections and global efficiency in the CB and EB groups. The relatively preserved local efficiency of the EB subjects may be a result of the compensatory plasticity that has been extensively reported in these subjects (Liu et al. 2007; Amedi et al. 2010; Bedny et al. 2011) or the preserved functional specialization in most brain areas (Mohan et al. 2001; Ricciardi et al. 2009; Ma and Han 2011).

In the AB and LB groups, the local efficiency assessed by $C_p$ and $E_{loc}$ was significantly lower than that of the SC group, but the network sparsity assessed by $D_p$ and the global efficiency assessed by $E_{glob}$ and $L_p$ did not significantly differ from that of SC group. This finding indicates that late visual deprivation after the completion of brain development can only result in a decrease in the local efficiency but cannot affect the global efficiency, as the early visual deprivation does. The connections ($D_p$) in the AB and LB groups are relatively preserved, which is consistent with a previous DTI study that did not detect any significant deficits in the optic radiation and pyramidal tract of LB subjects (Schoth et al. 2006).

The degree ($D_p$) and global efficiency ($E_{glob}$ and $L_p$) were positively correlated with the age of onset of blindness, while the local efficiency ($C_p$ and $E_{loc}$) was negatively correlated with this variable. In conjunction with the results of group comparisons, we can obtain a picture of the alterations of network properties in blind subjects at a global level. EB subjects show decreased global efficiency, whereas LB subjects show decreased local efficiency. These alterations may be a reflection of the complex interactions of development, plasticity, and disuse in blind individuals.

**Network Properties at the Node Level in Blind Subjects**

Comparisons of the degree ($D_p$), shortest path length ($L_p$), global efficiency ($E_{glob}$), clustering coefficient ($C_p$), and local efficiency ($E_{loc}$), have provided a perspective for investigating differences on a global level, and further nodal level comparisons can localize those regions with significant differences in the brain network topological properties. Our results showed that most of the alteration regions were located in the occipital and frontal lobes (Table 3).

**Disruptive Changes in the Visual Areas in the Blind**

The occipital lobe is the center for visual processing in sighted subjects. Compared with the SC group, the CB and EB groups showed decreased connections and global efficiency in the occipital areas, which is consistent with a previous anatomical network study on EB subjects (Shu, Liu, et al. 2009). This finding is supported by a loss of white matter volume (Noppeney et al. 2005) and a decrease in white matter integrity (Shimony et al. 2006; Yu et al. 2007; Shu, Li, et al. 2009) in the occipital lobe of EB subjects and is also supported by a decreased functional connectivity within occipital areas and between the occipital cortex and other areas in EB subjects (Liu et al. 2007; Yu et al. 2008). In LB subjects, the brain structural organization is almost unaffected by altered developmental factors, and plastic changes will contribute to shape the brain but to a lesser extent than in EB subjects. This may account for the relatively normal integrity in the optic radiation in LB subjects (Schoth et al. 2006). Consequently, the relatively reduced connections of occipital areas in the EB group and the relatively preserved connections in the late-onset one can account for the positive correlations between the degree ($D_p$) and global efficiency ($E_{glob}$ and $L_p$) of the occipital areas and the age of onset of blindness.

Most of the frontal areas, especially the IFG, showed reduced global efficiency but increased local efficiency in EB subjects. This finding was also confirmed by a positive correlation between the global efficiency and the age of onset of blindness and a negative correlation between the local efficiency and the age of onset of blindness. The decreased global efficiency of the IFG may be able to be explained by the reduced white matter integrity of the inferior frontooccipital fasciculus, which connects the IFG and the occipital lobe (Shu, Liu, et al. 2009). The increased local efficiency of the IFG may represent a compensatory or plastic change in response to the decreased global efficiency in this region. In agreement with this, Liu et al. (2007) has found increased functional connectivity between the visual cortex and IFG regions in a previous study.

**Plastic Changes in Motor and Memory/Learning Region in the Blind**

The importance of a node in a network can be assessed by betweenness centrality ($b_n$) (Gong et al. 2009; He et al. 2009). The node betweenness can capture the influence of a node over information flow between other nodes in the network (He et al. 2008) and also can measure if the node is an important one in the network (Rubinov and Sporns 2010). The $b_n$ of the SMA_L, PHIP_L, and PUT_L was significantly negatively correlated with the age of onset of blindness, and group comparisons revealed that the $b_n$ of the SMA_L and PHIP_L was significantly increased in the CB and EB groups, whereas the value of the PUT_L was significantly decreased in the LB group.

The SMA plays a role in the planning of motor actions and bimanual control and is recruited in actions that are under internal control, such as the performance of a sequence of movements from memory (as opposed to movements indicated by a visual cue) (Shima and Tanji 1998). Due to visual deprivation, early-onset blind people need more practice to perform the same routine activities as sighted subjects, especially in complex sequential movements in which the SMA plays an important role. Thus, experience-dependent plasticity can partly explain the increased $b_n$ of the SMA_L. A similar mechanism has also been used to explain increases in white matter volume in the sensorimotor areas of EB subjects (Noppeney et al. 2005), as well as increases in white matter...
integrity in corticospinal tracts (which are partly originated in the SMA) of EB subjects (Yu et al. 2007).

The hippocampus plays an important role in memory encoding and retrieval (Lepage et al. 1998) and in visual-auditory associative learning and integration (Gonzalo et al. 2000; Calvert 2001; Chan et al. 2011). The PHIP is the principal neocortical input pathway to the hippocampus (Suzuki and Amaral 1994) and also plays an important role in visual memory formation (Epstein 2008), as well as in learning or recall of topographical information. Previous studies even found that the parahippocampus is involved in the recognition of scenes (Epstein and Kanwisher 1998; Epstein et al. 2007). As in sighted subjects, CB subjects also activated the PHIP and occipital cortex during a spatial navigation task (Kupers et al. 2010), which suggests the importance of the PHIP in spatial navigation in EB subjects. Experience-dependent plasticity induced by extensive practice can also explain the increased $h_1$ of the PHIP_L. Our finding is also partly supported by the increased volume of the hippocampus in EB subjects (Fortin et al. 2008; Leporé et al. 2009), a structure involved in navigation function.

The putamen region, especially the posterior part, is primarily connected with the SMA and motor cortex, and receives converging inputs from the primary and secondary motor cortices (Pandya and Vignolo 1971). The putamen is involved in motor control but also regulates other cognitive and emotional processes (DeLong, Alexander, et al. 1984; Delong, Georgopoulos, et al. 1984; Alexander and Crutcher 1990; Ell et al. 2006), such as learning (Packard and Knowlton 2002; Marchand et al. 2008). In comparison with SCs, the $b_1$ of the PUT_L was slightly higher in the CB subjects but significantly lower in the LB subjects. This finding suggests that the patterns of movement regulation and learning may differ in blind subjects with different ages of onset of blindness.

The relationship between the node betweenness and age of onset also suggested an experience-dependent plasticity in the LB individuals. This suggests that visual experience at an early period of development is critical for establishing the brain network in the human brain, although the exact mechanism needs to be further studied.

**Preserved Structural Specialization in the Blind**

Although several previous fMRI studies have revealed that the functional organization of most of the visual areas and other brain areas whose functions are primarily dependent on visual inputs, develop independently of visual experience (Ricciardi et al. 2009; Kupers et al. 2011; Reich et al. 2011; Striem-Amit et al. 2011), there are few studies focused on the independence of structural organization on visual experience. In the present study, in addition to the findings of altered anatomical network properties in blind subjects, we also found a number of brain areas (such as part of the visual areas and other brain areas) that have preserved their structural specialization. These findings may at least partially relate to the preserved functions in blind subjects. However, the exact relationship between the preserved structural organization and the preserved functional specialization needs to be studied in detail.

**Methodological Issues**

Given the small sample size and the large number of regions, we noted that in the present study some of the statistical measures could not be corrected by certain conservative multiple comparisons methods, such as a Bonferroni or false discovery rate correction. Therefore, we do not claim strong type I error control for these multiple exploratory analyses and for the relationship between brain network measures and the age of the onset of blindness on the global and nodal levels. The result of this is that some of our results must be interpreted cautiously. From a different perspective, in order to see if our results were robust, we performed a permutation test method to determine if our result is really significant at the global and nodal levels. For each property, we did the permutation statistical analysis 100 000 times. The permutation results also demonstrated that our results were significant and logical (for details please see Supplementary Part VI). Additionally, to test whether the relationship between the network measurements and the age of onset of blindness was affected by some outlier subjects in the blind groups, we randomly selected 91-95 subjects 100 000 times, and evaluated the Pearson correlation coefficients between the network measures and the age of onset after regressing out age and gender effects. The simulation results demonstrated that our results are significantly robust at the global and nodal levels (for details please see Supplementary Part VI).

We should also point out that some of our subjects have studied Braille, and one of our previous studies found that the longer and/or the earlier Braille was studied by the blind, the stronger the functional connectivity between the visual cortex and the somatosensory/motor regions in the blind (Liu et al. 2007). In the present study, however, we found that Braille reading did not have a significant effect on the network properties in the blind (for details please see the Supplementary Part V). This might be because our previous studies examined relatively well-educated blind subjects (all of them were students in the Special Education College of Beijing Union University and used Braille in their everyday lives). Hence, these plastic changes in the brain deserve to be studied further.

Because the basic elements of a network are the nodes and edges, the definition of the nodes and edges is an issue. The nodal scales, parcellation templates, and image acquisition protocols as well as the fiber tracking methods tailored to these protocols, can affect the network properties (Zalesky et al. 2010). Further study should divide the brain into more nodes based on a more precise template in order to locate the areas of alteration more accurately, obtain higher resolution images, and employ advanced fiber-tracking methods to reconstruct connections between nodes. Another issue is whether to choose a binary or a weighted network. The connectivity measure of a weighted network could be fiber numbers, fiber density, mean fiber length, and mean fraction anisotropy (Hagmann et al. 2007; Iturria-Medina et al. 2007; Zalesky and Fornito 2009). Because of a lack of clarity in the physiological meaning and the difficulty of validating these measures, we employed a binary network in our study without weighing the strength of the connections.

In conclusion, our findings suggest that sensory deprivation during different developmental periods may influence the topological properties of the anatomical brain networks at various levels. The most significant alterations are present in subjects with early sensory deprivation, possibly reflecting complex interactions between developmental, plastic, and disuse factors after sensory deprivation.

**Supplementary Material**

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


