Changes in the Vision-related Resting-state Network in Pituitary Adenoma Patients After Vision Improvement

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Abstract

Background: The aim of this research was to investigate the changes in the vision-related resting-state network (V-RSN) in pituitary adenoma (PA) patients after vision improvement, which was induced by operative treatment.
Methods: Ten PA patients with an improved visual acuity or/and visual field after transsphenoidal pituitary tumor resection were recruited and underwent a complete neuro-ophthalmologic evaluation, as well as an magnetic resonance imaging (MRI) protocol, including structural and resting-state functional MRI sequences before and after the operation. The regional homogeneity (ReHo) of the V-RSN was evaluated. Two sample *t*-test was performed to identify the significant differences in the V-RSN in the PA patients before and after transsphenoidal pituitary tumor resection.
Results: Compared with the preoperation counterparts, the PA patients with improved vision after the operation exhibited reduced ReHo in the bilateral thalamus, globus pallidus, caudate nucleus, putamen nucleus, supplementary motor area, and left hippocampal formation, and increased ReHo in the bilateral cuneus gyrus, calcarine gyrus, right lingual gyrus, and fusiform gyrus.
Conclusions: PA patients with improved vision exhibit increased neural activity within the visual cortex, but decreased neural activity in subareas of the multisensory and multimodal systems beyond the vision cortex.

Key words: Multisensory and Multimodal System; Pituitary Adenoma; Resting-state Functional Magnetic Resonance Imaging; Visual Improvement

INTRODUCTION

The human visual cortex is immature at birth, and acquires deep perception at approximately 6 months after birth, with complete maturation in late childhood.[1] Prior to maturation, the visual cortex is subjected to internal and external influences, which modulate the neural signal pathway and synapsis, and irreversibly alter the developing visual cortex and pathway.[2] This experience–dependent neural plasticity is mainly present in the developing visual cortex. The best time to correct congenital cataract is before 6 months of age, whereas the best time to correct strabismus is before 7 years of age. However, the experience–dependent neural plasticity exists in not only the immature visual cortex, but also the adult visual cortex. For example, the learning process and visual restoration after certain visual system diseases in adulthood are based on experience-dependent neural plasticity. To date, increasingly robust evidence supports the potential plasticity in the adult visual cortex.[3]

Jenkins *et al*. demonstrated that adult optic neuritis (ON) patients with improved vision exhibit an enhanced response in the lateral occipital complex (LOC) in functional magnetic resonance imaging (fMRI) scans, and a stronger fMRI response is associated with a better vision prognosis. It is likely that the increased response in the LOC is involved in synaptic regeneration, which is exactly the basis for vision recovery.[4] Gallo *et al*. identified a significant disconnection in the visual-resting network in normal-sighted multiple sclerosis (MS) patients compared with healthy controls, as well as enhanced neural activity in the extrastriate visual cortex in the MS patients with previous ON compared with the patients without previous ON.[5] These findings confirm that visual recovery after ON might be associated with cortical reorganization within the extrastriate visual areas. Visual cortex plasticity is diversified in form and includes, declarative memory, location face event encoding

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and perceptual learning (vision perception improvement following repeated practice).[6] Because declarative memory and perceptual learning extend throughout the lifespan, the cortical plasticity based on these processes should not be restrained by any period.[2] Polat *et al*. determined that after systemic correction exercises, adult strabismus patients had a significant improvement in visual acuity (letter recognition).[7] These previous studies demonstrated that the adult visual cortex has potential plasticity, and vision improvement is associated with a corresponding neural reconstruction.

Pituitary adenoma (PA) originates from the anterior lobe of the pituitary gland. When a PA is sufficiently large to compress the visual pathway (typically the optic chiasm, optic nerve and optic tract), the patients often present visual deficiencies, including a visual acuity impairment and/or visual field defect. The current treatment for PA includes medicine, a craniotomy and a microscopic or endoscopic transsphenoidal operation.[8,9] Our study recruited PA patients with improved vision after transsphenoidal surgery. A transsphenoidal tumor resection surgery primarily involves an epidural manipulation, which can decompress the anterior visual pathway and do little influence on the visual cortex and other adjacent constructions.

Our study is focused on the changes in the vision-related resting-state network (V-RSN) in PA patients after vision improvement. Furthermore, it is aimed to explore the plasticity of the visual cortex after vision improvement in terms of the functional changes of both some specific subareas within the visual cortex and higher cognitive networks that extend beyond the visual cortex.

METHODS

Study population

Pituitary adenoma patients with visual damage who underwent transsphenoidal tumor resection surgery and had restored vision were recruited at the Department of Neurosurgery, Beijing Tiantan Hospital. PA patients with visual damage were selected according to the following inclusion criteria: Age ranged from 18 to 60 years; prior to the operation, the corrected vision acuity was below 1.0 (20/20) or the visual field defect was more than 50% at least unilaterally; the tumor was not sufficiently large to distort or displace the visual cortex; ophthalmologic diseases or other intracranial lesions that involved the visual pathway or cortex were excluded, as assessed by a neuro-ophthalmologic evaluation (see details below) and MRI; significant vision improvement after the operation (the corrected vision acuity improved by more than 0.2 or the visual field defect decreased more than 30% at least unilaterally) were required; and no severe electrolyte disturbance, hypopituitarism or other complications presented at the 3-month follow-up after the operation.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University and an informed consent form was signed by all participants.

Clinical and neuro-ophthalmologic assessments

The cognition of all participants was evaluated using the mini-mental state examination, which has been widely used to clinically screen for cognitive impairment prior to the operation.[10] The patients underwent a complete neuro-ophthalmologic examination within 2 weeks prior to the operation and at approximately 3 months after the operation. The best-corrected visual acuity for distance was measured with the E chart (which works on the same principle as Snellen's distant vision chart) and was reported in the decimal scale. The visual field examination was performed with a standardized automated perimetry (Octopus 900 Perimetry, Switzerland). An ophthalmic fundus examination was performed with a nonmydriatic retinal camera (Topcon, Japan).

Magnetic resonance imaging scanning protocol

All functional and structural images were acquired on a 3.0 Tesla scanner (Siemens Trio, Erlangen, Germany) using 12-channel head coil. Head movement was minimized using foam pads, and earplugs were used to attenuate acoustic noise during scanning. During the resting-state fMRI (RS-fMRI) scan, the participants were instructed to remain still and keep their eyes closed, not to fall asleep nor think of anything systematic. RS-fMRI data were acquired using an echo-planar image pulse sequence (41 axial slices, slice thickness/gap = 3.5/0.7 mm, repetition time = 2500 ms, echo time = 30 ms, flip angle = 90°, and field of view [FOV] = 240 mm × 240 mm with in-plane resolution of 3.75 mm × 3.75 mm). A T1-weighted sagittal anatomical image was also obtained using a gradient echo sequence (176 slices, slice thickness/gap = 1/0 mm, inversion time = 900 ms, repetition time = 2300 ms, echo time = 3 ms, flip angle = 7°, number of excitations = 1, FOV = 240 mm × 240 mm with in-plane resolution of 0.9375 mm × 0.9375 mm).

Resting-state functional magnetic resonance imaging analysis

Data preprocessing

The RS-fMRI data were preprocessed using SPM8 (*http://www.fil.ion.ucl.ac.uk/spm*) and a pipeline analysis toolbox, DPARSF (*http://www.restfmri.net/*).[11] To avoid transient signal changes before the longitudinal magnetization reached a steady state, the first ten volumes were discarded. The remaining images were preprocessed using a procedure, which included slice timing correction, head motion correction, T1-weighted image based spatial normalization to the Montreal Neurological Institute space, linear trend removal, and band-pass filtering (0.01–0.08 Hz). All of the participants' head motion parameters were <3 mm in translation and <3° in rotation. To further reduce the effects of head motion on estimates of resting-state activity, we censored volumes within each participant's fMRI time series that were associated with sudden head motion.[12,13] For each participant, fMRI volumes were censored if the framewise displacement of head position, calculated as the sum of the absolute values of the derivatives of the realignment estimates, was above 0.5.

Regional homogeneity analysis

Regional homogeneity analysis is the analysis of ReHo, which reflects the local synchrony of neural activity. Kendall's coefficient of concordance (ranged from 0 to 1) was used as a measurement of ReHo for each voxel, an indication of similarity between the time series of that voxel and its nearest neighboring voxels.[14] It was measured in a voxel-wise way for each participant within a whole brain mask provided by REST.[15] To reduce nuisance sources of variation,[16] individual ReHo maps were divided by the global mean value within the whole brain mask for normalization. Then, all normalized ReHo maps were subsequently spatially smoothed with a 6-mm full width at half-maximum Gaussian isotropic kernel. Two-sample *t*-tests were used to analyze the differences in the V-RSN between the pre- and post-operation groups based on the ReHo maps. The AlphaSim method, which has been implemented in REST, was used to correct for multiple comparisons. The corrected $P < 0.05$ (uncorrected $P < 0.001$ and minimum 60 voxels in a cluster) was used as threshold.

RESULTS

Studied population

According to the inclusion criterion, 12 patients were recruited in our study. As a result of head motion or the lack of sufficient data after scrubbing, 2 patients were excluded; thus 10 patients (male/female 4:6) were included in the final analyses. Mean age was 34.4 (Range 23–51) years, while mean education years were 15.3 (Range 7–22). Range of mean MMSE was 29.

Ophthalmologic evaluation

Detailed results of the neuro-ophthalmologic evaluation are reported in Table 1.

Resting-state functional magnetic resonance imaging analysis

Compared with the preoperative counterparts, the PA patients with improved visual results after the operation exhibited reduced ReHo in spots of the bilateral thalamus, globus pallidus, caudate nucleus, putamen nucleus, supplementary motor area, and left hippocampal formation, and increased ReHo in the bilateral cuneus gyrus, calcarine gyrus, right lingual gyrus, and fusiform gyrus [Figure 1].

DISCUSSION

Regional homogeneity primarily reflects the synchrony of neural activity.[17] The synchronized oscillation of the cortex is indispensable for anatomically separated, yet functionally connected neural units to complete the temporal and spatial integration and concordance. Increased ReHo may indicate an abnormal enhancement of intraregional neural activity.[17,18] In contrast, decreased ReHo reflects the destruction of the intraregional neural activity synchronization and implies functional deficits.[17,18]

Increased regional homogeneity within the visual cortex

In our study, the PA patients with improved visual results after the operation exhibited increased ReHo in the bilateral cuneus gyrus, calcarine gyrus, right lingual gyrus, and fusiform gyrus, all of which are within the visual cortex. Increased ReHo indicates improved neural activity. It is justified that improved vision associates increased ReHo. Toosy *et al*. demonstrated that ON patients with improved vision exhibit an enhanced response in LOC in fMRI scans, and a stronger fMRI response is associated with a better vision prognosis.[4,19] The LOC, which is located in the ventral pathway, is composed of the lateral occipital cortex and the posterior fusiform gyrus. It comprises the cognitive visual cortex, which specializes in object recognition and confirmation.[20] It is suggested that the LOC is involved in visiual cortex reconstruction and functional compensation. In an fMRI study, Giulia *et al*. demonstrated that one female patient who restored her vision after keratoprosthesis exihibited enhanced responses in the fusiform, lingual and calcarine gyri, but a decreased response in the visiual cortex that engaged the dorsal pathway especially the middle temporal complex (MT+).[21] Consistent with these results, our study also identified increased ReHo in part of the LOC (fusiform), lingual gyrus and calcarine gyrus in patient with improved vision after the transsphenoidal surgery. However, a large-sample study and multiple-model research design are necessary to clarify the key points regarding the vision recovery mechanism.

Decreased regional homogeneity beyond the visual cortex

Compared with the preoperative counterparts, the PA patients with improved visual results after the operation exhibited reduced ReHo in spots of the bilateral thalamus, globus pallidus, caudate nucleus, putamen nucleus, supplementary motor area, and left hippocampal formation. These regions are subareas of the multisensory system. The multisensory regions at the cortex are mainly located in the parietal lobe, temporal lobe, frontal lobe, and insular, whereas the regions beneath the cortex are mainly located in the superior colliculus, and basal ganglia (globus pallidus, caudate nucleus, putamen nucleus, amygdaloid body, claustrum nucleus).[22-24] The insular has previously been confirmed as a multisensory region.[25] Insular lesions can lead to a multisensory deficiency.[26] The anterior insular has far-reaching connections with the orbital – frontal lobe, thalamus and limbic lobe and whereas the posterior insular has close interactions with the frontal, temporal, and parietal lobe as well as thalamus.[27,28] Increasingly converging evidence suggests the thalamic nuclei (the thalamus pulvinar, and the dorsal and medial divisions of the medial geniculate body) have anatomical connections to structures of different sensory modalities and/or corresponding neurons to integrate multisensory information, sometimes even before the information has reached the neocortical areas.[29,30] Other thalamic nuclei (the suprageniculate, posterior intralaminar,

Table 1: Ophthalmologic data of pituitary tumor patients

ID	Age (Years)	Vision impairment onset and side (by complaint)	Visual acuity (left)	Visual acuity (right)	Vision field defect (left) (%)	Vision field defect (right) (%)
1-preoperation	38	10 months (bilateral)	0.8	0.5	40 (temporal quadrants)	40 (temporal quadrants)
1-postoperation			1.2	1.2	0	0
2- preoperation	43	1.5 years (bilateral)	0.15	0.6	90 (tubular vision field left)	50 (temporal quadrants)
2-postoperation			0.5	0.6	50 (inferior quadrants)	40 (temporal quadrants)
3-preoperation	51	6 months (bilateral)	0.6	0.1	60 (temporal quadrants)	90 (tubular vision field left)
3-postoperation			0.8	0.5	Normal	50 (temporal quadrants)
4-preoperation	40	6 months (bilateral)	0.8	0.06	10 (temporal quadrants)	80 (temporal and nasal superior quadrants)
4-postoperation			0.8	0.25	0	10 (superior temporal quadrants)
5-preoperation	50	4 months (left)	0.01	1.2	95 (tubular vision field left)	0
5-postoperation			0.6	1.5	25 (superior temporal quadrants)	0
6-preoperation	46	3 months (bilateral)	0.3	0.6	45 (temporal quadrants)	50 (temporal quadrants)
6-postoperation			0.4	0.8	0	45 (temporal quadrants)
7-preoperation	49	1-year (bilateral)	0.25	0.12	50 (temporal quadrants)	50 (temporal quadrants)
7-postoperation			0.12	0.3	20 (temporal quadrants)	20 (temporal quadrants)
8-preoperation	26	1-year (bilateral)	0.8	0.1	50(temporal quadrants)	90 (tubular vision field left)
8-postoperation			1	0.3	0	0
9-preoperation	24	1-year (left)	0.12	0.2	10 (temporal quadrants)	45 (temporal quadrants)
9-postoperation			0.4	0.25	0	0
10-preoperation	23	9 days (bilateral)	0.25	0.05	10 (temporal quadrants)	0
10-postoperation			0.25	0.4	10 (temporal quadrants)	0

laterodorsal, lateral, ventral posterior and posterior thalamic nuclei) also exhibit diverse multisensory responses and have multiple connections with the subcortical and cortical areas of various sensory modalities.[31-33] The putamen, also as a multisensory neucleus, has different types of neurons, which receive visual information, somatosensory information, or both visual and somatosensory information.[34,35] Gentile *et al*. in his high power fMRI study demonstrated that the coexistence of visual tactile and tactile signal could significantly enhance the blood oxygen level dependent signal in the putamen, which confirms the important role of the putamen in the integration of visual and tactile signals.[36] The superior temporal sulcus and adjacent cortex are both multisensory and multisensory integration regions, especially regarding social information, for example, face and voice recognition, and face and voice integration.[37] The claustrum neucleus has complicated projections with the visual cortex, and modulates the earlier visual cortex (lingual, cuneus, and calcarine gyri) and vision-related thalamic nucleus.[38] The claustrum neucleus receives visual and hearing information, and mediates the integration of visual and tactile information.[39,40] Multisensory convergence and modulation are two common classes of multisensory interaction. Multisensory convergence involves bringing together information from distinct sensory streams. Multisensory modulation, in contrast, involves activity from one sensory channel that modulates the activity in another sensory channel. The multisensory modulation can influence the perception threshold of one sensory modality under the coexistence of different sensory modalities, and it can modulate the priority of multiple sensory information.[41,42] In a visual stimulus fMRI study, Werring *et al*. determined that healthy individuals exhibit a reaction in only occipital lobe, whereas ON patients with corrected-to-normal vision exhibit reactions in not only occipital cortex, but also the insular, putamen nucleus, pallidus nucleus, claustrum neucleus, posterior parietal region, and thalamus.[43] These regions beyond the vision cortex, can not be normally activated by a simple visual stimulus, however, they have wide connections with visual function, as subareas of the multisensory system or multisensory interaction.[22-37,44,45] The multisensory interaction can modulate attention, and bias the vision processing by top-bottom regulation.[46-48] It is proposed that additional activation of the multisensory region is initiated by vision impairment, as a type of feedback mechanism to enhance the perception of decreased visual input, and it is involved in the neural reconstruction for vision recovery. With vision improvement, this compensatory mechanism was correspondingly attenuated. Thus in line with these findings, the activation in the multisensory region in PA patients with vision improvement is weakened compared with the activation before the operation. We may conclude that decreased visual input leads to the feedback excitation of neural activity within the multisensory system, and with visual recovery, the feedback excitation of neural activity within the multisensory system is inhibited.

In conclusion, visual improvement can promote the reconstruction within the visual cortex, and initiate the compensatory mechanism in the multisensory/multimodel system beyond visual cortex. Thus the visual network is continuously modified through the process of neural plasticity even after maturation. Further studies are needed to unravel the mechanism of neural plasticity and provide us

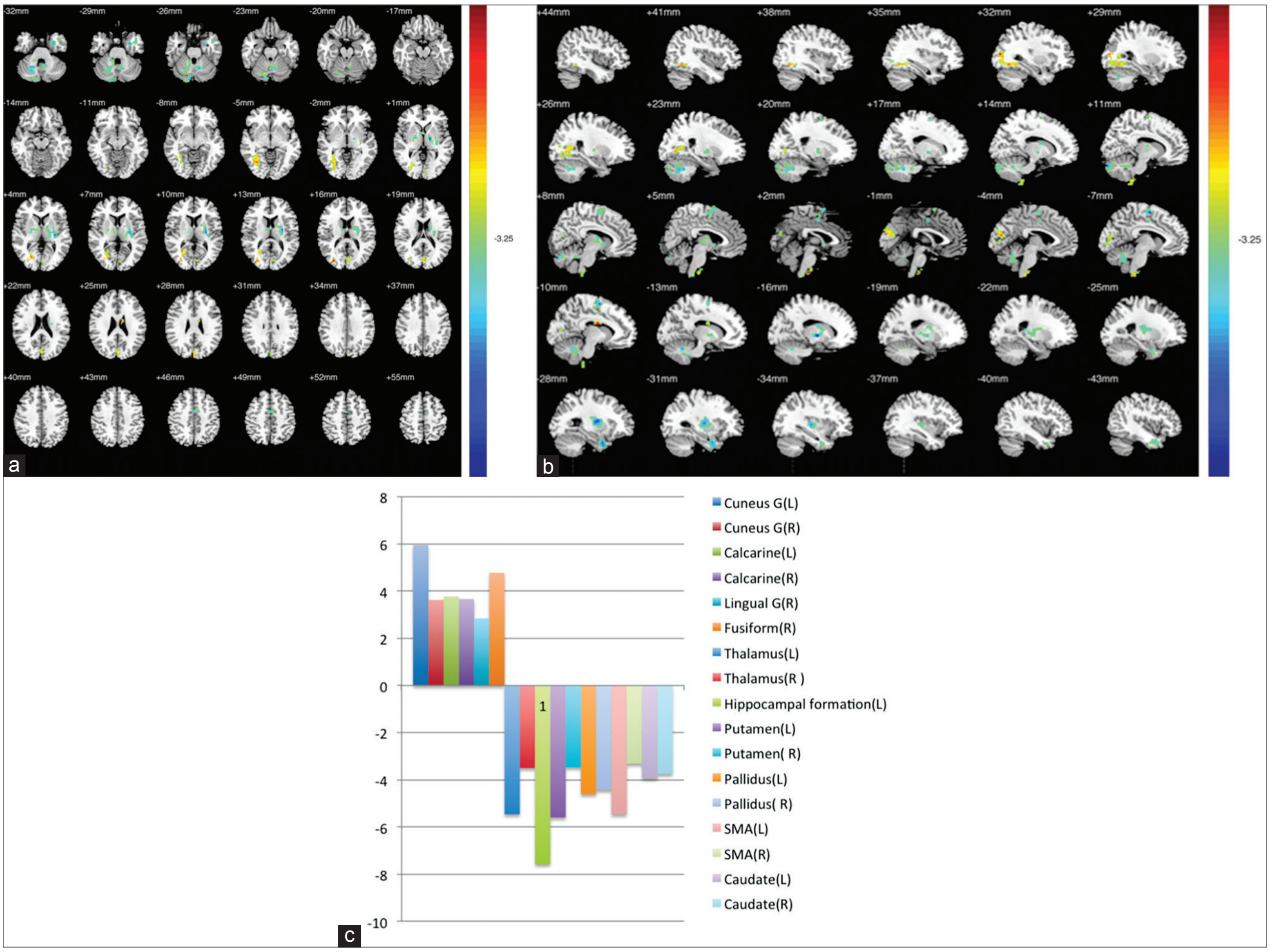

Figure 1: Regional homogeneity (ReHo) differences in the postoperative pituitary adenoma (PA) patients compared with the preoperative PA patients. (a) Statistical parametric map (axial view); (b) Statistical parametric map (sagittal view). In (a) and (b), the cyan-blue colors indicate decreased ReHo in postoperative PA patients compared with the preoperative PA patients, whereas the yellow-red colors indicate increased ReHo in the postoperative PA patients compared with the preoperative PA patients; (c) Bar graph based on statistical parametric maps. The abscissa axis indicates the brain areas with significantly different ReHo, whereas the ordinate axis indicates the peak intensity of each brain area. The brain areas with positive peak intensities exhibited increased ReHo in the postoperative PA patients compared with the preoperative PA patients, and the negative peak intensities indicate decreased ReHo ($P < 0.05$, AlphaSim corrected).

new perspectives to enhance the plasticity for patients with specific visual diseases.

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