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fMRI evidence of improved visual function in patients with progressive retinitis pigmentosa by eye-movement training

Masako Yoshida [a], Maki Origuchi [b], Shin-ichi Urayama [c], Akira Takatsuki [b], Shigeyuki Kan [d], Toshihiko Aso [c], Takayuki Shiose [e], Nobukatsu Sawamoto [c], Satoru Miyauchi [d], Hidenao Fukuyama [c], Akitoshi Seiyama [b,*]

[a] Yoshida Eye Clinic, 9 Higashi-honncho, Shimogamo, Sakyo-ku, Kyoto 606-0863, Japan
[b] Division of Medical Devices for Diagnoses, Human Health Sciences, Kyoto University Graduate School of Medicine, 53 Kawahara-cho, Syogoin, Sakyo-ku, Kyoto 606-8507, Japan
[c] Human Brain Research Center, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Syogoin, Sakyo-ku, Kyoto 606-8507, Japan
[d] National Institute of Communication and Information Technology, Iwaoka 588, Nishi-ku, Kobe, Hyogo 651-2492, Japan
[e] The Kyoto University, Yoshida Honmachi, Sakyo-ku, Kyoto 606-8501, Japan

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ABSTRACT

To evaluate changes in the visual processing of patients with progressive retinitis pigmentosa (RP) who acquired improved reading capability by eye-movement training (EMT), we performed functional magnetic resonance imaging (fMRI) before and after EMT. Six patients with bilateral concentric contraction caused by pigmentary degeneration of the retina and 6 normal volunteers were recruited. Patients were given EMT for 5 min every day for 8–10 months. fMRI data were acquired on a 3.0-Tesla scanner while subjects were performing reading tasks. In separate experiments (before fMRI scanning), visual performances for readings were measured by the number of letters read correctly in 5 min. Before EMT, activation areas of the primary visual cortex of patients were 48.8% of those of the controls. The number of letters read correctly in 5 min was 36.6% of those by the normal volunteers. After EMT, the activation areas of patients were not changed or slightly decreased; however, reading performance increased in 5 of 6 patients, which was 46.6% of that of the normal volunteers ($p < 0.05$). After EMT, increased activity was observed in the frontal eye fields (FEFs) of all patients; however, increases in the activity of the parietal eye fields (PEFs) were observed only in patients who showed greater improvement in reading capability. The improvement in reading ability of the patients after EMT is regarded as an effect of the increased activity of FEF and PEF, which play important roles in attention and working memory as well as the regulation of eye movements.

1 Introduction

Representative visual defects are concentric contractions (CCs) and central scotoma (CS). The former disease (i.e., concentric contractions) is caused by pigmentary degeneration of the retina or glaucoma. This disease, also known as tunnel vision, causes the loss of peripheral vision but retains central vision, thus, resulting in a constricted, circular, and tunnel-like field of vision. Further, this disease progressively causes the loss of the peripheral to central visual field as well as a decrease in central visual acuity. In particular, the progressive concentric contraction caused by retinitis pigmentosa (RP) induces an inhomogeneous loss of central vision (Sugawara et al., 2010; Mitamura et al., 2012; Makiyama et al., 2013). It has been reported that during walking, patients with CC, whose visual fields were less than 10°, showed increases in fixation eye-movements; however, the movements were not sufficient to orient to the whole environment (Sumitani et al., 2000). Furthermore, the same group has reported that during reading, simulated patients with CC (volunteers with normal vision whose visual fields were restricted to less than 20°) showed increases in the number of pauses (indicating poor reading ability), prolongation of reading time, appearance of optokinetic nystagmus, and compensatory actions such as hand motions to move the characters being read into the center of the visual field or head motions to extend the reading distance (Tabuchi et al., 1998). The researchers concluded that progressed patients required effective training to utilize their preserved vision (i.e., the acquisition of preferred retinal locus (PRL) in the remaining locus of the fovea) (Sumitani et al., 2000).

In contrast, the latter disease, CS, is known as a visual depression that corresponds to the point of fixation and interferes with central vision, and it can be caused by age-related macular degeneration (AMD), optic nerve disease, chorioretinal atrophy, or diabetic maculopathy.

* Corresponding author at: Division of Medical Devices for Diagnoses, Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Syogoin, Sakyo-ku, Kyoto 606-8507, Japan. Tel: +81-75-751-3915; fax: +81-75-751-3915.
E-mail address: seiyama.akitoshi.7x@kyoto-u.ac.jp (A. Seiyama).

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As central visual acuity becomes progressively poorer, compared to the diseased fovea, a parafoveal locus for fixation or a PRL is able to obtain better vision (Crossland et al., 2005; Fletcher et al., 1999). It has also been reported that the reading capability of patients with CS decreases because of increased saccades, and eccentric viewing training reduces the saccade frequency and results in an improvement in the number of letters read in a given time (McMahon et al., 1993).

Functional magnetic resonance imaging (fMRI) may be useful to investigate the neural substrate associated with oculomotor function as well as word recognition and processing during reading in patients with low vision. There are several functional neuroimaging studies on CS (Sunness et al., 2004; Little et al., 2008; Masuda et al., 2008; Szlyk et al., 2009; Dilks et al., 2009; Ming et al., 2012), but few for CC, except for some reports on its pathology (Sugawara et al., 2010) and medical treatments (Somani et al., 2006; Bainbridge et al., 2008; Klauke et al., 2011). Recently, we observed that eye-movement training (EMT), consisting of eccentric fixation training, pursuit training, and binocular vision training, induced acquisition of smooth eye movements and remarkable decreases in impulsive saccade frequency and improved the reading ability of patients with progressive RP experiencing a loss of peripheral vision accompanying an inhomogeneous loss of central vision (Yoshida et al., 2012). However, the reorganization of visual processing caused by eye-movements and functional alteration of the visual cortical regions V1, V2, V3, and V5/MT, which possibly relate to the improved reading capability, is still unknown.

In the present study, we hypothesized that the EMT induced improved neural functions relating to smooth eye movements, attention, and working memory during reading. Then, we used fMRI to evaluate the effects of EMT on the visual processing of patients with progressive RP, including those who had acquired improved reading capabilities. Thereby, we discuss the role of functional connectivity between the FEF, PEF, and other visual recognition-related areas in relation to improved reading abilities.

2 Materials and methods

2.1 Participants

This study was approved by the Kyoto University Graduate School and the faculty of the medical ethics committee and adhered to the tenets of the Declaration of Helsinki. All subjects provided written informed consent prior to participation.

2.2 Control subjects

We recruited an age- and gender-matched control group of 6 healthy subjects (4 women and 2 men; age range 24–53 years) with normal or corrected-to-normal vision.

2.3 Patients

Six patients (4 women and 2 men, age range from 23 to 53 years) with concentric contractions (CCs) caused by progressive retinitis pigmentosa (RP) were enrolled (cf. Supplementary Fig. 1). Detailed information about age, sex, disease duration, and acuity of the patients is shown in Table 1. In brief, for the present experiments, the corrected visual acuities (near vision at 40-cm distance) of patients ranged from 0.16 to 0.7 in logMAR for pre-EMT and from 0.16 to 1.0 for post-EMT. Fields of vision measured using the I/4 target of Goldmann perimeter were less than 8° in diameter.

2.4 EMT

Patients showed inhomogeneous loss (or decrease sensitivity) of central vision (see Supplementary Fig. 1), and the levels differed between left and right eyes of individual patients as well as from patient to patient. Therefore, patients are required to understand their own PRLs in their central vision and to utilize them during reading. The patients adhered to the following EMT routine for 8–10 months depending on the symptoms of the individuals, although some modifications were added.

(1) Eccentric fixation training on a single letter: First, the patients were made to understand their own PRL of each eye using an appropriate letter size, thickness, and font. Then, to establish eccentric fixation, the PRL was used while patients were made to stare at the letter, which stayed in front of their visual focus for 10–20 s.
(2) Pursuit training on a single letter: To enable eccentric fixation in every direction, patients were guided to move their eyeballs smoothly 20 cm/min horizontally, perpendicularly, and obliquely while maintaining the eccentric fixation.
(3) Binocular vision training on a single letter: To reduce the chances of an erroneous line break or abrupt change in visual object as patients changed their fixation target, they were required to follow a moving object using both eyes.
(4) The above training was repeated several times for 5 min/day at their own residence.

Further, all of the above training was performed using a handmade moving object for the self-training, in accordance with the guidance of an oculist. Once a month, the physician checked if patients were performing the self-training correctly.

2.5 Reading task

The subjects read horizontally written Japanese sentences (in both Kana and Kanji scripts) in words for 5 min and 3 times, and the averaged number of letters correctly read was counted to evaluate reading performance before and after EMT (see Table 2). The sentences were cited from one of the chapters of the autobiography of a Japanese athlete. Font and size of letters were MS Mincho and 20 pt, respectively, and were displayed on A4 paper in a matrix containing 18 rows and 22 columns (letters). Before and after EMT, subjects read the sentences displayed 40 cm away.

2.6 fMRI task

For functional neuroimaging, tasks were displayed on a black background (horizontal and vertical visual angles were 20 and 15°, respectively) with white letters used for sight stimulation (visual angle of a single letter was 1.4°). The task letters appeared individually amidst an interfering surround of meaningless characters lined up in a matrix containing 7 rows and 10 columns. At the onset, the task letters were displayed at a position of 2 rows and 2 columns and the position shifted to the right (horizontal) every 500 ms (cf. Supplementary video file 1). Five to 7 letters were displayed on each line, and just before shifting to a new line, a mark (i.e., white star) was displayed (Sign or Kana, cf. Supplementary Fig. 2). The Kana tasks were to form a TANKA with a meaning, but the Sign tasks were to form a string of meaningless characters. During the resting conditions, the white star was shown at a position of 2 rows and 2 columns without the interference background.

We used a block design in all experiments. In all sessions, the task condition was repeated 4 times (18 s each), with a baseline resting condition (21 s) prior to each reading block and after the end of the last condition. Thus, 1 session lasted 2 min 57 s, and each participant completed 4 sessions (2 Sign tasks and 2 Kana tasks). Before each session, a 2-min 'introduction and resting' time was held. Subjects were instructed to fixate on the fixation point, a white star, during the resting conditions, to read each letter silently during the Sign or Kana tasks, and to press a button when they recognized each letter change (1 time during reading). After reading (silent reading), the

Table 1
Pathological information of patients suffering from concentric contraction.

					Acuity (pre)				Acuity (post)			
Patient	Age (year)	Sex	Disease duration (years)		logMAR[a)] (F)	logMAR (N)	HFA10-2MD[b)] (dB)	Goldmann perimetry (°)	logMAR (F)	logMAR (N)	HFA10-2MD (dB)	Goldmann perimetry (°)
1	40	M	20	L	0.7	0.7	−32.66	2	1	0.5	−33.0	ND
1	40	M	20	R	0.4	0.5	−29.39	2	0.7	0.4	−29.78	ND
2	23	F	16	L	0.4	0.7	−29.71	ND	0.3	0.7	−31.55	3
2	23	F	16	R	0.4	0.5	−31.76	2	0.5	0.7	−32.65	1
3	53	F	26	L	0.16	0.3	−29.91	3	0.16	0.3	−31.67	3
3	53	F	26	R	0.16	0.4	−29.64	3	0.16	0.4	−30.49	2
4	38	F	7	L	0.4	0.7	−17.56	5	0.5	0.8	−20.13	5
4	38	F	7	R	0.3	0.5	−15.21	5	0.4	0.5	−17.51	8
5	42	F	28	L	0.3	0.5	−34.84	ND	0.3	0.5	ND	ND
5	42	F	28	R	ND[c)]	ND	−34.84	ND	ND	ND	ND	ND
6	25	M	13	L	0.3	0.3	−21.51	6	0.2	0.5	−24.23	5
6	25	M	13	R	0.2	0.4	−23.71	4	0.2	0.5	−23.81	3

a) logMAR denotes logarithm of Minimum Angle of Resolution (corrected values). The abbreviation F (=far) denotes the measurement at 5-m distance and N (=near) denotes the measurement at 40-cm distance.
b) HFA10-2MD denotes the Mean Deviation determined with a Humphrey field analyzer 10-2.
c) Goldmann perimetry was expressed in diameter. ND denotes "not detected".

Table 2
Effect of eye-movement training on reading task performance.

Normal	A	1920		
	B	2048		
	C	2017		
	D	2038		
	E	2463		
	F	2164		
	Average	2108		
	SE	77.7		
Patient		Pre	Post	Rate of change (%)
	1	740	945	27.8
	2	552	553	0.2
	3	1147	1371	19.5
	4	1039	1173	12.9
	5	194	329	69.6
	6	2217	1741	−21.5
	Average	981.5	1018.7	18.1
	SE	284.0	213.5	12.5

The number of letters correctly read is shown in the table.
Pre and post denote before and after eye-movement training.

subjects were asked to press a button 1 or 2 times, depending on the meaning of the Kana (TANKA) task, and 2 times for the meaningless Sign tasks.

2.7 Imaging procedure

MRI data were acquired on a Siemens TRIO 3.0-T MRI system (Siemens, Erlangen, Germany). A blood oxygen level-dependent (BOLD) sensitive T-2*-weighted echo planar imaging (EPI) gradient-echo sequence with the following parameters was acquired: TR = 3000 ms; TE = 30 ms; flip angle = 90°; matrix = 64 × 64; FOV = 192 × 192 mm^2; and slice thickness = 3 mm. After acquiring the functional images, anatomical images were acquired using a transverse magnetization prepared rapid acquisition with gradient echo (MP-RAGE) T1-weighted sequence (TR = 2000 ms; TE = 4.38 ms; flip angle = 8°; matrix = 224 × 256; FOV = 246 × 230 mm^2; slice thickness = 1 mm).

2.8 Data analysis

Image preprocessing and analysis were performed using the Statistical Parametric Mapping software SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) running under MATLAB R2007b (MathWorks Inc., Sherborn, MA). The first 3 scans were discarded from the analysis to minimize T1 relaxation artifacts, and the remaining 59 volumes per session were used for analyses. The EPI images were realigned to the first image. Next, the DARTEL toolbox was used to create structural templates across subjects as well as individual flow fields, which were used for spatial normalization (Ashburner, 2007). Data were smoothed using an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Trials in each of the 3 conditions (Sign, Kana, and Rest) were separately convolved with the canonical hemodynamic response function by using a general linear model. A one-lag auto-regression (AR(1)) model was used to correct for serial autocorrelations. The time series was filtered using a discrete cosine-transform filter with a 128-s cut-off period.

The contrast images during the Kana (TANKA) tasks were obtained by concatenation of all 4 sessions and subtractions (post − pre). The contrast images were at a threshold of $p < 0.001$ (uncorrected) at the voxel level and $p < 0.05$ corrected for multiple comparisons at the cluster level, which was applied for all contrasts. To define overlapping areas between activated areas (especially visual cortex, FEF, and PEF) and anatomical structures, the MarsBar toolbox (*http://marsbar.sourceforge.net/*) was used. Thereafter, to exactly allocate the activated clusters to the appropriate anatomical sites, the Montreal Neurological Institute (MNI) coordinates were used along with the parcellation method and the automated anatomical labeling software (Tzourio-Mazoyer et al., 2002).

2.9 Statistical analysis

Statistical analyses were generally performed using non-paired Welch's *t*-test or Student's *t*-test to assess statistical differences between the normal volunteers and patients, and paired Student's *t*-test between pre- and post-EMT for patients, except as noted. A *p*-value of <0.05 was considered statistically significant.

3 Results

3.1 Effect of EMT on task performance during the reading task

The average number of correctly read letters for volunteers with normal vision (n= 6) was 2108 ± 190, whereas that for patients (n= 6) was 981.4 ± 695.6 before and 1018.7 ± 523.1 after EMT, respectively (Table 2). Although the effects of EMT on task performance (i.e., rate of change [%] in Table 2) varied between patients depending on the extent of their disease, 5 of the 6 patients showed an increase in the number of correctly read letters in 5 min of the reading task (patients 1–5 in Table 2) after EMT. Here, we included patient 2 in the category of improved patients. Because patient 2's disease was progressive and such patient was concomitantly suffering central scotoma-like retinal degradation of the left eye (see Supplementary Fig. 1), the retained task performance (552 before EMT vs. 553 after EMT) could be considered as a positive effect of EMT.

Although averaged task performances of the 6 patients were 46.6% (p< 0.01) and 48.3% (p< 0.05) of the normal volunteers before and after EMT, respectively (Fig. 1A), there was no significant difference in the number of correctly read letters before and after EMT (Fig. 1A). However, averaged task performances of the 5 improved patients (i.e., patients 1–5) were 34.8% (p< 0.01) and 41.5% (p< 0.01) before and after EMT, respectively, and the number of correctly read letters significantly increased (p< 0.05) after EMT (Fig. 1A). The performances obtained with the reading tasks were almost similar to those obtained with the fMRI task during fMRI measurements (Fig. 1B). It should be noted that the rejection test, the Smirnov–Grubbs' test, indicated that patient 6 could not be statistically excluded; however, as we discuss later, the patient may be clinically excluded.

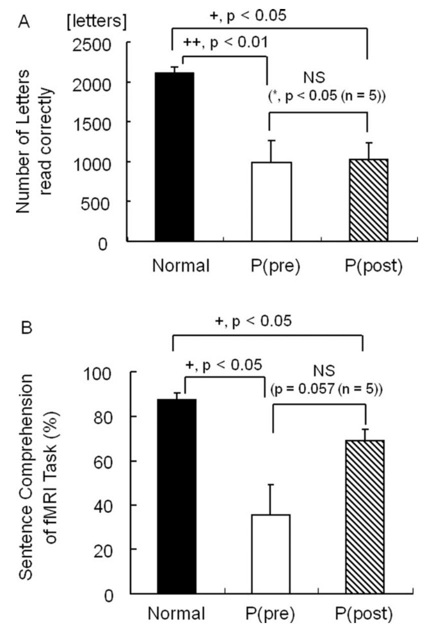

Fig. 1. A: Effect of eye-movement training (EMT) on reading task performance. Statistical analyses were performed on data from 6 normal volunteers (Normal) vs. 6 patients with concentric contraction where P (pre) and P (post) denote before and after EMT, respectively. Data are shown as mean ± standard error (SE). Normal vs. patients, unpaired Welch's t -test (+, p < 0.05; + +, p < 0.01). P (pre) vs. P (post), paired t-test. Statistical analysis of P (pre) vs. P (post) without patient 6 (see Tables 1 and 2) yielded p < 0.05 (n = 5). B: Effect of EMT on fMRI task performance. Data are shown as mean ± SE. Normal vs. patients, unpaired Welch's t-test (+, p < 0.05; + +, p < 0.01). P (pre) vs. P (post), paired t -test. NS denotes no significance. Statistical analysis of P (pre) vs. P (post) without patient 6 (see Tables 1 and 2) yielded p = 0.057 (n = 5).

3.2 Activation of the visual cortex

Fig. 2A shows examples of the activation areas for the normal volunteers (left) and those for patients before (middle) and after (right) EMT, as measured by fMRI during the fMRI task. Activated areas of the visual cortices (mainly V1 and V2) in patients were noticeably decreased post-EMT. This result indicates that the impairment in visual information transfer from the retina to the primary visual cortex (V1) was progressing. Fig. 2B shows the results of statistical analyses of the volume size of the activation area along the calcarine sulcus. The activation areas of the visual cortex before and after EMT were fewer in patients (n= 6) than in the normal volunteers (<52% on average, p< 0.01). Furthermore, their volume/size after EMT showed a tendency to decrease as compared with that before EMT; however, the difference was not significant (p= 0.280), although the activation area of the visual cortex in some patients decreased markedly (see Supplementary Fig. 3).

Fig. 3 shows brain activation during the fMRI tasks (Kana tasks minus rest contrast) before EMT. To visualize the effect of EMT on neural activation, cognitive subtractions before and after EMT of individual patients are shown in Fig. 4. Activations of the V3 (in the axial slice at z= +25) and V1/V2 and medial temporal lobule (V5/MT) (in the slices at z= +5 and −15) could be observed in Figs. 3 and 4. Increases in activities of both V3 and V5/MT areas were observed after EMT in all patients, in spite of individual differences (Fig. 4).

3.3 Activation of the frontal and parietal eye fields

Fig. 3 also shows brain activations of the superior parietal lobules (SPLs) and inferior parietal lobules (IPLs), supplementary motor area (SMA), supplementary eye fields (SEFs), FEF, dorsolateral prefrontal cortex (DLPFC), and primary motor area (M1) at z= +55 and those areas except for SMA and SEFs at z= +35. Activations of both FEF and PEF were clearly observed in all normal volunteers (cf. Fig. 3, top). Before EMT, levels of activations in the FEF and/or PEF of the patients differed among individuals, depending on their symptoms and reading abilities; however, after EMT, increases in the activity of the FEF and/or PEF were observed in all patients (Fig. 4). The activated clusters of FEF and PEF, and their coordinates, are summarized in Tables 3 and 4, respectively. Fig. 5 summarizes the statistical effect of EMT on the number of activated voxels in the FEF and PEF of the patients (activation of normal volunteers is shown for comparison). After EMT, the number of activated voxels in the FEF increased significantly (p< 0.01), whereas such increases of the activated voxels in the PEF were not significant.

4 Discussion

When acquiring visual information, eye movements and visual processing must function cooperatively. For this to occur, the following 3 basic eye movements are necessary (Brown, 1997): 1) spotting (quickly discovering and fixating on an object), 2) scanning (searching for an object to understand its whole aspect), and 3) tracking or tracing (staring and following an object). When reading a book, it has been well documented that saccades (but not pursuit) and fixation pauses play an important role in reading sentences; moreover, during fixation pauses, the target is perceived as a block of several characters or words but not as individual words (Abrahms et al., 1972; Mackworth, 1976; Holmes et al., 1977; Bouma, 1978). Similar findings have also been reported regarding the reading of Japanese sentences (Saida et al., 1979; Ikeda et al., 1979; Osaka, 1987). It is also well known that visual information captured on the retina is transmitted to the primary visual cortex; however, the area of the retina that can capture information is small and less than 10° from the visual center (i.e., the central fovea). Thus, for visually impaired patients, the basic eye movements described above may be critical for processing a wide

Table 3
Coordinates and size of activated frontal eye field (FEF) in patients with CC.

P	FEF (BA 6)	Pre					Post				
		Activated cluster size	Center of mass			*t*-Value	Activated cluster size	Center of mass			*t*-Value
			x	y	z			x	y	z	
1	Left	9808	−41	−6	46	7.12	9296	−41	−7	42	6.32
	Right	10856	44	−3	47	9.41	25368	36	−7	54	13.55
2	Left	5008	−34	−14	54	7.40	5840	−39	−12	53	9.33
	Right	5768	32	−18	60	8.57	11104	37	−12	54	10.04
3	Left	1832	−51	6	32	6.42	10800	−38	−7	52	11.84
	Right	624	52	10	34	6.72	2400	27	1	63	9.76
4	Left	6712	−46	0	36	7.96	12952	−42	−1	43	11.84
	Right	7040	45	−2	45	7.29	13088	44	−3	47	13.15
5	Left	0	–	–	–	–	3136	−35	−14	48	8.26
	Right	144	40	−6	61	5.28	9392	40	−14	54	9.73
6	Left	14056	−38	−4	48	5.64	6152	−36	−15	51	7.75
	Right	8008	43	−3	45	8.83	6248	45	−11	46	11.81

In the left column, P denotes the abbreviation for patient, and the number denotes the individual patients.
Cluster size is expressed as number of voxels. Pre and post denote before and after eye-movement training.

Table 4
Coordinates and size of activated parietal eye field (PEF) in patients with CC.

P	PEF (BA 7)	Pre					Post				
		Activated cluster size	Center of mass			*t*-Value	Activated cluster size	Center of mass			*t*-Value
			x	y	z			x	y	z	
1	Left	6144	−26	−62	60	9.91	5168	−26	−65	56	11.67
	Right	4336	29	−62	60	7.23	4896	28	−66	57	7.39
2	Left	1304	−29	−65	50	8.98	344	−29	−67	48	7.47
	Right	1512	26	−67	51	8.57	616	27	−66	51	7.07
3	Left	5272	−22	−67	49	15.41	8912	−23	−64	53	18.13
	Right	5168	28	−60	55	10.2	6528	29	−57	58	14.53
4	Left	5376	−24	−65	52	9.58	8848	−23	−64	52	10.49
	Right	5520	25	−66	55	9.66	5336	24	−66	54	10.82
5	Left	144	−26	−80	47	7.13	2392	−23	−74	48	12.58
	Right	880	34	−51	60	6.88	344	33	−66	51	12.33
6	Left	5256	−23	−70	51	14.63	0	–	–	–	–
	Right	4464	26	−68	54	11.86	0	–	–	–	–

In the left column, P denotes the abbreviation for patient, and the number denotes the individual patients.
Cluster size is expressed as number of voxels. Pre and post denote before and after eye-movement training.

range of situations because patients with defects in portions of the central fovea have difficulty in reading and searching for objects.

In this study, we have demonstrated that EMT elicited improvements in the reading ability of patients with progressive RP experiencing a loss of peripheral vision accompanying an inhomogeneous loss of central vision. We have also shown, for the first time, that it caused changes in the neural activity of these patients, by using fMRI. Specifically, increases in FEF and PEF activity were observed. Here, we discuss the relationship between the improvement in reading performance and the evoked neural activation of the FEF and PEF by EMT as well as the alteration of activities of the visual cortices (V1/V2, V3) and medial temporal lobules (V5/MT).

4.1 Improvement of reading ability by EMT

The present EMT caused head and/or eye aches at the beginning of training. Therefore, only 5 min of training time per day was suitable and was continued for a period of several months. Once a month, a physician checked if the patients were performing the self-training correctly. All 6 patients suffered from pigmentary degeneration of the retina (Table 1). This disease causes progressive loss of the peripheral visual field and results in reduced activity in the primary visual field along the calcarine sulcus (Fig. 2A and 2B). Progressed patients with CC such as the present subjects suffer inhomogeneous loss or decrease in the sensitivity of central vision. This causes a decrease in reading abilities due to the increase in saccade frequency, appearance of optokinetic nystagmus, and compensatory actions such as hand and head motions (Tabuchi et al., 1998; Sumitani et al., 2000; Yoshida et al., 2012). In the present study, we defined a positive EMT effect as no change in the number of correctly read letters (e.g., patient 2) or as an increase in this number because the EMT possibly sustained the reading capability by balancing the loss of visual field and acquiring a suitable PRL in the remaining visual field. Five of the 6 patients (i.e., patients 1–5) demonstrated increasing or steady numbers of correctly read letters for the reading task after EMT (Table 2). Task performance on the reading task was similar to that of the fMRI task (Fig. 1), although the conditions of the 2 tasks were slightly different (i.e., the former had a pursuit-like character and the latter a saccade-like character). In separate eye-tracking measurements using an eye mark recorder (Yoshida et al., 2012), the 5 patients showed remarkable decreases in saccade frequency (especially vertical orientation) and an improvement in fixation of the target letter after EMT. These results suggest that the increased task performance could be because of improvements in eye movement (i.e., regulation of saccade and fixation of reading). As described before, patient 2's disease was progressive, and such patient was concomitantly suffering

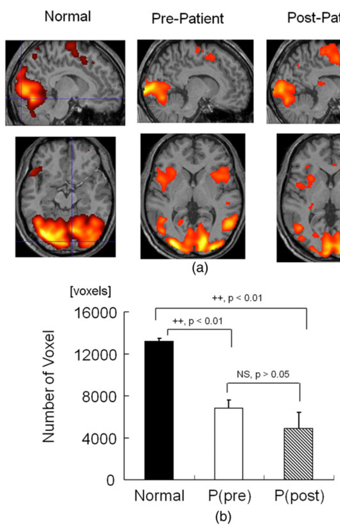

Fig. 2. A: Examples of activation maps during the fMRI task (TANKA tasks) of a normal volunteer (left) and a patient with concentric contraction before (middle) and after (right) eye-movement training (EMT). Top, sagittal slice at x = 10 (MNI). Bottom, axial slice at $z = -8$ (MNI). B: Number of activation voxels in the primary visual cortex along the calcarine sulcus. Data are shown as mean ± SE. Normal volunteers (Normal) ($n = 6$) vs. patients ($n = 6$), unpaired Welch's t-test (+ +, $p < 0.01$). P (pre) vs. P (post), paired t -test. NS denotes no significance..

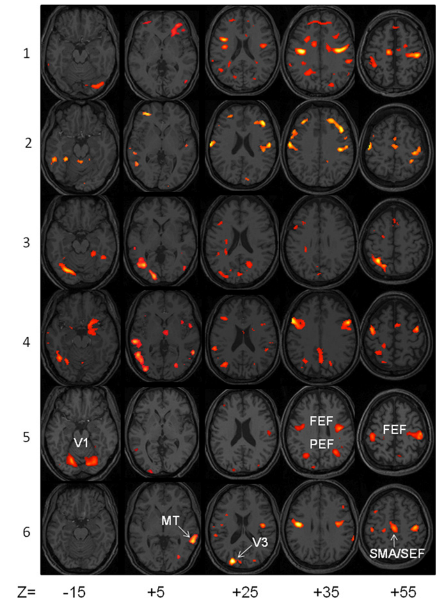

Fig. 4. Subtraction of neural activity during the fMRI task (TANKA tasks) before and after eye-movement training (EMT). Axial slices at $z = -15, +5, +25, +35$, and $+55$ are shown.

central scotoma-like retinal degradation of the left eye. Thus, the retained task performance (552 before EMT vs. 553 after EMT) could be considered a positive effect of EMT. Other researchers (Seiple et al., 2005, 2011) have successfully used eye movement training to improve reading ability in patients with central vision loss. Thus, the present EMT is also effective for patients with CS, but we have no evidence for patients with hemianopic alexia.

It should be noted that in both experiments, only patient 6 demonstrated a decrease in performance (i.e., from 2217 to 1741 for the number of correctly read letters in the reading task, and from 75% to 62.5% for sentence comprehension in the fMRI task). We observed a decrease in visual acuity and/or field relating to a decrease in activation of V1/V2 (cf. patients 2 and 5 in Table 1 and Fig. 3). During the 8–10 month training period, patient 6 showed a large decrease in activity of the visual cortices, especially of V1/V2 (see Supplementary Fig. 3 and Figs. 3and 5 at $z = -15$). It should be noted that the subjects were instructed to press a button when they recognized each letter change (1 time during reading). There was no difference in performance of button pressing among the subjects. Thus, there was no fear that patient 6 fell asleep or was distracted during the fMRI measurement after EMT. Furthermore, only this patient showed decreases in the acuity (logMAR(N)) of both eyes (from 0.3 to 0.5 for the left eye and from 0.4 to 0.5 for the right eye), while other subjects retained the acuity, at least in 1 eye. Additionally, since patient 6 regularly works with a personal computer, the effects of EMT might be masked by habitual eye movements during work. Therefore, further prolonged daily training might be required for this patient for EMT to result in some positive effects.

Although the EMT was focused on helping find a PRL, pursuit and binocular eye movements, the cortical activities correlating with fMRI reading tasks are relatable to those underlying EMT training (Petit and Haxby, 1999; Dieterich et al., 2009).

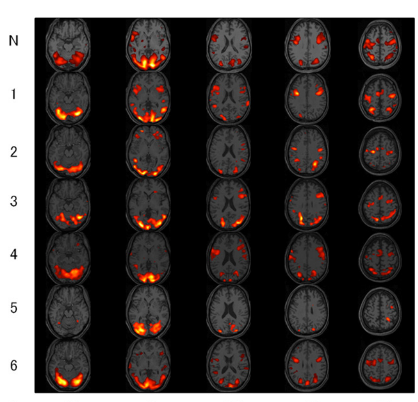

Fig. 3. Activation maps during the fMRI task (TANKA tasks) of a normal volunteer (N) (top: typical example) and individual patients (only the number is shown) before eye- movement training (EMT). Axial slice at $z = +55$ is focusing on the superior parietal lobule (SPL), inferior parietal lobule (IPL), supplementary motor area (SMA), supple- mentary eye fields (SEFs), FEF, dorsolateral prefrontal cortex (DLPFC), and primary motor area (M1). Axial slice at $z = +35$ is focusing on those areas except for SMA and SEFs. Activations of the V3 and those of V1/V2 and medial temporal lobule (V5 / MT) can be observed in the slice at $z = +25$ and $z = +5$ and -15, respectively.

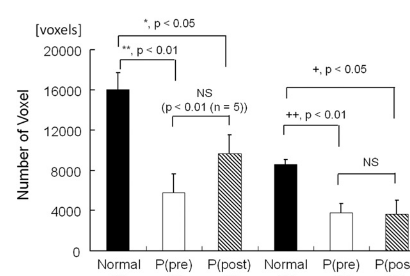

Fig. 5. Number of activation voxels in the frontal eye fields (FEFs) and parietal eye fields (PEFs). P (pre) and P (post) denote before and after eye-movement training of patients, respectively. [F] and [P] denote the FEFs and PEFs, respectively. Data are shown as mean ± SE. Normal volunteers (Normal) ($n = 6$) vs. patients ($n = 6$) at FEFs (Normal [F] vs. P (pre) [F] or Normal [F] vs. P (post) [F]), unpaired Student's t -test (*, p < 0.05; **, p < 0.01). Normal volunteers (Normal) ($n = 6$) vs. patients ($n = 6$) at PEFs (Normal [P] vs. P (pre) [P] or Normal [P] vs. P (post) [P]), unpaired Welch's t -test (+, $p < 0.05$; + +, p < 0.01). P (pre) vs. P (post), paired t -test. NS denotes no significance. Statistical analysis of P (pre) [F] vs. P (post) [F] without patient 6 (see Tables 1 and 2) yielded p < 0.01 ($n = 5$).

4.2 Activity changes in the visual cortex

Concentric contraction (CC) disease caused by RP progressively induces a loss of visual field from peripheral to central and inhomogeneous decreases in central visual acuity (Sugawara et al., 2010; Mitamura et al., 2012; Makiyama et al., 2013). The present patients showed inhomogeneous loss (or decrease in the sensitivity) of central vision (see Supplementary Fig. 1). Therefore, patients are required to understand their own PRLs in the remaining central vision and to utilize them during reading, similar to patients with CS (Crossland et al., 2005; Fletcher et al., 1999). Although the symptoms of these diseases are different, in both patients with progressive RP (Yoshida et al., 2012) and CS (McMahon et al., 1993), reduced saccades and improved reading capabilities by eccentric fixation training have been reported. Masuda et al. (2008) reported that passive viewing decreases the neural activity of the V1 in central scotoma caused by juvenile macular degeneration, which in turn suggests that increases in attention induce an increase in neural activity in V1 (Dilks et al., 2009). In the present study, patients did not show increases in the neural activation of V1. As described before, the disease was progressive in the studied patients and caused a loss of peripheral and inhomogeneous central visual fields, resulting in reduced V1 activity. However, our present observation was similar to an fMRI study of patients with CS whose disease had been caused by AMD, reported by Szlyk et al. (Little et al., 2008; Szlyk et al., 2009). These authors reported that the neural activity of the striate cortex was reduced because of the decreased visual field. Moreover, they also detected that activities in the frontal and parietal cortices increased to compensate the decrease in the activity of V1.

Schenk et al. (2000) suggested that the motion area V5/MT, which is located at an early stage of the extrastriate hierarchy, provides input to both the perception and action processing streams. In the present study, we used 2 types of tasks: a reading task and an fMRI task. As described before, the former had a pursuit-like character and the latter a saccade-like character. Therefore, especially for the latter task, the striate and extrastriate projections into the posterior parietal cortex play an important role in the visual processing of object localization and its action. The visual fields of present patients were ≤5° (Table 1). Moreover, there was heterogeneous loss of sensitivity in their remaining visual field (cf. Supplementary Fig. 1), which greatly hampered their ability to read (Table 2 and Fig. 1). However, their reading abilities were improved by EMT, as shown by the results of both reading and fMRI tasks. Moreover, activations of V3 and V5/MT in our patients increased after EMT (Fig. 4), in spite of progressive decreases in the visual field and decreased activity in V1/V2 during the experimental period (see Figs. 2, 3, and 4). Activations of V3 and V5/MT were also observed in patient 6, although this patient showed large decreases in V1/V2 activity (see Supplementary Fig. 3) and task performance in both the reading and fMRI tasks. These results suggest that a top-down process, as well as a bottom-up process, is involved in visual information processing during reading in fMRI-TANKA tasks.

4.3 Increased activity in the FEF and PEF

In the present study, the visual field of patients was considerably smaller than that of normal volunteers (cf. Table 1) and, thus, the activation area in the visual cortex was significantly smaller in patients than in normal volunteers (Fig. 2B). Nevertheless, after EMT, the reading task performance improved in all patients except for patient 6 (Table 2). As stated in the previous section, this improvement appears to result from patients acquiring suitable control over eye movements (i.e., regulation of saccade and fixation) after EMT. This improved regulation of eye movements possibly leads to increased activity in the FEF or vice versa (Figs. 4 and 5, and Table 3). Furthermore, patients who attained higher reading task performance after EMT (i.e., patients 1 and 5 in Table 2) showed a larger increase in PEF activity (Figs. 4 and 5, and Table 4). This result indicates that the PEF also plays an important role in reading task performance.

Increases in the activity of FEF and PEF play an important role in controlling eye movement and processing visual information. The PEF is related to the positional information of an object; this information is transmitted from the primary visual cortex to the PEF, which determines the position of an object and transmits the information to the FEF. The FEF transforms the positional information into eye-movement information and transmits this to the superior colliculus and brain stem. Thus, the FEF is closely related to the regulation of eye movement (Pierrot-Deseilligny et al., 2004). In addition, the FEF is critical for the visual selection of a target in both a conjunction and a feature-search task (Muggleton et al., 2003). It is also reported that the oculomotor and attentional systems strongly overlap, and the FEF is responsible for the coupling between shifts of visuospatial attention and eye movements (Muggleton et al., 2003; Bosch et al., 2012). Furthermore, the supramarginal gyrus, along the intraparietal sulcus, is critical for mediating both spatial working memory and shifts in spatial attention (Silk et al., 2010). Thus, the FEF and PEF are possibly related to attention and working memory. These reports obtained with normal volunteers and patients with CS are in agreement with our results.

4.4 Activity change in other cortices

The dorsolateral prefrontal cortex (DLPFC) is also considered to be involved in the control of predictive saccades, i.e., anticipating the location to which the target is moving as well as in saccade inhibition and short-term spatial memory (Pierrot-Deseilligny et al., 2004). During the fMRI task, task letters of "Kana" are shown individually that form "TANKA" as a whole, which is similar to a short poem consisting of 37 letters. Thus, we expected activation of the DLPFC in the present experiments on the basis of previous reports on patients with CS (Little et al., 2008; Szlyk et al., 2009). In some patients, however, activation of the DLPFC was observed before and after EMT (Figs. 3 and 4). Thus, in contrast to that in patients with CS, improvement of reading capability in the present patients by EMT is not essentially due to the activation of V1 and DLPFC.

Little et al. (2008) and Szlyk et al. (2009) also observed an increase in the activity of the supplementary eye field (SEF) that is located on the medial surface of the superior frontal gyrus and connected with all areas involved in eye-movement control as well as in the motor programs comprising a saccade combined with body movement (Pierrot-Deseilligny et al., 2004). In the present patients, we also observed the activation of the SEF (Fig. 3). However, we imposed a button-press task as the subjects performed the fMRI task. Therefore, in the present case, we could not discriminate whether activation of the SEF was due to the reduced saccade regulation or the motor action of pushing the button. Further experiments are required to elucidate the role of the SEF in improving saccade regulation and the reading capability of the patients who underwent EMT.

In conclusion, we regard the improvement in reading abilities of patients with progressive RP after EMT as an effect of the increased activity of the FEFs and PEFs, although more in the FEF, which plays an important role in attention and working memory as well as in the regulation of eye movements.

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Appendix A. Supplementary Material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2014.02.007.

References

Abrams, S.G., Zuber, B.L., 1972. Some temporal characteristics of information processing during reading. Reading Research Quarterly 8, 40. http://dx.doi.org/10.2307/746979.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113. http://dx.doi.org/10.1016/j.neuroimage.2007.07.00717761438.

Bainbridge, J.W., Smith, A.J., Barker, S.S., Robbie, S., Henderson, R., Balaggan, K., Viswanathan, A., Holder, G.E., Stockman, A., Tyler, N., Petersen-Jones, S., Bhattacharya, S.S., Thrasher, A.J., Fitzke, F.W., Carter, B.J., Rubin, G.S., Moore, A.T., Ali, R.R., 2008. Effect of gene therapy on visual function in Leber's congenital amaurosis. New England Journal of Medicine 358, 2231–2239. http://dx.doi.org/10.1056/NEJMoa080226818441371.

Bosch, S.E., Neggers, S.F., Van, der Stigchel S., 2012. The role of the frontal eye fields in oculomotor competition: image-guided TMS enhances contralateral Target selection. Cerebral Cortex (New York, N.Y. : 1991)22455840.

Bouma, H., 1978. Visual search and reading, eye movements and functional visual fields: a tutorial review. In: Requin, J. (Ed.), Attention and Performance. VII. Lawrence Erlbaum Associates, Hillsdale, NJ.

Brown, B. Optical low vision aids. In: The Low Vision Handbook (1997). Chap 2. SLACK Incorporated, Thoroe NJ, pp. 7–28

Crossland, M.D., Culham, L.E., Kabanarou, S.A., Rubin, G.S., 2005. Preferred retinal locus development in patients with macular disease. Ophthalmology 112, 1579–1585. http://dx.doi.org/10.1016/j.ophtha.2005.03.02716087239.

Dieterich, M., Müller-Schunk, S., Stephan, T., Bense, S., Seelos, K., Yousry, T.A., 2009. Functional magnetic resonance imaging activations of cortical eye fields during saccades, smooth pursuit, and optokinetic nystagmus. Annals of the New York Academy of Sciences 1164, 282–292. http://dx.doi.org/10.1111/j.1749-6632.2008.03718.x19645913.

Dilks, D.D., Baker, C.I., Peli, E., Kanwisher, N., 2009. Reorganization of visual processing in macular degenerations is not specific to the "preferred retinal locus. Journal of Neuroscience 29, 2768–2773. http://dx.doi.org/10.1523/JNEUROSCI.5258-08.200919261872.

Fletcher, D.C., Schuchard, R.A., Watson, G., 1999. Relative locations of macular scotomas near the PRL: effect on low vision reading. Journal of Rehabilitation Research and Development 36, 356–36410678458.

Holmes, D.L., Cohen, K.M., Haith, M.M., Morrison, F.J., 1977. Peripheral visual processing. Perception and Psychophysics 22, 571–577. http://dx.doi.org/10.3758/BF03198765.

Ikeda, M., Uchikawa, K., Saida, S., 1979. Static and dynamic visual fields. Optica Acta 26, 1103–1113. http://dx.doi.org/10.1080/713820103.

Klauke, S., Goertz, M., Rein, S., Hoehl, D., Thomas, U., Eckhorn, R., Bremmer, F., Wachtler, T., 2011. Stimulation with a wireless intraocular epiretinal implant elicits visual percepts in blind humans. Investigative Ophthalmology & Visual Science 52, 449–455. http://dx.doi.org/10.1167/iovs.09-441020861492.

Little, D., Thulborn, K., Szlyk, J., 2008. An fMRI study of saccadic and smooth pursuit eye movement control in patients with AMD. Investigative Ophthalmology and Visual Science 49, 1728–1735. http://dx.doi.org/10.1167/iovs.07-037218385097.

Mackworth, N.H., 1976. Stimulus density limits the useful field of view. In: Monty, R.A., Senders, J.W. (Eds.), Eye Movements and Psychological Processes. Lawrence Erlbaum Associates, Hillsdale, NJ.

Makiyama, Y., Ooto, S., Hangai, M., Takayama, K., Uji, A., Oishi, A., Ogino, K., Nakagawa, S., Yoshimura, N., 2013. Macular cone abnormalities in retinitis pigmentosa with preserved central vision using adaptive optics scanning laser ophthalmoscopy. PLOS One 8, e79447. http://dx.doi.org/10.1371/journal.pone.007944724260224.

Masuda, Y., Dumoulin, S., Nakadomari, S., Wandell, B., 2008. V1 projection zone signals in human macular degeneration depend on task, not stimulus. Cerebral Cortex 18, 2483–2493. http://dx.doi.org/10.1093/cercor/bhm25618250083.

McMahon, T.T., Hansen, M., Stelmack, J., Oliver, P., Viana, MAG., 1993. Saccadic eye movement as a measure of the effect of low vision rehabilitation on reading rate. Optometry and Vision Science 70, 506–510. http://dx.doi.org/10.1097/00006324-199306000-00010.

Ming, J., Thulborn, K.R., Szlyk, J.P., 2012. Reproducibility of activation map for longitudinal studies of visual function by functional magnetic resonance imaging. Investigative Ophthalmology and Visual Science 53, 6153–6163. http://dx.doi.org/10.1167/iovs.11-837522879425.

Mitamura, Y., Mitamura-Aizawa, S., Nagasawa, T., Katome, T., Eguchi, H., Naito, T., 2012. Diagnostic imaging in patients with retinitis pigmentosa. Journal of Medical Investigation 59, 1–11. http://dx.doi.org/10.2152/jmi.59.122449988.

Muggleton, N.G., Juan, C.H., Cowey, A., Walsh, V., 2003. Human frontal eye fields and visual search. Journal of Neurophysiology 89, 3340–3343. http://dx.doi.org/10.1152/jn.01086.200212783960.

Osaka, N., 1987. Effect of peripheral visual field size upon eye movements during Japanese text processing. In: O'Regan, J.K., Levy-Schoen, A. (Eds.), Movements from Physiology to Cognition. Elsevier, North-Holland, pp. 421–429.

Petit, L., Haxby, J.V., 1999. Functional anatomy of pursuit eye movements in human as related by fMRI. Journal of Neurophysiology 82, 463–47110400972.

Pierrot-Deseilligny, C., Milea, D., Müri, R.M., 2004. Eye movement control by the cerebral cortex. Current Opinion in Neurology 17, 17–25. http://dx.doi.org/10.1097/00019052-200402000-00005.

Saida, S., Ikeda, M., 1979. Useful visual field size for pattern perception. Perception and Psychophysics 25, 119–125. http://dx.doi.org/10.3758/BF03198797.

Schenk, T., Mai, N., Ditterich, J., Zihl, J., 2000. Can a motion-blind patient reach for moving objects? European Journal of Neuroscience 12, 3351–3360. http://dx.doi.org/10.1046/j.1460-9568.2000.00194.x10998118.

Seiple, W., Szlyk, J.P., McMahon, T., Pulido, J.S., Fishman, G.A., 2005. Eye movement training for reading in patients with age-related macular degeneration. Investigative Ophthalmology and Visual Science 46, 2886–2896. http://dx.doi.org/10.1167/iovs.04-129616043863.

Seiple, W., Grant, P., Szlyk, J.P., 2011. Reading rehabilitation of individuals with AMD: relative effectiveness of training approaches. Investigative Ophthalmology and Visual Science 52, 2938–2944. http://dx.doi.org/10.1167/iovs.10-613721296824.

Silk, T.J., Bellgrove, M.A., Wrafter, P., Mattingley, J.B., Cunnington, R., 2010. Spatial working memory and spatial attention relay on common neural processes in the intraparietal sulcus. Neuroimage 53, 718–724. http://dx.doi.org/10.1016/j.neuroimage.2010.06.06820615473.

Somani, S., Brent, M.H., Markowitz, S.N., 2006. Visual field expansion in patients with retinitis pigmentosa. Canadian Journal of Ophthalmology 41, 27–33. http://dx.doi.org/10.1016/S0008-4182(06)80062-1.

Sugawara, T., Hagiwara, A., Hiramatsu, A., Ogata, K., Mitamura, Y., Yamamoto, S., 2010. Relationship between peripheral visual field loss and vision-related quality of life in patients with retinitis pigmentosa. Eye 24, 535–539. http://dx.doi.org/10.1038/eye.2009.176.

Sumitani, M., Tabuchi, A., Kikuiri, A., 2000. Fixation eye movements during walking in persons with low vision. Folia Ophthalmologica Japonica 51, 1140–1147.

Sunness, J., Liu, T., Yantis, S., 2004. Retinotopic mapping of the visual cortex using functional magnetic resonance imaging in a patient with central scotomas from atrophic macular degeneration. Ophthalmology 111, 1595–1598. http://dx.doi.org/10.1016/j.ophtha.2003.12.050.

Szlyk, J.P., Little, D.M., 2009. An fMRI study of word-level recognition and processing in patients with age-related macular degeneration. Investigative Ophthalmology & Visual Science 50, 4487–4495. http://dx.doi.org/10.1167/iovs.08-225819387076.

Tabuchi, A., Hiraki, Y., Oka, Y., Kamiyoshikawa, M., Nakamura, T., Murakami, N., 1998. Eye movements in visually handicapped person. Folia Ophthalmologica Japonica 49, 738–745.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289. http://dx.doi.org/10.1006/nimg.2001.097811771995.

Yoshida, M., Origuchi, M., Osaki, K., Seiyama, A., 2012. Studies on eye movements of concentric contraction patients under reading. Abstract of the 66th Annual Congress of Japan Clinical Ophthalmology 202 in Japanese.