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

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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.

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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