Abnormal Activation in the Visual Cortex after Corneal Refractive Surgery for Myopia

Demonstration by Functional Magnetic Resonance Imaging

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Objective: To try to correlate subjective photophobic symptoms with visual pathway modifications (from the retinal image to the visual cortex) after refractive surgery by exploring brain activation on photic stimulation.

Design: Noncomparative case series.

Participants: Four subjects reporting discomfort produced by luminance (glare, halos, starbursts, or a combination thereof) in one eye after laser in situ keratomileusis (LASIK) were enrolled. The contralateral myopic eye (control) had no visual impairment and had undergone LASIK without complications or had not had previous surgery.

Methods: Functional magnetic resonance imaging was performed during photic stimulation, delivered by an optical fiber, of the affected and unaffected eyes.

Results: Functional magnetic resonance imaging provided evidence that most subjective visual symptoms correlated with anatomic flap abnormalities are associated with a higher signal increase in the visual association cortices compared with a nonsymptomatic eye.

Conclusions: Functional magnetic resonance imaging of the visual cortex may help in exploring the mechanisms involved in glare effects after refractive surgery. *Ophthalmology 2001;108:2213–2218 © 2001 by the American Academy of Ophthalmology.*

Refractive surgery has become a widely accepted method of correcting refractive errors, particularly laser assisted in situ keratomileusis (LASIK), which enjoys increasing interest worldwide.[1] Important issues of refractive surgery concern not only postoperative visual acuity and residual refractive status, but also patients' functional outcome, satisfaction, and quality of vision.[2,3] Patients may be dissatisfied by an imperfect postoperative quality of vision, reporting symptoms such as glare, halos, starbursts, and ghost images.[4] These potential side effects, which are secondary to optical aberrations and intraocular light scattering,[2,3] have been reported whatever the refractive procedure, and more recently in 8.8% of patients after LASIK.[5] The evaluation of this reduced quality of vision is essentially based on the subjective quantification of the complaints of the patient. New objective evaluation methods, such as wavefront analysis,[6] based on the analysis of blurred retinal image secondary to the corneal aberration, are currently under evaluation. Despite this technological advance, the evaluation of the quality of vision after refractive surgery still remains complex and incomplete.[2,3] Thus, it seemed interesting to approach this problem with what we call "central analysis," based on the consequences of the optical quality of the eye on the visual cortex. This approach has been made possible by the recent progress of the functional neurosensory explorations of the central nervous system such as functional magnetic resonance imaging (fMRI).

We report here the use of fMRI to analyze four patients reporting glare, halos, starbursts, or a combination thereof after refractive surgery.

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Patients and Methods

Patients

Each patient included in this study reported subjective photophobic symptoms (glare, halos, starbursts, or a combination thereof) in his or her daily life in one eye after LASIK surgery without any complaint of a decrease in contrast sensitivity. Glare, halos, and starbursts were assessed subjectively using not only a question-

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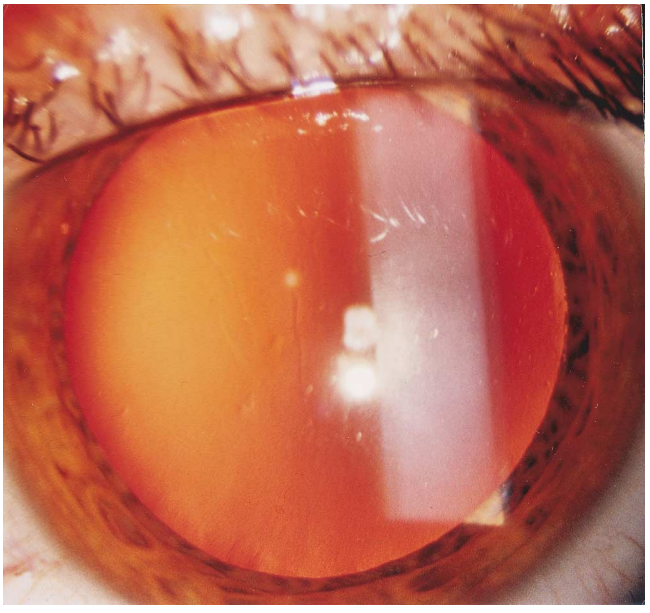

Figure 1. Slit-lamp photomirograph of the left cornea shows Bowman rupture lines.

naire but also picture cards representing lights of incoming cars at night, allowing patients to characterize visually what type of phenomenon they were seeing, and thus allowing us to clarify the patient's response. These side effects theoretically were the result of the presence of flap abnormalities (flap striae or Bowman's rupture), which were located in the pupillary area and were not associated with any significant loss of visual acuity. Moreover, some operated eyes had corneal topographic abnormalities.

The contralateral eye, that is, the control eye, was not reported as having any deterioration in the quality of vision. It either had undergone LASIK surgery without any anatomic or functional complications (patients 3 and 4) or had not had previous refractive surgery (patients 1 and 2).

All subjects were recruited in 2000 and gave written informed consent for a neuroimaging exploration. The protocol was approved by the institutional ethical committee (Toulouse I, France).

Case Reports

Patient 1. A 28-year-old woman was referred to us for glare, halos, and starbursts 6 months after LASIK surgery in her right eye. She did not want LASIK surgery in her left eye. Preoperative refractions were $-6.50\ -1.0 \times 0$ in the right eye and $-7.25\ -0.75 \times 25$ in the left eye, and with this correction she had a visual acuity of 20/25 in both eyes. Postoperative uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were 20/25, identical to the preoperative BCVA. Corneal examination showed Bowman rupture lines in the pupillary area outside the visual axis. Corneal topography that was performed using an EyeSys Corneal Analysis System (EyeSys Laboratories, Houston, TX) showed a slight decentration of the ablation. Contrast sensitivity, assessed using the CVS1000 (Vector Vision, Dayton, OH), was unaltered without any difference between the affected and the nonaffected eye.

Patient 2. A 45-year-old woman who had undergone unilateral LASIK in her right eye was referred to us 5 months after the surgery because she was dissatisfied with the result because of postoperative glare. Preoperative BCVA was 20/32, with a preoperative refraction of $-9\ -1.50 \times 20$. Postoperative UCVA and BCVA were 20/40, and the examination under the slit lamp showed a wrinkled flap. To improve the patient's symptoms, a flap-stretching technique was performed that was unsuccessful, without improvement in BCVA or glare disturbance. The topographic studies indicated a correct centration of the photoablation with some irregularity. The contralateral, myopic eye BCVA was 20/25 with a refraction of $-7.50\ -1.00 \times 5$. Contrast sensitivity was not available for this patient.

Patient 3. A 33-year-old man had undergone bilateral LASIK. Preoperative refractions were $-5.50\ -1.00 \times 100$ in the right eye and $-6.00\ -1.00 \times 90$ in the left eye. With this correction, the patient had a visual acuity of 20/25 in both eyes. Four months after surgery, the UCVA and BCVA were 20/28 in both eyes, but the

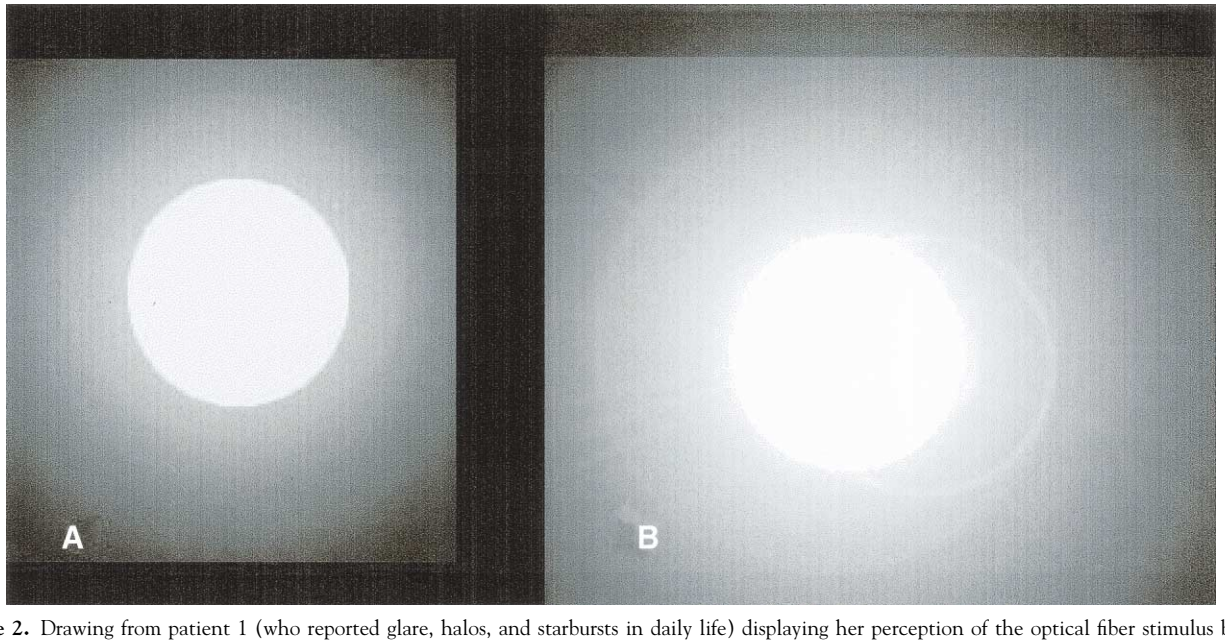

Figure 2. Drawing from patient 1 (who reported glare, halos, and starbursts in daily life) displaying her perception of the optical fiber stimulus by the control (**A**) and the symptomatic eye (**B**).

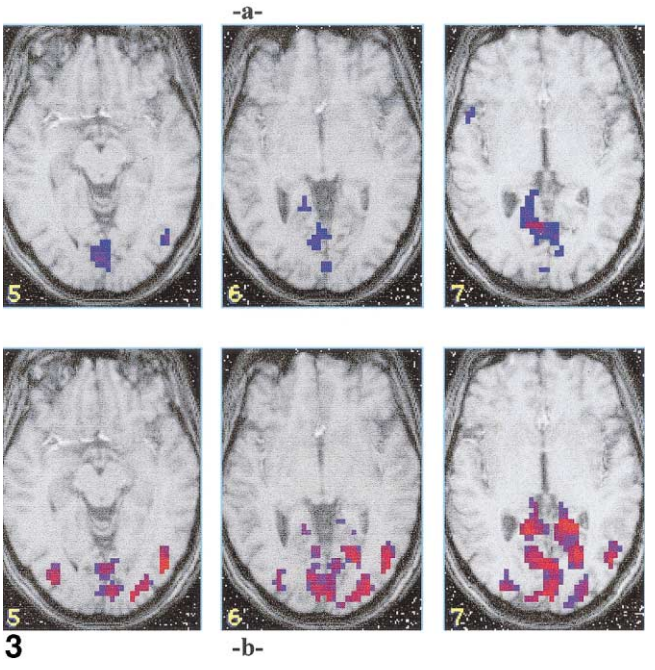

Figure 3. Activation map for activation of control and affected eyes. Axial T_1-weighted anatomic magnetic resonance imaging slices in patient 1 located at the bicommissural plane (slice 7), and the 5-mm slice (slice 6) and 10-mm slice (slice 5) below. Functional magnetic resonance images obtained in this subject were coregistered to anatomic ones, showing activations in both the control (**A**) and the affected eye (**B**). Activations in visual association cortex are moderate for the control eye and enhanced for the affected eye. The color table was set so that purple corresponds to $P < 0.005$ and red corresponds to $P < 0.0001$. By convention, the left cerebral hemisphere is shown on the right.

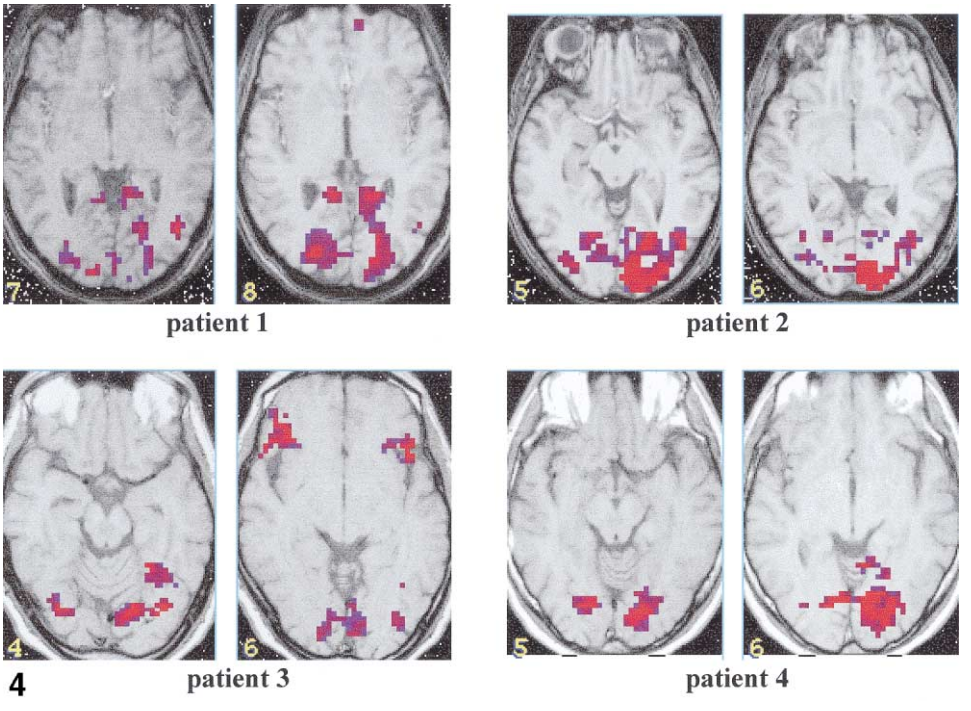

Figure 4. Differential maps of the four patients. Comparison between affected eye and control eye in the four patients (2 selected slices of 16). Increase of activation is located in the primary and association visual cortex. The left cerebral hemisphere is shown on the right.

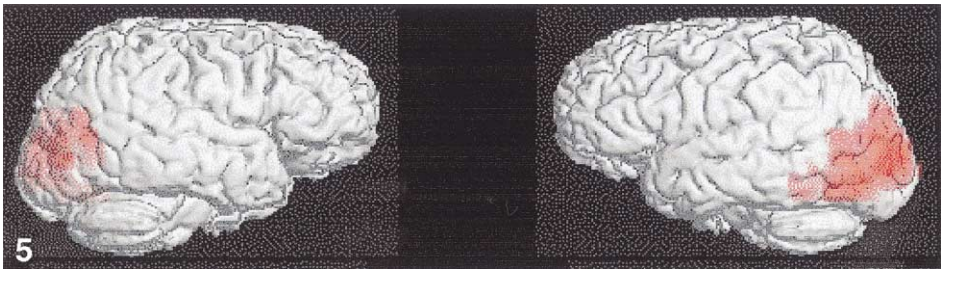

Figure 5. Three-dimensional rendering map. Hyperactivated areas in patient 2 after the comparison of stimulation of the affected eye with glare against that of the control eye, projected on the subject's brain anatomic image.

patient reported starbursts in the right eye, probably the result of flap striae in the pupillary area. Corneal topography showed a subtle irregular astigmatism in the right eye. Contrast sensitivity was evaluated using the CVS1000, and the curves were found to be subnormal and similar in both eyes.

Patient 4. A 38-year-old man was examined 4 months after bilateral LASIK surgery. He was dissatisfied because of the presence of postoperative glare in his left eye. Preoperative refractions were $-4.50\ -2.0 \times 175$ in the right eye and $-7.50\ -1.0 \times 35$ in the left eye, and preoperative BCVA was 20/25 in both eyes. Postoperative UCVA and BCVA in the left eye were identical (20/25), and Bowman rupture lines were seen within the LASIK flap (Fig 1). Postoperative UCVA and BCVA in his right eye were 20/25. Corneal topographies were considered normal for both eyes. Contrast sensitivity was not available for this patient.

Functional Magnetic Resonance Imaging

Imaging was performed with an MRI machine with rapid acquisition capabilities (Echo-Planar Imaging technique), using a Siemens (Siemens, Erlangen, Germany) Magnetom Vision scanner at 1.5 Tesla (flip angle = 90°; echo time (TE) = 66 ms, repetition time (TR) = 3 seconds, field of view (FOV) = 20 cm). Sixteen 5-mm thick axial slices were acquired parallel to the bicommissural plane; in-plane voxel size was $3.2 \times 3.2\ mm^2$. T_1-weighted images were also acquired to obtain structural three-dimensional images to locate activated areas. Continuous image acquisition was performed (one image acquisition every 3 seconds) for 240 seconds. The background visual scene was dark and simple, providing the conditions of dim light. Subjects were asked to watch an intermittent light stimulus delivered by an optical fiber (5 mm diameter) placed 7 cm in front of the stimulated eye close to the center of the visual field. The light stimulation was delivered every 3 seconds for 1 second during four periods of 30 seconds alternated with four rest periods of 30 seconds. The same stimulation was applied separately to the right eye and then to the left eye. The level of illumination of the stimulating light (from 1 to 22 lux in pupil plane) was set so that for all patients glare was experienced by the affected eye during the experiment, mimicking in a simplified version the daily life conditions of glare (Fig 2). Provided that the pattern of the stimulation was intermittent, the discomfort induced by the experimental glare was not disturbing enough for the patient to avoid fixation, as shown by a pre-fMRI experiment. Scans over a period of 4 minutes were conducted for each eye, resulting in 80 observations per voxel (40 in rest period and 40 in stimulation period), allowing single subject statistical analysis. The series of scans were realigned to compensate for artifactual signal intensity changes caused by head movement and smoothed with a Gaussian filter of 6 mm full width half maximum (FWHM). Statistical analyses were performed on a voxel-by-voxel basis with SPM99 software (Wellcome Department of Cognitive Neurology, London, England) to obtain two maps of activated areas corresponding to the stimulation of each eye and two maps of differentially activated areas in the two conditions. Only voxels at $P < 0.005$ were considered and projected on the structural images of each subject.

Results

In all the patients, the stimulation of the control eye activated bilaterally the primary visual cortex and lingual and median occipital gysi (Fig 3A). This is in line with the observations of discrete associative visual cortex activation in normal subjects.[7–10] For the affected eye, results showed larger changes in both signal increase and size of activated clusters. Moreover, the activation spread bilaterally from the primary visual cortex toward associated visual areas mainly in the inferior, ventral part of the visual system. These areas involve the lateral (inferior, median, and superior occipital gyri) and mesial (lingual and fusiform gyri) association cortex, as well as the inferior temporal gyrus and posterior cingulum (Fig 3B).

Such a difference is particularly clear when the activities evoked by the stimulation of either eye are compared by the subtractive method. This differential analysis between the affected eye and control eye shows brain activities that are specifically associated with the glare, halos, and starbursts effects. It reveals an increase of activation in visual cortical areas on stimulation of the affected eye compared with stimulation of the control eye. In all subjects, areas showing higher signal increase for illumination of the operated eye were located in the primary visual cortex and, more surprisingly, in visual association cortices mainly in the left hemisphere (Table 1, Fig 4 and 5). Activation was also found in

Table 1. Localization and Extent of Significantly ($P < 0.0005$) Activated Areas in the Comparison of Affected Eye versus Control Eye.

Areas of Activation	No. of Pixels
Subject 1	
Lateral visual cortex	
Left, MO IO SO IT	90
Right, MO IO IT MT	78
Medial visual cortex	
Left, VI, LG FG MO HG Cuneus	99
Right, VI	9
Posterior cingulum	200
Anterior cingulum (prefrontal)	129
Subject 2	
Lateral visual cortex	
Left, MO IO IT	182
Right, MO IO IT	132
Medial visual cortex	
Left, VI, LG FG	220
Right, VI, LG	57
Subject 3	
Lateral visual cortex	
Left, MO IO IT	105
Right, MO IO IT	89
Medial visual cortex	
Left, VI, LG FG Cuneus	113
Right, VI, Cuneus	48
Posterior cingulum	50
Left frontal	85
Right frontal	105
Subject 4	
Lateral visual cortex	
Left, MO OI SO IT MT	104
Right, MO SO MT	37
Medial visual cortex	
Left, VI, LG FG	123
Right, LG FG	57
Posterior cingulum	54

FG = fusiform gyrus; HG = hippocampal gyrus; IO = inferior occipital gyrus; IT = inferior temporal gyrus; LG = lingual gyrus; MO = middle occipital gyrus; MT = middle temporal gyrus; SO = superior occipital gyrus; V1 = primary visual cortex.

The anatomic localization relied on both coordinates in the standard stereotactic space from the Talairach and Tournoux atlas (1988) and the brain atlas from Duvernoy (1992).

the posterior cingulum (patients 3 and 4), anterior cingulum, prefrontal cortex (patient 1), and frontal cortex (patient 3). In all subjects, the striking difference between the activation pattern generated by the stimulation of the affected eye and the control eye was observed regardless of whether the control eye had undergone LASIK.

No activation was found in the reverse comparison, that is, stimulation of the control eye versus the affected eye.

Discussion

The evaluation of the quality of vision after refractive surgery, which today is essentially subjective, remains a difficult problem. New objective evaluations such as wavefront analysis have recently been used to appreciate the optical quality of the retinal image, but these continue to be evaluated.[6] Despite these new technological advances, refractive surgery lacks a technology that provides a good objective measurement of the quality of vision.[2,3] We propose here a new approach to investigate patient reports of side effects at the level of the visual cortex. Among the recently introduced functional imaging techniques, positron emission tomography has a potential risk of radioactive toxicity. However, fMRI, which has a better spatial and temporal resolution, is a noninvasive technique for measuring hemodynamic responses to changes in neural activity induced by stimulations or any cognitive task. Functional magnetic resonance imaging signal reflects the local changes in blood flow oxygenation (known as BOLD) correlated with neural local metabolic activity.[11] Functional magnetic resonance imaging has been used extensively to clarify our understanding of the human visual cortex.[8–10]

This technique allowed us to evaluate the pattern of cortical activation when comparing the affected eye with the control eye in an experimentally induced glare. We noted, not systematically, activation in the posterior cingulum and in the region including the anterior cingulum and some areas of the frontal cortex (especially in patient 3, who had a particularly vivid sensory experience), which suggests a possible involvement of attentional processes.[12]

The most striking result was the constant observation in all patients of higher activation in visual association areas when stimulating the symptomatic eye by comparison with the control eye. Importantly, this higher activation in the association areas was observed even when the control eye itself had undergone a LASIK intervention, but without complication (patients 3 and 4). The increase of activation in the visual association areas probably originates from the optical aberration in the operated cornea. The minimal stimulus represented by a round homogeneous spot delivered by an optical fiber should have induced a minimal response restricted mainly to the primary visual cortex, as observed in the control eyes. The striking additional activity of the association areas is very likely to result from the imperfect blurred retinal image secondary to the optical aberration induced by the flap wrinkles. This effect, therefore, is not related to the LASIK per se but to the flap complication.

Involvement of visual association areas suggests a processing pathway projecting from the primary visual cortex toward the inferior part of the extrastriate cortex and the inferior temporal cortex. This occipitotemporal pathway, or "ventral stream," is crucial for object identification and known as the "what" system.[13,14] The irregular contours of the remodeled light stimuli are likely to prompt object recognition processes, because such complex shapes may resemble fragments of known objects.[15] In addition to its object identification role, the what system is also involved in awareness, as suggested by Crick and Koch[16] and reviewed by Koch and Braun.[17] The amplified activation, which we obtained in the areas of the what system, may correspond to the amplification of awareness so that the abnormal brightness of the stimulus contours is perceived as a severe glare, which is unsettling for the patient. Finally, one cannot rule out that emotional or autonomic changes in the brain functions may account for the alteration of activation pattern seen on stimulation of symptomatic eyes. However, none of our patients reported intense discomfort under this condition.

Although the interpretation of these changes in activation patterns remains complex, we believe that functional neuroimaging may be helpful to explore some aspects of the pathophysiologic substrates of glare observed after refractive surgery. Obtaining higher resolution of functional neuroimagery will improve the quality of this type of analysis and may allow the correlation of measurements of the optical quality of the eye with a particular pattern of brain stimulation. Further investigations using fMRI combined with new technologies allowing the analysis of retinal images will help in distinguishing the consequences of optical aberrations on retinal image and the glare effect. Such advances will also allow the investigation of results of treatments for LASIK complications such as flap stretching techniques and customized ablation for irregular astigmatism.

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