Objective Ocular Discomfort: Noninvasive Evaluation by Functional Near-Infrared Ray Spectroscopy

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PURPOSE. Patients express their discomfort by subjective complaints, which may not clearly express the extent of their discomfort. This study noninvasively and objectively quantified ocular discomfort, a form of feeling, from the prefrontal cortex by functional near-infrared ray spectroscopy topography.

METHODS. This case-controlled study enrolled six dry eye patients (male:female, 1:1; 51.8 ± 15.9 years) with ocular discomfort and six normal controls (male:female, 1:1; 48.8 ± 15.2 years). Ocular discomfort was created by Schirmer 1 test in normal controls. The extent of prefrontal cortex activity was evaluated as the number of signal-positive channels using the system by using an eye-opening task with spontaneous blinking in the dark. Changes in the signal-positive channels count by lubricant or anesthetics instillation were analyzed.

RESULTS. Low prefrontal cortex activation was detected in normal controls without ocular discomfort, and high activation was detected in both normal controls and dry eye with ocular discomfort. Prefrontal cortex activity was confirmed with ocular discomfort when the eyes were open, decreased with lubricant, and almost disappeared with anesthetic for all participants.

CONCLUSIONS. These changes in the prefrontal cortex activity exhibited a significant correlation to subjective complaint scores, suggesting that such discomfort may be objectively quantifiable, independent of subjective expressions.

Keywords: dry eye, fNIRS, objective symptom

Even subtle unpleasant stimuli cause discomfort. Although discomfort is one of the important complaints related to reduced quality of life in patients with incurable or chronic diseases, communicating the details of such discomfort to other people is difficult. Subjective verbal or vocal expressions are often the only means with which to ascertain the patient’s inner feelings.1 Functional near-infrared spectroscopy (fNIRS) is an emerging functional neuroimaging technology proffering a relatively noninvasive and safe method of indirect and direct monitoring of brain activity. fNIRS detects increases in cerebral blood flow due to elevated cerebral nerve activity in terms of cerebral hemoglobin (Hb). The advantage of fNIRS is its potential to allow more physiologically valid investigations that can translate laboratory work into more realistic everyday settings and clinical environments for investigation of neurocognitive processes associated with neurological and psychiatric disorders.2 It has been reported that signals detected by fNIRS (brain optical topography) show good correlation with functional magnetic resonance imaging (fMRI) signals in the primary motor and sensory areas.3 Even with different parameters in individual studies, fMRI findings have been reliably reproduced.4

Clinical studies have been conducted on psychophysiological and neurophysiological pain.5–11 However, few studies have directly, noninvasively, and objectively assessed discomfort, a form of feeling or emotion directly linked to patient complaints.5–11

Dry eye is a syndrome characterized by ocular surface disorders caused by tear-related abnormalities, and most patients complain of various ocular discomforts.12 Patients with severe dry eye have often difficulty in opening their eyelids. Tests included in the diagnostic standards for dry eye lack sufficient sensitivity and specificity,13 and although complaints are important for diagnosis,13–17 some diagnostic standards for dry eye and Sjögren’s syndrome do not include them.18,19 In clinical settings, discrepancies exist between objective findings involving tear dynamics and corneal and conjunctival epithelial disorders and subjective symptoms involving patient complaints.15,20–23 In diseases involving dry eye where improving complaints is an important therapeutic goal, objectively quantified complaints are necessary.

As this technique is relatively noiseless and convenient, fNIRS is superior in terms of reducing mental and psychological stress to the subject compared to fMRI.12–24 This study investigated whether fNIRS could directly, noninvasively, and objectively quantify subjective ocular discomfort caused by subtle unpleasant stimuli in dry eye patients by prefrontal cortex activities.

METHODS
Participants
Subjects were six patients with dry eye, diagnosed by the 2006 Japanese criteria16,17 (three males, three females; mean

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Objective Ocular Discomfort Assessed By fNIRS

Induction of Artificial Ocular Discomfort Symptoms in Normal Controls and fNIRS Measurement Conditions

We previously reported that intentionally created ocular discomfort symptoms, after the Schirmer 1 test or with facial wind load in normal controls, could be detected by measuring frontal lobe activation by using fNIRS.8,9,11 We were also able to assess the relief of such symptoms by eye drops by this methodology.

For this study, in a rested state, the Schirmer 1 test was used to induce artificial ocular discomfort in either one or both eyes (preparation from a negative ocular discomfort state to a positive one).8 The subjects then performed an experimental task involving 1-minute tasks of eye opening (spontaneous blinking with no squinting) twice between 1-minute periods of eye closing in a 5-minute test (Fig. 1). This was repeated after the instillation of 0.1% hyaluronic acid,28 a therapeutic agent for dry eye, and also after instillation of 0.4% oxybuprocaine hydrochloride, an anesthetic eye drop.

Cerebral activities in the frontal lobe were measured using an ETG-100 fNIRS system (semiconductor laser near infrared wavelength 780 nm, 850 nm; 16 probes; probe interval, 3.0 cm; 24-channel; Hitachi Medical, Tokyo, Japan).29 The 16 probes for the 24-channel fNIRS were placed at 3.0-cm intervals around the forehead so that the anterior margin of the probes was about 3 cm from the eyebrows (Fig. 2). Without immobilizing the head and neck region, subjects were placed in a sitting position in a quiet, windless, dark room at 24–28°C and 45%–65% humidity. Eye opening/closing and blinking were observed using a high-sensitivity imaging monitor. Room brightness was adjusted manually during dark adaptation, and during each measurement, the lights were turned on. The test was redone if subjects experienced sleepiness, pain, or another form of discomfort or irregular eye opening or head position. In each subject, serial measurements were taken and the entire test was completed within 70 minutes of probe attachment.

Using a high-sensitivity video camera (Fig. 3), eye opening and blinking were monitored. Hb grand averaged waveform (WAVE) was calculated by subtracting the average data for closed eyes from the average data for opened eyes (average of two measurements). According to past studies,3,8,9,11 cerebral activation was defined as either unchanged or minimally

### Table. Clinical Characteristics of the Subjects

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<th>RB (R/L)</th>
<th>BUT (R/L)</th>
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* Dry eye was diagnosed by the 2006 Japanese criteria.16,17 BUT, tear-film break-up time (seconds); C-B, corneal aesthesiometry by Cochet-Bonnet (mm); CN, corneal neovascularization; DBDE, decreased BUT type dry eye;16 FL, fluorescein score (9 points); HT, healed trachoma; L, left; N, negative; NC, normal control; OD, ocular discomfort; P, positive; PO, punctal occlusion; R, right; RB, rose bengal score (9 points); S1, Schirmer 1 test (mm); SJS, Stevens-Johnson syndrome; SS, Sjögren’s syndrome.

age, 51.8 ± 15.9 years) and six healthy subjects matched for age (±10 years) and sex (three males, three females; mean age, 48.8 ± 15.2 years) (Table). The diagnostic criteria are as follows: (1) presence of dry eye symptoms, (2) presence of qualitative or quantitative disturbance of the tear film (Schirmer 1 test ≤ 5 mm or TBUT ≤ 5 seconds), and (3) presence of keratoconjunctival epithelial damage (either fluorescein or rose bengal staining score ≥ 3/9 points). The presence of all three criteria was necessary for a definite diagnosis of dry eye. Subjects showing the presence of two of the three criteria were diagnosed with probable dry eye, whereas those with one or no positive criteria were diagnosed as non-dry eye. All subjects gave their written informed consent in accordance with the research protocol approved by the Institutional Review Board of Tokai University Hospital (number 04-085). The study adheres to the tenets of the Declaration of Helsinki. Slit lamp examination with fluorescein and rose bengal and Schirmer 1 tests were performed in all subjects. Tear clearance tests25 were conducted to exclude cases of lacrimal punctal occlusion. All dry eye subjects had at least moderate unilateral/bilateral ocular pain (≥ 3 points as assessed using the National Eye Institute Visual Function Questionnaire),26 and were positive for ocular discomfort. Subjects with allergic conjunctivitis were excluded to avoid the influence of decreased tear break-up time.27 Subjects wearing contact lenses, with glaucoma medication, previous ocular surgery, and pterygia were also excluded. Patients with bilateral punctal occlusion were also excluded. Furthermore, patients with bilateral corneal vascularization and patients with unilateral or unilateral symblepharon, which affects blinking, were also excluded. Moreover, patients with psychological or neurological diseases affecting near-infrared spectroscopy (NIRS) measurements were excluded and those in whom prefrontal cortical activities could not be detected due to physical characteristics were excluded. All subjects with chronic pain from other systemic diseases were also excluded.

Corneal sensitivity measurements were normal in at least one eye in all dry eye and control subjects (Table). At rest, all dry eye subjects were ocular discomfort positive (ODP) in at least one eye, and all healthy subjects were ocular discomfort-negative (ODN). All subjects were right-handed.
changed deoxy-Hb combined with persistently high oxy- and total-Hb values. At the same time, the number of signal-positive channels in the frontal head (SPCF) was calculated. Cerebral activity was defined as high oxy- and total-Hb values lasting ≥20 seconds including a 10-second delay in relation to the experimental task (Fig. 4). The reader of the data was not masked, but SPCFs were counted strictly according to the definition above.

Assessment of Ocular Discomfort Induced by Eye Opening Tasks in Dry Eye Patients by fNIRS

Similarly we conducted the same tests in dry eye patients with preexisting discomfort without artificial induction of ocular discomfort by Schirmer 1 tests.

Quantification of Changes in Prefrontal Cortex Activity Due to Changes in Ocular Stimuli in Normal Controls and Dry Eye

In each of the following conditions, the same methods were used to determine SPCF counts and draw topographic images (TOPOs): normal control negative for ocular discomfort (NC-ODN), normal control positive for ocular discomfort (NC-ODP), NC-ODP + 1% hyaluronic acid instillation (HAI), NC-ODP + 0.4% oxybuprocaine hydrochloride instillation, dry eye positive for ocular discomfort (DE-ODP), DE-ODP + 0.1% HAI, and DE-ODP + 0.4% oxybuprocaine hydrochloride installation (OBI). The effects of oxybuprocaine hydrochloride, an anesthetic, were confirmed in terms of decreases of ≥20 mm, as assessed using a Cochet-Bonnet corneal aesthesiometer.

Correlation Between Subjective Ocular Discomfort and Objective Prefrontal Cortex Activity

Subjective symptom scores were determined in relation to the degree of ocular discomfort at the time of the Schirmer 1 test (on a 10-point scale) for the following conditions: negative for ocular discomfort; positive for ocular discomfort; positive for ocular discomfort + 1% HAI; and positive for ocular discomfort.
+ 0.4% oxybuprocaine hydrochloride instillation. The correlation between ocular discomfort score and SPCF count was analyzed, and a laterality index was calculated based on distribution of SPCFs.

Statistical Analysis

The Wilcoxon rank sum test was used for statistical analysis. Spearman’s coefficients were also used for correlation analysis, and a binormal test was used for laterality index analysis. As to blink rate, numerical values were considered continuous quantities, and a paired Student’s t-test was used for intragroup analysis, while an unpaired Student’s t-test was used for intergroup analysis.

RESULTS

WAVE and TOPO findings are shown in Figure 5 for case 9 (normal control) and in Figure 6 for case 1 (dry eye). In normal controls prior to the Schirmer 1 test (NC-ODN), signal-positive channels in the frontal lobe were barely seen with the experimental task, and in control subjects after the Schirmer 1 test (NC-ODP), signals indicating persistently high oxy- and total-Hb values but not deoxy-Hb were detected over a broad area of the frontal lobe (Fig. 5). In dry eye patients (DE-ODP), as was the case with NC-ODP, signals were seen over a broad area with the experimental task (Fig. 6). In both normal controls and dry eye, as far as prefrontal cortex activities positive for ocular discomfort were concerned, signal-positive channels in the frontal lobe count increased with the experimental task, decreased with 1% HAI as a lubricant and almost disappeared with 0.4% OBI as an anesthetic (Figs. 5, 6).

Prefrontal Cortex Activity Under Each Ocular Stimulation Condition

Figure 7 shows changes of SPCF count for each normal control and dry eye condition. In NC-ODP, the mean SPCF count for the experimental task (eye opening) was low at 3.0 ± 1.5. After stimulating the eye using the Schirmer 1 test, the SPCF count significantly increased to 9.3 ± 2.2 (P = 0.026), significantly decreased locally with 1% HAI (lubricant) to 4.8 ± 1.7 (P = 0.042), and significantly decreased with 0.4% OBI (anesthetic) to 1.5 ± 0.8 (P = 0.027). In dry eye, ODP was confirmed at rest, and the mean SPCF count was similar to NC-ODP at 8.3 ± 4.4, decreasing locally with HAI to 5.0 ± 4.4 (P = 0.399) and decreasing significantly with OBI to 2.2 ± 3.1 (P = 0.046). In all 12 subjects, after combining healthy and dry eye subjects, the mean SPCF count for ODP was 8.8 ± 3.3, decreasing with HAI to 4.9 ± 3.1 (P = 0.029) and with OBI to 1.8 ± 2.0 (P = 0.005).

No significant difference was seen in laterality index with almost all conditions. Blink rate was significantly greater for NC-ODP than for NC-ODN and was significantly lower for DE-ODP + OBI than for DE-ODP.

For both normal controls and dry eye, a significant correlation existed between the count of SPCF and subjective complaint score (10 points for ocular discomfort at the time of the Schirmer 1 test). When combining dry eye patients and normal controls, a significant correlation existed between subjective ocular discomfort and objective prefrontal cortex activity (r = 0.65; Fig. 8). No significant correlation existed between blink rate and discomfort score.

DISCUSSION

Ocular discomfort caused by ocular surface stimuli is exacerbated when the eyes are open. Hence, by qualitatively...
and quantitatively changing the ocular surface stimuli, the blood flow changes, including frontal lobe activation, were quantified while eyes were open with spontaneous blinking as an experimental task. As optical path length cannot be set with ETG-100 and results are qualitative, a quantitative comparison of cerebral activation was performed based on signal-positive channels in SPCF count, or the number of cerebral activation patterns. The results of the study are summarized as follows: (1) in both dry eye patients and healthy subjects with ocular stimuli, changes in prefrontal cortex activities related to ocular discomfort were mostly comparable (Fig. 7); (2) prefrontal cortex activities related to ocular discomfort were seen regardless of dry eye type, laterality (uni- or bilateral), or absence of corneal and conjunctival epithelial disorders (case 1) (Table; Fig. 6); and (3) prefrontal cortex activities related to ocular discomfort exhibited a significant correlation to subjective symptoms (Fig. 8). These results are extremely similar to patient complaints observed in routine clinical settings, suggesting that ocular discomfort, a subjective complaint, can be objectively quantified.

Spontaneous blinking in the absence of discomfort under normal conditions did not activate the frontal lobe. Therefore, the frontal lobe activation observed during the experimental task with spontaneous blinking and stimuli is likely to represent ocular discomfort from difficulty in eye opening. Also, blinking is one of the major factors complicating the pathology and subjective symptoms of dry eye. The blinking reflex is complex and displays both voluntary and involuntary control. Despite being suppressed by general anesthesia, this primitive reflex remains even after removing the entire cerebrum. In animal models of dry eye with an underdeveloped frontal lobe, the eyelids are generally closed with ocular stimuli, and eyelid opening (suppression of the blinking reflex, which is a physiological need) is seen only in self-protective behavior. In humans, as far as blinking is concerned, relationships with dry eye and eye fatigue and the effects of volition and concentration on blinking have been reported. A previous study has shown the involvement of the frontal lobe and visual area. These findings suggest that, in humans, suppression of blinking due to subtle unpleasant stimuli in the anterior region of the eyes activates the frontal lobe.

This result of SPCF by fNIRS may be affected by skin blood flow and whole-body blood flow in the frontal head. In addition, there is no established method for detecting only the NIRS signal of the cerebral blood flow. However, in this study, because the extent of eyelid opening is monitored on the screen and excessive eye opening or squinting was forbidden under all conditions, its effect on blood flow measurement values in the frontal lobe is minimal. We plan to analyze the relationship between restricted blinking and frontal cortex activation in the future.

A previous study has shown that task difficulty affects frontal activity and complete elimination of these factors during measurements is difficult. The eye opening task selected for this study is a behavior that becomes more difficult with increased ocular discomfort. Further investigations are necessary to ascertain relationships of these factors to the extent of discomfort.

As another subjective disturbance factor, we reported that the subjective symptoms of dry eye are also affected by the patient’s personality traits.
Figure 7. Prefrontal cortex activity under each ocular stimulation condition. Changes of SPCF count (for 24-channels) for the six healthy subjects and six dry eye patients are shown for each condition. In NC-ODP, mean SPCF count for the experimental task (eye opening) was low at 3.0 ± 1.5. After stimulating the eye using the Schirmer 1 test, the SPCF count significantly increased to 9.3 ± 2.2 (P = 0.026), significantly decreased locally with 1% HAI (lubricant) to 4.8 ± 1.7 (P = 0.042), and significantly decreased with 0.4% OBI (anesthetic) to 1.5 ± 0.8 (P = 0.027). In dry eye, ODP was confirmed at rest, and the mean SPCF count was similar to NC-ODP at 8.3 ± 4.4, decreasing locally with HAI to 5.0 ± 4.4 (P = 0.399), and decreasing significantly with OBI to 2.2 ± 3.1 (P = 0.046). In all 12 subjects, after combining healthy and dry eye, mean SPCF count for ODP was 8.8 ± 3.3, decreasing with HAI to 4.9 ± 3.1 (P = 0.029), and with OBI to 1.8 ± 2.0 (P = 0.003). No significant changes were seen in the laterality index for almost all conditions, and the laterality index was dominant in the right direction at 57.6% ± 37.9% only in DE-ODP + HAI (P = 0.031). A significant intergroup difference in blink rate (blinks/m) was identified between NC-ODN (21.0 ± 15.4) and NC-ODP (27.0 ± 19.3; P = 0.037) and between DE-ODP (40.0 ± 11.8) and DE-ODP + OBI (25.0 ± 19.4; P = 0.023).

However, a study has shown that the suppressive effect of thinking by the cerebrum on sensation is 20%–30%, and thinking alone cannot completely negate the present results.

The overall picture of feelings in the human body has not been fully elucidated, and although studies have suggested the involvement of areas besides the prefrontal cortex, the results of this study on ocular discomfort show a clear correlation with prefrontal cortex activities. This correlates with past studies that found that feelings were localized in the frontal lobe.

As to past noninvasive techniques used to investigate discomfort, a study has shown not only frontal lobe activation but also broad cerebral activation in an air hunger model. Air hunger is a strong form of discomfort affecting survival and is qualitatively and quantitatively different from the subtle unpleasant stimuli in this study. However, like blinking, respiration is a special function that is controlled voluntarily and involuntarily, and artificial air hunger also represents a conflict to a physiological need. Studies have shown that a conflict between intention and sensation activates the frontal lobe. These findings suggest that ocular discomfort caused by the experimental task in this study activates the frontal lobe in various manners, and this can be detected as activity changes over a relatively broad area in the frontal lobe.

The number of subjects is a limitation in this study. We conducted this preliminary experiment on six subjects in each group based on our previous experience with three subjects. We plan to further investigate with a larger sample size to confirm the findings of this preliminary study.

Figure 8. Subjective discomfort and objective prefrontal cortex activity. The correlation between subjective discomfort score (10 points for ocular discomfort created by the Schirmer 1 test) and objective SPCF count was investigated. The correlation coefficient was 0.66 for healthy subjects (P = 0.001) and 0.61 for dry eye (P = 0.007), and a significant correlation was seen for both groups. When healthy and dry eye were combined, the correlation coefficient was 0.65 (P = 0.001), and a significant correlation was noted between subjective ocular discomfort and objective prefrontal cortex activity. The results suggest that subjective ocular discomfort caused by subtle ocular stimuli can be objectively quantified as increased prefrontal cortex activities when the eyes are open in subjects with artificial or natural dry eye.

Future studies will need to minimize the effects of disturbances, such as skin blood in the frontal head and/or systemic blood flow changes, on the frontal lobe signal. Further studies on the objective measurement of the effect of personality on dry eye symptoms, and measurement of discomfort in other eye diseases and in other organs such as dry mouth in patients with Sjogren syndrome are also important. As this is a new methodology in this field with few previous studies, specificity, sensitivity, and reproducibility issues need to be further assessed.

Conclusions

This study suggests the possibility that fNIRS can be used to directly, noninvasively, and objectively quantify subjective ocular discomfort caused by subtle unpleasant stimuli in dry eye patients in terms of frontal lobe activities. Frontal lobe activation related to discomfort in this study may result from conflict between volition and physiological need, and although the results represent only a part of discomfort, subjective discomfort may be objectively quantifiable, independent of subjective expressions.

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Objective Ocular Discomfort Assessed By fNIRS

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