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Effects of tenotomy surgery on congenital nystagmus waveforms in adult patients. Part I. Wavelet spectral analysis

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Abstract

Congenital nystagmus (CN) is an aperiodic oscillatory eye movement disorder. Horizontal rectus tenotomy with simple re-attachment has been proposed as a therapy for CN. This therapy might affect vision and/or eye movements. Another paper deals with improvements in visual acuity. This and the companion paper examine changes in eye movements. In this study, we examined the effect of tenotomy on nystagmus waveforms using wavelet spectral analysis. No common effect was found across the patients on the wavelet spectra of the CN beat, suggesting that tenotomy surgery has no effect, or only a quite small effect, on the waveform structure of CN.
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1. Introduction

Congenital nystagmus (CN) is an aperiodic oscillatory eye movement disorder of unknown etiology. Typical CN is conjugate, predominantly horizontal and manifests a variety of waveforms. CN can be a pendular type (symmetric or asymmetric bi-directional slow phase movements), a jerk type (alternating slow and fast phase movements, with the slow phases showing increasing velocity profiles) or their variations. Dell'Osso and Daroff (1975) have described at least 12 distinct waveforms. Fig. 1 shows examples of waveforms from our data set. Generally, an individual patient demonstrates more than one type of waveform. The characteristics of the waveforms depend on a variety of factors including orbital position (Dell'Osso, 1973), intensity of attempted fixation (Abadi & Dickinson, 1986; Dell'Osso, Flynn, & Daroff, 1974) and so on (cf., Leigh & Zee, 1999). This wide variety of waveforms makes the underlying mechanism hard to understand. For example, simple jerk type nystagmus waveforms can be thought of as the result of two mechanisms, one like an integrator with too much positive feedback (which gives the increasing velocity slow phase) and one like a saccadic eye movement (which resets the eye back to the target with a quick phase) (Optican & Zee, 1984). Such a simple, two-component mechanism is not as obvious for other waveforms, such as pendular CN, nor is it obvious what mechanism gives rise to the non-stationarity of the waveform within patients. Not surprisingly, there is no agreed upon model for all forms of nystagmus. Thus, to make our results as general as possible, we have used analytical methods that look for any changes in the nystagmus waveform, independent of any specific model or underlying mechanism. Such an approach is more robust, albeit less sensitive, than a model-based approach.

Decreased visual acuity is common in patients with CN. Visual sensitivity for both pattern and movement detection is reduced because of these eye movements (Abadi & Sandikcioglu, 1975). Some patients with CN exhibit compensations to improve their vision. For example, they can adopt an anomalous head position to shift the null position (area of minimal oscillation and better vision) to straight ahead (cf., von Noorden, Munoz, & Wong, 1987). This has led to the use of surgical procedures to effectively treat certain patients with congenital nystagmus. Dell'Osso and Flynn (1979) examined eye movements with infrared oculography, documenting the effect of extraocular muscle surgery on

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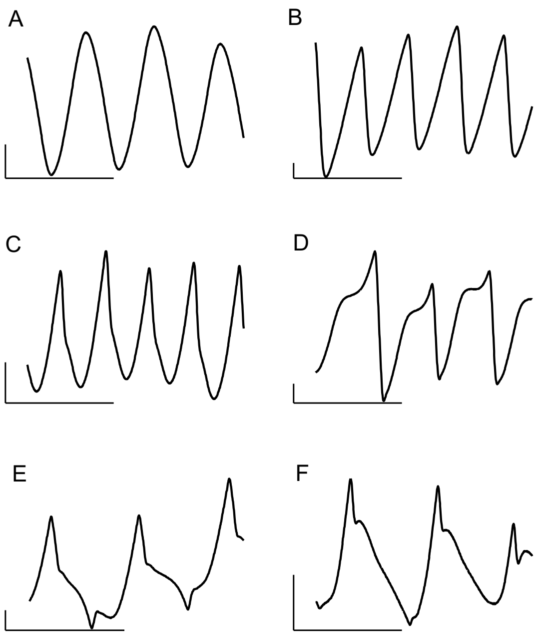

Fig. 1. Various types of waveforms recorded from patients with congenital nystagmus. The dominant waveforms for individual segments can be classified as pendular (A), jerk (B), pseudo-cycloid (C), dual jerk (D), pseudo-pendular (E) and pseudo-jerk (F) based on the closest type classified by Dell'Osso and Daroff (1975). Horizontal and vertical bars shown in left bottom of each panel indicates 0.5 s and 1°, respectively.

patients with CN. It was revealed and subsequently confirmed that the Andersen-Kestenbaum resection and recession procedure (AK procedure) produced several beneficial secondary effects on the CN in addition to its original aim (the expected shifting of the null position to the straight ahead position). It was found that the breadth of the null region (i.e., the range of gaze angles with damped CN) was increased and that the off-null CN was reduced in intensity, i.e. amplitude × frequency (Dell'Osso & Flynn, 1979; Flynn & Dell'Osso, 1979). Dell'Osso (1998) has proposed that the same broadening and damping could be achieved by performing a variation of the AK procedure, without the resection or recession. That is, simply tenotomizing the four horizontal recti and reattaching them at their original insertions. Recently, Dell'Osso, Hertle, Williams, and Jacob (1999) reported that both CN and SSN (see–saw nystagmus) were reduced (damped) after this new surgical procedure in an achiasmatic canine with CN and SSN. On the other hand, Wong and Tychsen (1999) reported the effect of the same tenotomy on congenital nystagmus in two macaque monkeys, showing no improvement in visual acuity and an increase in nystagmus intensity and retinal slip velocity. The effect of this new surgical treatment on human patients with CN is now being studied. Obviously, there are two important, but separate, questions to ask. One is whether the surgery improves the patient's visual performance, because this tells something about visual function that is clinically relevant. The other is whether the surgery affected the motor system that generates the nystagmus, because this may shed light on the etiology of the disease.

Sheth, Dell'Osso, Leigh, van Doren, and Peckham (1995) proposed the nystagmus acuity function (NAF), a monotonic increasing function of the duration of the foveation period and a monotonic decreasing function of positional error and magnitude of eye velocity during the foveation period. They documented that this measure was correlated with visual acuity. A recent study developed an extension of NAF, called NAFX (Jacobs & Dell'Osso, 1998). This new measure has been used in the preliminary study of the effect of tenotomy on CN, on some of the patients included in this study (Dell'Osso et al., 2000). Although NAF and its extension give a description of temporally local features of CN waveforms, these quantities are specifically designed to predict a patient's visual acuity, and are not necessarily suitable to describe global characteristics of the CN waveform. All the other conventional quantities used in the examinations of the difference associated with the surgical or non-surgical treatment of CN, including peak-to-peak amplitude, frequency and intensity (amplitude × frequency) of the nystagmus (Dell'Osso & Flynn, 1979; Mezawa, Ishikawa, & Ukai, 1990; Roberti, Russo, & Segrè, 1987; Sharma, Tandon, Kumar, & Anand, 2000) are one-dimensional quantities, which are poor at describing the generally complex CN waveforms. Spectral analysis based on the Fourier transform has been performed to examine the characteristics of some types of CN waveform (Reccia, Roberti, & Russo, 1989; Reccia, Roberti, Russo, & Segrè, 1986), and to obtain the nystagmus intensity measure (Reccia, Roberti, & Russo, 1990). That use of the spectral density for the examination of the effect of the surgery was limited to obtaining the intensity measure (product of peak frequency and its power). However, the spectral density function may be more useful to describe global features of waveforms than the conventional measures above described, in that the rich features of the waveforms can be more completely characterized.

Thus, the results from tenotomy surgery can be analyzed in two different ways, either by describing how the different components (e.g., slow and fast phases) are affected, or by considering the waveform holistically. As of yet, no computational model for CN generation has been established that fits all the data and is agreed upon by all researchers. Therefore, in our analyses of muscle tenotomies, we are using approaches that do not depend on any specific model of the generation of CN. Instead, we used two approaches to investigate surgery-related effects from different aspects: one is phenomenological (spectral analysis) and the other is from dynamical systems theory (dimensionality of underlying mechanism). Both approaches can be used without specifying a model of the generation of CN. The only assumption we make (in dynamical systems analysis, second paper) to interpret our data is that CN is generated by a deterministic system. We believe our approaches lead to reasonable quantifications of surgical effects.

In the study described in this paper, we applied a wavelet spectral analysis to the eye movements of patients with CN; the waveforms were described in terms of their *wavelet spectrum* (also called *wavelet variance*). The wavelet spectrum is a representation of energy for individual time scales. This quantity is a regularized version of a spectral density function and can be easily computed from the wavelet coefficients obtained by a wavelet transform (Percival & Walden, 2000). The concept of the wavelet analysis is similar to that of the Fourier analysis. However, there is an important difference in the basis functions used in these analyses. Whereas the Fourier analysis uses global basis functions extending over all time, the basis functions in wavelet analysis are localized in time. From a phenomenological point of view, the eye movements of patients with CN consist of several components that change with different time scales. The CN changes from quick to slow phases on a short time scale, whereas on larger time scales, the offset of beats, the shape of beats and sometimes the direction of beats change. The wavelet method provides a meaningful decomposition of the signals into several components associated with individual scales for the time series, whereas the Fourier transform only gives a meaningful decomposition if the CN waveform is periodic, which is usually not the case. An example for the eye movements of a patient with CN is shown in Fig. 2, which can be beneficial for interpreting the physical meaning of the resultant quantity, i.e. the wavelet spectrum.

A separate study is examining the effect of the tenotomy surgery on the visual performance of CN patients using visual acuity measures and the NAFX, whose preliminary results have been shown by Dell'Osso et al. (2000). The results of the studies suggest that, for a few patients, visual acuity increased after tenotomy surgery. The visual acuity measures for the patients included in the current analyses are shown in Table 1. Thus, we may infer that the tenotomy procedure had at most a small effect on the probability that a patient's acuity would improve. Despite those few cases of acuity improvement, it is still not known whether the tenotomy surgery changed the motor function of patients with CN. The beat pattern of CN might be able to change without any increase in visual acuity. Conversely, if the tenotomy surgery does affect the motor mechanism generating CN, we expect that common effects would be observed in eye movement waveforms across all the patients who received the same surgery. Examining this common effect is quite important for the search for a clue to the etiology of CN. This paper and its companion paper concentrate specifically on this aspect (*not* on visual performance on a patient-by-patient basis).

The present paper concentrates on the phenomenology of the effects of tenotomy surgery using wavelet spectral analysis. The wavelet spectral analysis described in this paper demonstrates whether there are changes in waveforms of CN, such as reducing or increasing the magnitude of the nystagmus beats. In the companion paper, we also examine changes in the underlying system by using a dimensionality measure. The dimensionality measure reflects the effective number of parameters in the underlying mechanism. Thus, the second paper concentrates more on the effect of the tenotomy surgery on the underlying mechanism of CN. These two approaches examine whether there are any effects of the tenotomy surgery on the mechanism of the generation of the CN waveform.

2. Methods

2.1. Patients

Eight patients (P2–P8 and P10) with CN, who had the tenotomy surgery were examined. P1 and P9 were excluded from the analyses in this and the companion paper, because of the difficulty in obtaining a reliable calibration of eye position data (P1) or difficulty in eye movement recordings using the technique described below (P9). Information on the patients is summarized in Table 1. The surgical procedure was as follows. The conjunctiva was incised near the horizontal recti and the tendons of the medial and lateral recti muscles were isolated on a muscle hook. An absorbable suture was placed no more than 1.0 mm posterior to the insertion of the tendon on the globe. The tendon was cut off the globe and immediately re-sutured to the globe at its original insertion site. The conjunctiva was closed with absorbable sutures and topical antibiotic steroid ointment placed in the eyes. All patients had the procedure performed under general anesthesia. Standard post-operative care consisted of daily application of antibiotic/steroid ointment or drops Q.I.D. for 7 days and follow-up examinations. All patients gave their informed consent prior to inclusion in the study, after receiving an explanation about the purpose of the study and risk of the surgery. The protocol was approved by the NEI Investigational Review Board.

2.2. Eye movement recording

The patients wore eye coils (Collewijn, Van Der Mark, & Jansen, 1975) on both eyes. Horizontal and vertical eye positions were recorded from both eyes using the scleral search coil technique (Fuchs & Robinson, 1966). The signals encoding eye position were recorded at 1 kHz with a precision of 12 bits. Each patient had either 1 or 3 recording sessions before the surgery and 1

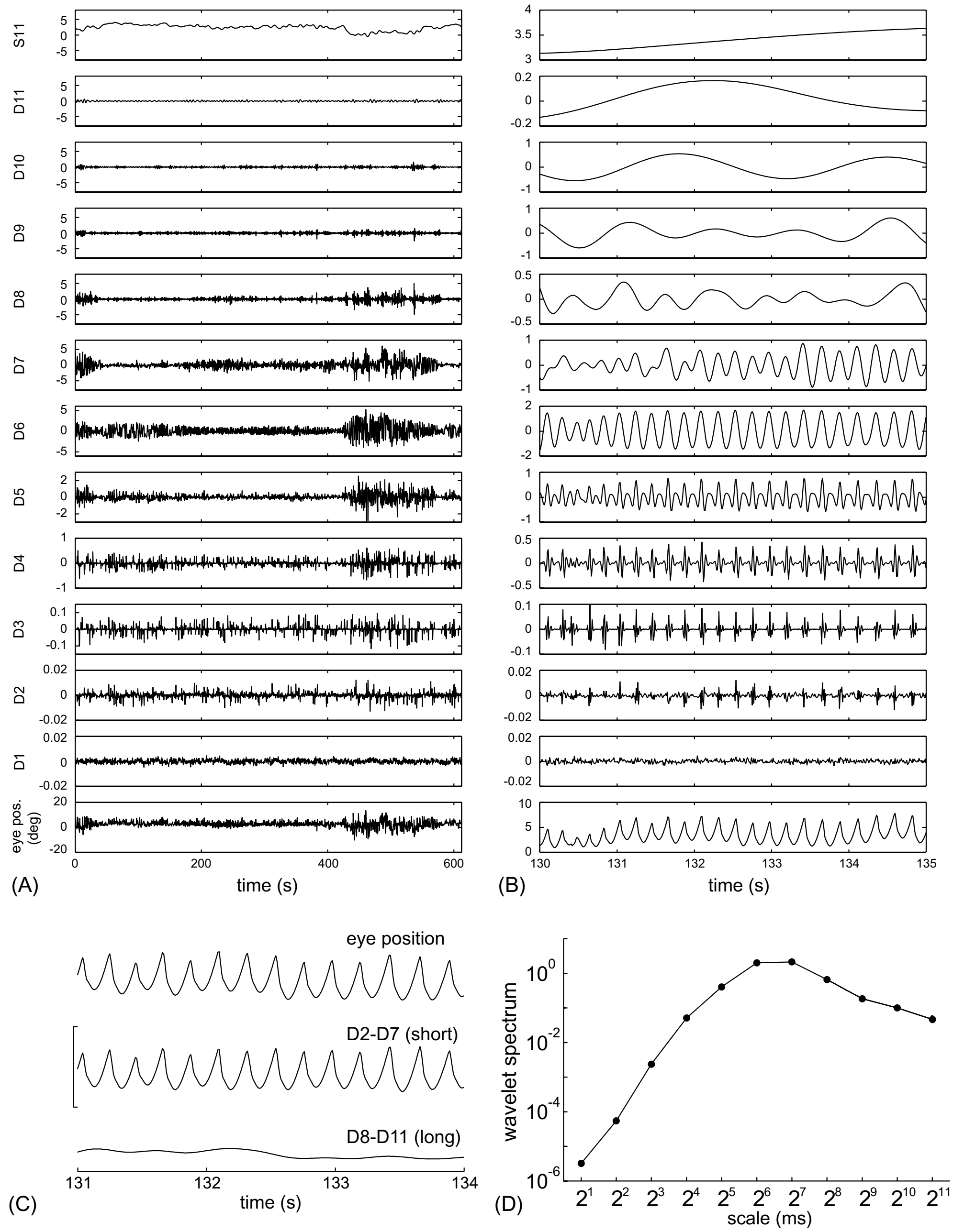

Fig. 2. Example of wavelet analysis. Decomposed signals of the eye movement when P5 looked straight ahead for about 10 min are shown (A: whole sequence, B: brief interval over 5 s starting at 130 s after beginning of the recording). From bottom to top, original eye position temporal profile, 1st–11th details (D1–D11) and the residual (S11) are shown (scale in degree). The eye movement, sum of D2–D7 and sum of D8–D11 during the interval of 3 s starting 131 s after beginning of the recording are shown in C. Upward deflections indicate leftward eye movement. The calibration bar indicates 10°. Wavelet spectrum computed from the whole sequence is shown in D.

recording session for each visit (at 1, 6, 26 and 52 weeks) after the surgery. For one patient (P10), the data recorded 52 weeks after the surgery was not available. Each recording session consisted of eight paradigms, of which the data for four paradigms were used in this study. In three of the four paradigms, the patients were encouraged to fixate a stationary target at known gaze angles, using one eye (right eye in paradigm 1, left eye in paradigm 2) or both eyes (paradigm 3). In these paradigms, the target was located, in turn, at 0°, 15° right, 15° left, 20° right, 20° left, 25° right, 25° left, 30° right and 30° left. The target stayed about 5 s at each location. This pattern was repeated 1–3 times for each recording session. In the remaining paradigm (paradigm 8), the patients were encouraged to look straight ahead for about 4–10 min using both eyes.

Table 1
Information about patients

PT	AGE	GROUP	P-EYE	VA PRE	VA POST	OTHERS
2	30	Albinism	Left	20/63	20/50	ET
3	39	Idiopath	None	20/40	20/25	OP
4	49	Albinism	Left	20/100	20/100	ET, APAN
5	39	Idiopath	None	20/40	20/32	OP, APAN
6	28	Albinism	Left	20/80	20/80	ET
7	39	Idiopath	Left	20/50	20/50	XT, APAN
8	20	Achiasma	Left	20/80	20/80	ET, HT
10	34	Albinism	Right	20/80	20/80	ET

PT, P-EYE, VA PRE and VA POST mean patient and their preferred eye, binocular visual acuity before and 52 weeks after the tenotomy surgery, respectively. The OTHERS column indicates other oculomotor findings as: ET: esotropia; XT: exotropia; HT: hypetropia; OP: orthophoria; APAN: acquired periodic alternating nystagmus.

2.3. Data analysis

2.3.1. Data

Before the wavelet analysis, the amplitude and the offset of eye position were calibrated using the method briefly stated here. The calibration parameters of the amplitude and offset for each eye's position were obtained by minimizing the difference between the target position and patient's mean eye position during the assumed foveation period (the interval when eye velocity was less than 5°/s, with a positional error of less than 10°). Note that the search coil was carefully calibrated before placing it on the patient's eye. The calibration parameters for one eye were obtained by using the data recorded when the patient looked at the target at a known visual angle with the same eye, during which the other eye was covered (paradigm 1 for right eye or paradigm 2 for left eye). This avoided miss-calibration due to strabismus, which many patients with CN had. Typically these patients looked at the target only using their preferred eye, even when both eyes were uncovered. The calibrated eye position data were re-sampled at 500 Hz for increased computational efficacy, without loss of information, in the subsequent analyses. In the wavelet analysis, the eye position data recorded when the patients performed paradigm 3 and paradigm 8 were used.

2.3.2. Wavelet analysis

The procedures to compute the wavelet coefficients, wavelet spectrum and signal decomposition is based on the standard one described in Percival and Walden (2000). The wavelet analysis was based on the maximal overlap discrete wavelet transform (MODWT). The least asymmetric filter (also called symmlet) with length of eight points was used throughout the wavelet analysis. Note that, our preliminary investigation showed that the analysis based on the MODWT was generally insensitive to the choice of the filters (not shown). The wavelet spectrum was always reported with its 95% confidence interval using a Chi-square approximation. The eye movements for the preferred eye, or for left eye if the patient had no preferred eye, were analyzed. For the data recorded when the patients performed paradigm 3 and paradigm 8, the wavelet analysis was carried out up to the 7th and 11th levels, respectively (the physical scale (τ_j) and the frequency interval associated with jth level wavelet coefficients is $2^{j-1}\Delta t$ (s) and $[1/(2^{j+1}\Delta t), 1/(2^{j}\Delta t)]$ (Hz) respectively, where $\Delta t = 0.002$ (s), see Percival & Walden (2000) for the details). All the analyses were done using the MATLAB program (MathWorks, Natick, MA) running on PCs.

Fig. 2 shows an example of wavelet-based decomposition (details of level 1–11 (denoted by D1–D11) and the residual (denoted by S11) of the eye movement signal when P5 looked straight ahead for about 10 min (paradigm 8) before the surgery. A decomposition signal for a particular level (scale) is obtained by inverse wavelet transformation only using the wavelet coefficients of the corresponding level (scale). Fig. 2A shows the whole sequence of the decomposition. To clearly indicate the relationship between levels (scales) and the characteristics of the CN waveform, the decomposition signals during an interval of 5 s is expanded in Fig. 2B. As seen in the eye position temporal profile (bottom panel in Fig. 2B), this patient exhibited a pseudo-cycloid type nystagmus of roughly 4–5 Hz during this interval, based on the classification of Dell'Osso & Daroff (1975). D1 detail has generally small amplitude and seems to be unrelated to the nature of each nystagmus beat, presumably reflecting measurement noise. D2–D5 details show transient oscillations synchronizing mainly with the quick phases (saccades) of the nystagmus. D5 detail is similar with D2–D4, but also seems to include, in part, a slow phase component of high acceleration after the quick phase. D6 and D7 details clearly synchronize with individual nystagmus beats. D7 detail is more sensitive to the amplitude of nystagmus beats than D6 detail. The higher details (D8–D11) are not associated with the individual beat structure of the CN. These details may reflect, in large part changes in the offset of beats, shape of beats or beat amplitude. Fig. 2C shows component signals of a 3 s segment of eye movement: sum of D2–D7 and sum of D8–D11. As seen in this figure, the sum of

D2–D7 is closely correlated with the nystagmus beats, while the sum of D8–D11 is not. The characteristics seen in D4 and D5 were somewhat variable depending on nystagmus waveforms. In some cases, D8 detail seemed to correlate with the nystagmus beat structure depending on waveforms. Details of the other levels showed quite similar characteristics over all the eye movement sequences we studied.

Fig. 2D shows the wavelet spectrum of the eye movement sequence shown in Fig. 2A. For scales τ_2–τ_7 (2^2–2^7 ms), the wavelet spectra increased monotonically as the time scales became large. This characteristic was seen for all the sequences we studied. For this patient, the wavelet spectra of scales τ_8–τ_{11} (2^8–2^{11} ms) decreased monotonically as the scales became large. However, this depended on patients and sometimes also on recording sessions (cf., Fig. 4).

3. Results

Fig. 3 compares eye movements with two components obtained from the decomposition based on the wavelet method (sum of D2–D7 and sum of D8–D11) of P3 during two brief intervals starting at 81 s (A) and 144 s (B) after beginning of the recording using paradigm 8. In Fig. 3, characteristic waveforms of CN can be clearly seen both before and after the surgery; this was common across all our patients.

Fig. 3 also demonstrates that the eye movements of patients are complex and the waveforms, e.g., shapes, magnitude of beats and so on, may vary over time even in a single recording session. We first point out that this characteristic may cause some confusion when one examines the effect of the treatment for CN. In the earlier interval (Fig. 3A, top), this patient exhibited predominantly dual jerk type waveforms with gradual change in amplitude before the surgery. During the identical interval in 1 week post-surgery, this patient exhibited bi-directional jerk type. These waveforms were very different from each other within this 3 s interval. However, in the later period (Fig. 3B), the pre- and post-operative waveforms were quite similar in terms of waveform shape (the dominant waveform shape was a bi-directional jerk type). Thus, the conclusions from these pre- and post-operative comparisons could be different if we compare waveforms of short duration. We saw more or less similar characteristics in the eye movements of all

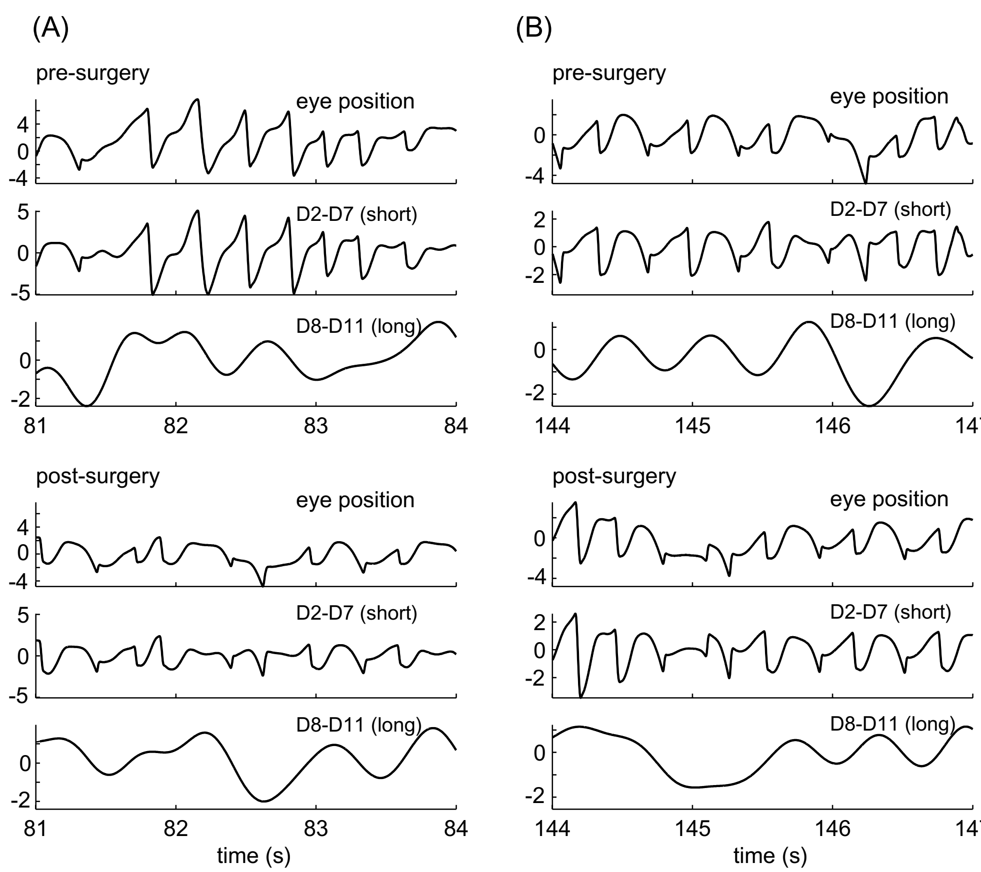

Fig. 3. Comparisons between pre- and post-operative eye movements of one patient (P3) during 3 s interval starting at 81 s (A) and 144 s (B) after beginning of the recording in which paradigm 8 was used. For each sequence, eye position, sum of D2–D7 (short scales component) and sum of D8–D11 (long scales component) are shown. Upward deflections indicate rightward eye movement (scale in degree).

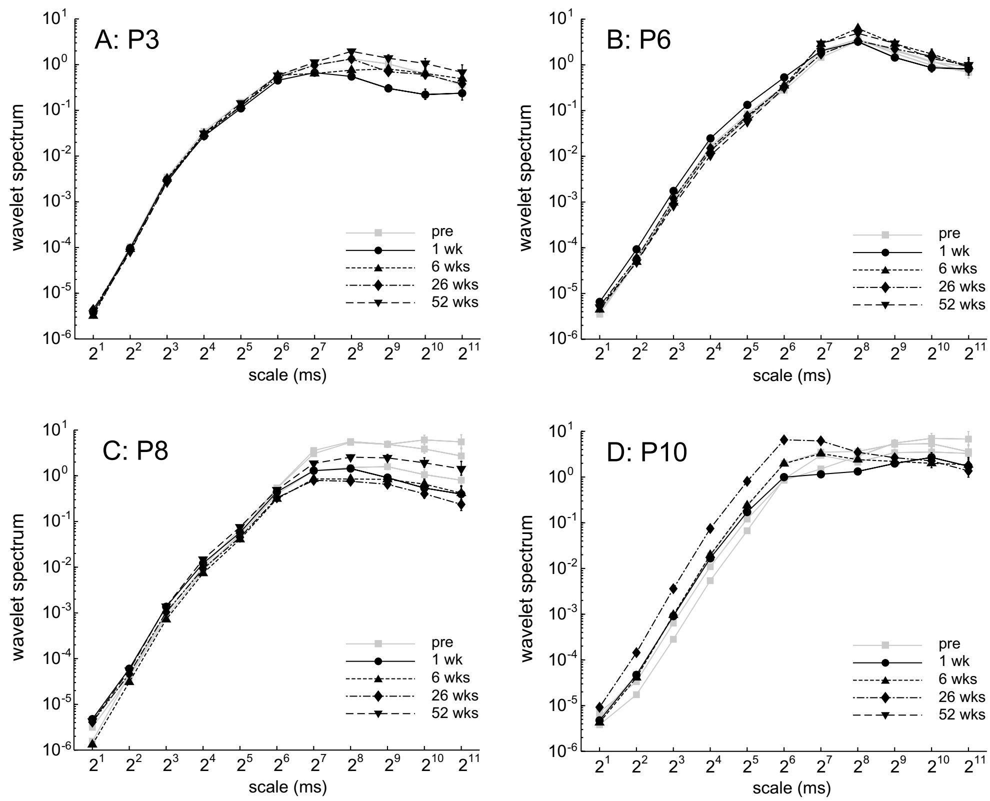

Fig. 4. The comparison of wavelet spectra among recording sessions for four patients. Error bar indicates 95% confident interval obtained by Chi-square approximation.

the patients. The result indicates that the comparison based on one segment of short intervals is not reliable. The use of segments with a long interval and/or a large number of observations with appropriate statistics is necessary to conduct a robust and reasonable examination of the effect of CN treatment.

Fig. 4 compares the wavelet spectrum among the recording sessions for four patients when they looked straight ahead for about 4–10 min (paradigm 8). In individual patients, there are some scales in which the 95% confidence intervals of the wavelet spectra in one recording session did not overlap those of the other sessions. (Note that, in many cases, 95% confidence intervals are smaller than the size of markers.) More importantly, this occurred even in the comparisons between two pre-surgery recording sessions. For example, we can see in Fig. 4C (gray symbols) that wavelet spectra for one pre-surgery recording session are significantly smaller than the other two at scales larger than 2^6. This indicates that non-overlapped 95% confidence intervals themselves do not directly indicate an effect of the surgery on the wavelet spectra. Therefore, although we can see from Fig. 4A significant differences in the wavelet spectrum between pre-operative values and post-operative values (1 week after the surgery) at larger scales (at 2^5–2^{10}, though not so clearly at 2^5 and 2^6), we cannot conclude that the differences are the effect of the surgery. These findings tell us that a few recordings in each visit are not enough to provide robust comparison of the effect of the surgery for individual patients, even if the length of the eye movement recording is as long as 4–10 min.

If the tenotomy really affects the oculomotor system that is critical for generating CN beats, there would be common effects of this surgery on CN waveforms across all of the patients who had the same surgical procedure. To understand this point, we concentrated on determining whether there is a common effect of the tenotomy on the CN waveform generation across the patients in the successive analyses. Fig. 5 summarizes the changes in wavelet spectra associated with the surgery (log-ratio of post-operative values to the pre-operative ones, $\log_{10}$(post/pre)) when the patients looked straight ahead for about 4–10 min. Here, we examined 95% confidence intervals of averaged log-ratio values across the patients. At all visits and at all scales, we did not find significant differences from the pre-surgery wavelet spectrum on the averaged log-ratio across the patients, whose 95% confidence intervals of the mean values always include 0 (see the rightmost column in Fig. 5), suggesting no, or small, effect of the tenotomy on CN waveform when the patients looked straight ahead.

We also studied the wavelet spectra when the patients fixated the targets at some eccentric positions. The eye

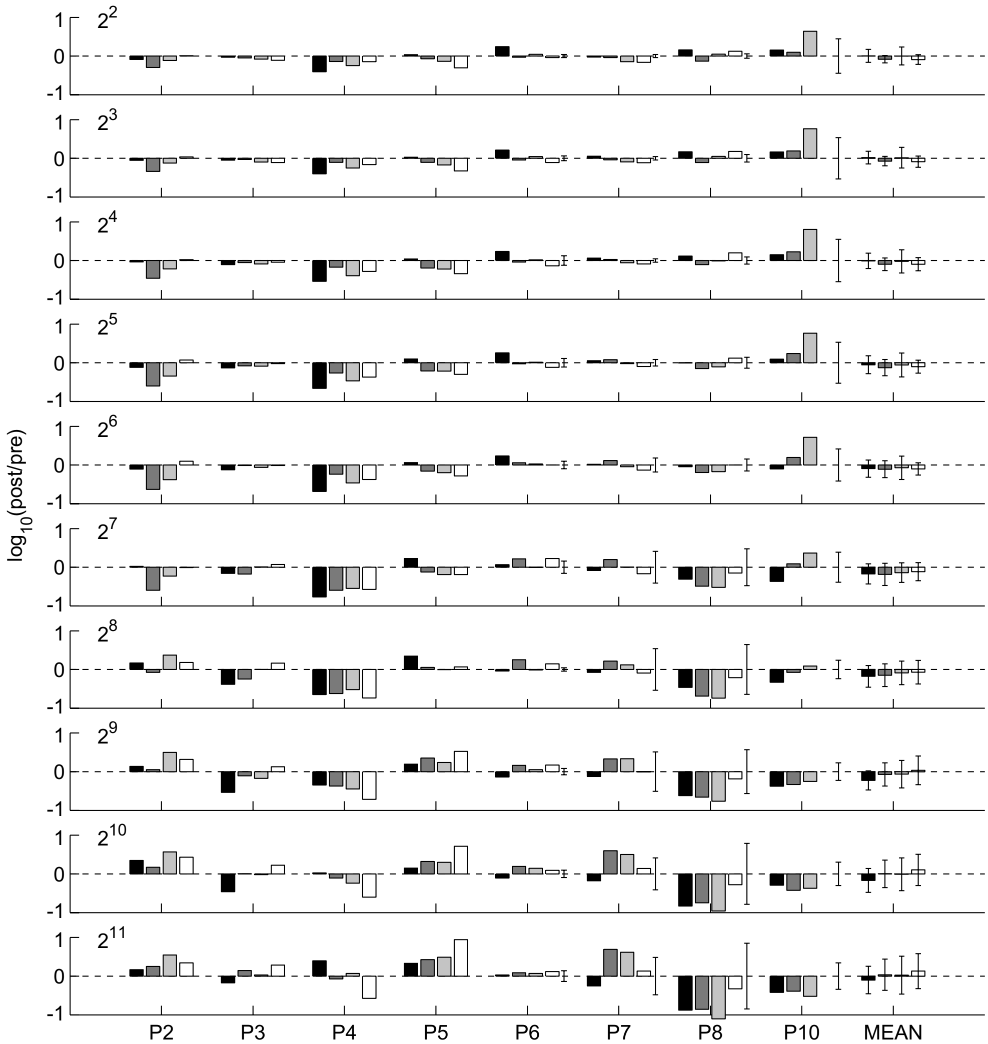

Fig. 5. Log-ratio of post-operative wavelet spectra to the pre-operative one when the patients looked straight ahead for 4–10 min. Each column shows the log-ratio values for each patient. In each column, the data of 1 week (black), 6weeks (dark gray), 26 weeks (right gray) and 52 weeks (white) after the surgery are shown from left to right. The lines inserted at the side of the data for four patients indicate ±2 SDs of pre-operative values. The rightmost column shows average log-ratio values across the patients. Error bars indicated 95% confidence intervals of the averages.

position data recorded using paradigm 3 were used to examine this. Available time length of the eye movement sequences for each target position (after deleting the saccadic excursion following the change in the target position) was about 4 s. Therefore our examinations for eccentric target position were limited to scales up to τ_7 (2^7 ms). However, it is expected that the components of these scales involve most of the properties of the nystagmus fine structures. Visual inspection of eye position data showed that several patients could not maintain or reach the eye position at some eccentric target positions. If the average eye position during the interval over which the wavelet spectra were computed was not within ±10° of target position, the data of this interval were excluded from the analysis. If more than one datum were available for one target position in one recording session, these data were averaged. Moreover, for the patients who had more than one recording session before the surgery, the pre-operative wavelet spectra of the individual patients were obtained by averaging over the sessions, prior to taking the average of all the patients. Fig. 6 shows the log-ratio of pre-operative wavelet spectra to the pre-operative one when the patients looked at the target at 15° left (A) and 15° right (B). We examined 95% confidence intervals of the average log-ratios across the patients. For both target positions, 95% confidence intervals generally include 0 (see rightmost column of Fig. 6). The numbers of the confidence intervals that do not include 0 were as small as nearly chance level when the patient looked at the target at 15° right. For 24 cases (6 scales × 4 post-operative visits), there were only two cases in which 95% confidence intervals did not include 0. When the patient looked at the target at 15° left, no confidence interval that did not

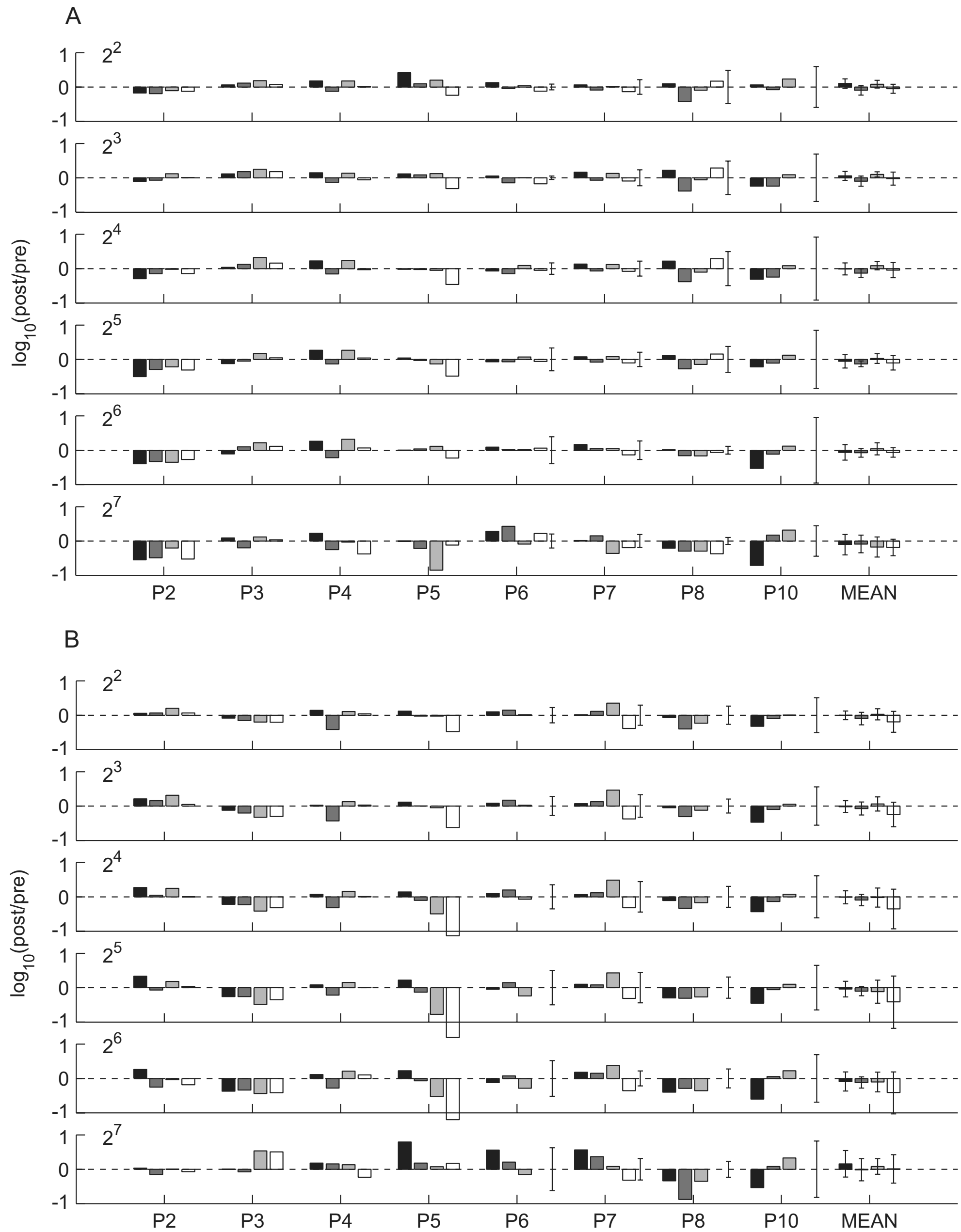

Fig. 6. Log-ratio of post-operative wavelet spectra to the pre-operative one when they fixated the target at eccentric positions (A: 15° right, B: 15° left). The other conventions as in Fig. 5.

include 0 in its range was found. This situation was common for the other eccentric positions. For all the target positions, 95% of the confidence intervals included 0, suggesting no significant changes.

It is known that the amplitude (also intensity) of CN more or less depends on the patient's orbital position (Dell'Osso, 1973; Dell'Osso et al., 1974). Which positions cause CN of large or small amplitude (also intensity) is different from patient to patient. Here, we examined whether the effect of the surgery depends on the original amplitude (energy) of the nystagmus before the surgery. We studied the wavelet spectra of the eye movements recorded when the patients ($N = 8$) looked at the target at which the sum of wavelet spectra of scales τ_2–τ_7 (2^2–2^7 ms) was minimal and maximal using the same methods described above. Note that wavelet details of the scales τ_2–τ_7 (2^2–2^7 ms) are correlated closely with the nystagmus beat structure as shown in Fig. 2. The same analysis described above showed that there were few cases in which 95% confidence intervals generally did not include 0 (0/24 for the minimal position and 1/24 for the maximal position).

4. Discussion

In this study, we examined the effects of tenotomy surgery on CN waveforms using the wavelet method. As shown in Fig. 2B, the wavelet based method successfully achieved decompositions that could be meaningfully related to features of the nystagmus. The decompositions of eye movement sequences revealed that the nystagmus, consisting of slow and quick phases, was generally represented in levels from 2 to 7 (sometimes, in levels 2–8). For pendular CN, which does not have a quick phase, the nystagmus beat structure was represented in levels from 4 to 7. This indicates that the well known beat structures of CN can be represented in the components of these lower levels. Moreover, the wavelet spectrum computed from long eye movement sequences (4–10 min) revealed that eye movements of patients with CN involve lower frequency components of relatively high energy (see Figs. 2D, 4 and 5). Fig. 2B shows that these components were not synchronized with the individual nystagmus beats. This is expected because these levels are associated with the frequency band that is much lower than the fundamental frequency of nystagmus beats (see Section 2 for the associated frequency band). They may reflect an irregularity of the nystagmus beats. Thus, wavelet methods successfully decompose the eye movement signals of CN into several meaningful components. This is quite useful in interpreting the physical meanings of the wavelet spectra.

Previous studies have described the CN waveforms in terms of amplitude, frequency and intensity of the nystagmus (Dell'Osso & Flynn, 1979; Mezawa et al., 1990; Roberti et al., 1987; Sharma et al., 2000). Each of them is a one dimensional quantity, which is poor at describing the generally complex CN waveforms. The wavelet spectrum simultaneously characterizes more features of eye movements of patients with CN than conventional measures. Moreover, the previous measures might sometimes be difficult to compute automatically when the eye movements have complex waveforms (e.g., Fig. 3). Furthermore, subjective corrections may be needed to compute these measures. In contrast, the wavelet spectrum is obtained by completely objective computations. Thus, for some applications, this measure may be superior to those used in the previous studies.

There is one concern when using spectral measures, because they are calculated from the amplitude, but not the phase, components of the signal. Thus two waveforms that look different in the time domain may have the same spectrum, because the appearance in the time domain is strongly determined by phase, which is not included in the spectrum. Thus, waveforms that have the same spectra but have different phase structures are not discriminated by our approach. Such an example is shown in Fig. 7. Fig. 7 shows a portion of a typical CN waveform (pre-operative eye movement of P3, top panel) and an artificial waveform that has the same spectra as this CN waveform but has a different phase structure. The artificial waveform was reconstructed with the inverse FFT with Fourier coefficients that are modified from those of the CN waveform shown in Fig. 7 (top) by shifting the phase by 180° for half of the coefficients chosen at random. Thus, the amplitude of the components are unchanged, and thus spectrum is unchanged. However, note that the artificial waveform (Fig. 7 bottom) has lost the defining characteristic feature of CN, which is the alternation of slow (but accelerating) and quick movement parts (Fig. 7 top). This is the kind of change that is not detected by spectral analyses. However, this breakdown of the alternating structure of the waveform would be easily observed from the time domain traces. Thus, if we assume that all waveforms in our study, both pre- and post-operatively, maintain a typical CN beat structure, the spectrum must reflect any change in the nystagmus. If there are separate slow and quick phase, the only possible change due to the surgery would be changes in beat structure, shapes of slow and/or quick movement parts or beat amplitude and frequency, which would alter the spectrum in a manner that would be detected by our approach.

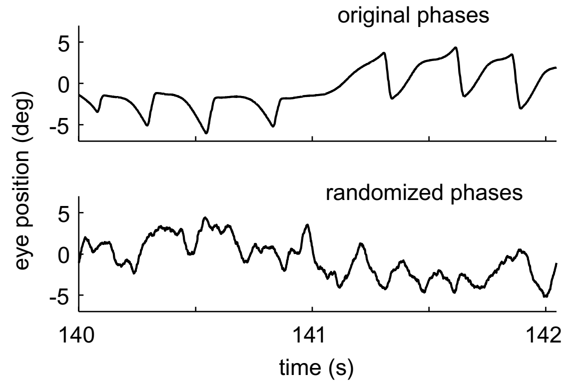

Fig. 7. A CN waveform and an example of an artificial waveform that has the same spectral content as that CN waveform, but a different phase structure.

A preliminary study of the effect of tenotomy surgery on visual acuity in CN patients was done using NAFX (Dell'Osso et al., 2000), as mentioned in Section 1. They compared the pre-operative NAFX value with that 6 weeks after the surgery. They reported that NAFX was increased for all the patients they examined, suggesting that potential visual performance of these patients was improved by the tenotomy surgery. In that preliminary study, five patients (P1–P5) were examined. Four of these five patients (P2–P5) were also included in the present study (we excluded P1 for the reason described in Section 2). We can see from Fig. 5 that the wavelet spectra for 6 weeks after the surgery on smaller scales (2^2–2^7) are less than those pre-surgery for these four patients, indicating that the amplitude of the nystagmus beats was smaller than the pre-surgery control. This result is consistent with the preliminary report. However, three of four patients whose data were added after the preliminary study (P6, P7 and P10) did not exhibit the reduced energy of nystagmus beats. Up to 52 weeks after the tenotomy, the binocular visual acuity measures were increased only for P2, P3 and P5 (see Table 1). Thus, the wavelet spectrum does not seem to be correlated with the changes in visual acuity, suggesting that the increases in visual acuity for these patients may not necessarily be due to changes in global properties of nystagmus waveforms. Because our study is not designed to examine the visual performance of individual patients, we do not discuss this point further. This issue is investigated in another study that will be presented elsewhere.

The effect of the tenotomy on congenital nystagmus waveforms has also been examined in two macaque monkeys (Wong & Tychsen, 1999). They demonstrated an increase in nystagmus intensity and retinal slip velocity resulting from the nystagmus, although nystagmus amplitude is not consistent between two monkeys they examined. Because only two monkeys were included in this study, their nystagmus waveforms were different, and their measures were different from ours, it is impossible to compare our results and theirs. Nonetheless, the two studies agree, in that the tenotomy certainly does not show any improvement in the motor behavior of the nystagmus.

The principal purpose of this study is to examine whether there is a common effect of the tenotomy on CN waveforms across the patient group (eight patients). If the tenotomy really affects the oculomotor system that is essential for generating CN beats, there would be common effects of this surgery on CN waveforms on all the patients who had the same surgical procedure. We think it is quite important to make this distinction, because the common effect may give a clue to the etiology of CN. In the findings described in this paper, there were few significant changes associated with the surgery on the fine structure of CN, i.e. the components on small time scales that are well correlated with the nystagmus beat structure. Moreover, there was also no significant change associated with the surgery in the component on larger time scales that may reflect changes in the offset of beats, shape of beats or beat amplitude. These findings suggest that the tenotomy surgery has no, or only small (relative to the random fluctuation), common effects on the waveform generator of the CN beats.

The wavelet spectral analysis is useful to examine the changes in waveform features of eye movements. However, the implications of that analysis do not go beyond phenomenological descriptions. Thus, the wavelet analysis may not be sufficient to explore the effect of the tenotomy on the underlying mechanism of CN. In the companion paper, this point will be examined using a more suitable method, i.e. dynamical systems analysis, which can quantify directly one property (dimensionality) of the underlying mechanism.

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