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The Effects of Afferent Stimulation on Congenital Nystagmus Foveation Periods

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Visual acuity in congenital nystagmus (CN) patients is related primarily to the duration of "foveation periods", during which the image of the target is relatively stationary in the foveal area. Thirteen individuals with CN were studied to test the hypothesis that somatosensory stimulation (vibration or electrical) of either the forehead or the neck damps CN and improves visual acuity. We identified characteristics of the nystagmus waveform that were likely to be important in determining visual acuity and combined these measures into an "acuity function" (NAFP) that correlated well with visual acuity ($r^2 = 0.91$). Statistically significant changes in NAFP were used to assess the effects of afferent stimulation; positive effects were found in nine subjects. Vibratory stimulation (especially on the neck) was found to be more effective than electrical stimulation. CN amplitude reduction alone was neither necessary nor sufficient to improve acuity. Foveation duration was the single most important factor determining acuity. Based on our findings, afferent stimulation should be considered as an alternative or additional treatment to improve visual acuity in CN patients.

Congenital nystagmus Somatosensory simulation Foveation Acuity

INTRODUCTION

Congenital nystagmus (CN) is an ocular motor oscillation that usually appears in early infancy. In spite of these oscillatory movements of the eyes, and the corresponding oscillation of all retinal images, many CN patients have relatively good (or normal) visual acuity. Most CN waveforms (i.e. the angular position of the eye vs time) contain periods during which the eyes are relatively stationary and the image of the target is in the foveal area. These *foveation periods* usually range from 20 to 150 msec, but may be as much as 400 msec in some individuals. Foveation-period duration has been found to be a good indicator of acuity (Dell'Osso, Flynn & Daroff, 1974; Dickinson & Abadi, 1985; Abadi & Dickinson, 1986).

An important and unique feature of CN is waveform variability, with most subjects exhibiting more than one of the 12 identified waveforms (Dell'Osso & Daroff, 1975). CN intensity and foveation-period duration depends on both the mental state (level of attention, excitement or anxiety) and the visual task (Dell'Osso, 1973; Abadi, Dickinson, Pascal, Whittle & Worfolk, 1991; Abadi & Dickinson, 1986). Therefore, visual acuity is also dependent on these variables *at the time of the acuity measurement*.

The following methods of treatment for CN are used with varying degrees of success:

(1) Surgery is usually limited to patients having either gaze-angle or convergence nulls. The first of the two most common surgical procedures rotates the eyes in a direction opposite and equal to the gaze-angle null, effectively eliminating a head turn. The second type of surgery recesses both medial recti muscles to produce divergence. This requires convergence to align the eyes, which in turn, damps the mystagmus (Sendler, Shallo-Hoffmann & Mühlendyck, 1990).

(2) Prisms take advantage of either gaze-angle or convergence nulls (or both) to reduce the nystagmus and improve acuity. *Version* prisms move the eyes toward their gaze-angle nulls for primary-position viewing, which improves vision and eliminates small head turns. *Vergence* prisms converge the eyes while viewing in primary position, thus reducing the nystagmus. To compensate for the accommodation induced by the vergence, −1.00 S O.U. must be added to the patient's refraction. A combination of vergence and version

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prisms (*composite* prisms) has also been used effectively (Dell'Osso *et al.*, 1974). Prism therapy cannot be used for large null angles, but can be used to "fine-tune" the null after surgery has been performed. Surgery and prisms are beneficial because they both shift the gaze-angle nulls (and eliminate head turns) and they reduce the fixation attempt or "effort to see", thereby enhancing the acuity further.

(3) Biofeedback takes advantage of CN amplitude reduction with relaxation and may depend more on an ability to calm oneself than the biofeedback itself. Biofeedback training has been found to suppress the nystagmus and improve acuity in the lab (Abadi, Carden & Simpson, 1980; Ciuffreda, Goldrich & Neary, 1982; Mezawa, Ishikawa & Ukai, 1990).

(4) Acupuncture involves the insertion of a needle in specific points in the neck muscle and mechanically or electrically stimulating it. A reduction in the intensity of nystagmus was reported in 9 of 16 patients (Ishikawa, Ozawa & Fujiyama, 1987).

(5) Drug therapy is effective for treating certain acquired forms of nystagmus. However, it is of limited benefit in the treatment of CN (Yee, Baloh & Honrubia, 1982; Larmande & Pautrizel, 1981).

(6) Soft contact lenses may damp CN and produce significant improvement in the visual acuity of some patients (Abadi, 1979; Allen & Davies, 1983; Matsubayashi, Fukushima & Tabuchi, 1992). Sensory information from the eyelids was found to be responsible for the CN reduction (Dell'Osso, Traccis, Abel & Erzurum, 1988).

Based on this finding, a preliminary study was performed on one subject (Dell'Osso, Leigh & Daroff, 1991) to explore the possibility that other cutaneous stimuli to the ophthalmic division of the trigeminal nerve (which supplies the eyelids), may damp CN. Both mechanical and electrical stimuli applied to the forehead, had a damping effect. Though the exact mechanism by which this effect occurs was not known, it was postulated that extraocular proprioception might play a role; these signals also travel to the brain stem with the ophthalmic division of the trigeminal nerve.

The above preliminary finding and the acupuncture study formed the foundation for this study of the effects on CN (and visual acuity) of afferent stimulation, applied to the forehead or the neck. There exist individuals with CN who have *neither* convergence nor gaze-angle nulls. Their acuity cannot be improved by therapies that exploit such nulls and both acupuncture and biofeedback are rarely employed therapies. Afferent stimulation could be an exclusive therapeutic treatment for this group. In others, it may be useful by itself or may be used in conjunction with other treatments to further improve acuity.

The hypothesis tested in this study was that afferent stimulation of either the ophthalmic division of the trigeminal nerve or of the skin over the neck muscle can be used therapeutically to damp CN and improve visual acuity.

METHODS

Recording

Horizontal eye movement recordings were made using the infrared (i.r.) reflection method. In the horizontal plane, the system is linear to $\pm 20°$ and monotonic to ± 25–$30°$ with a sensitivity of 0.25°. Eye velocities were obtained by analog differentiation of the position channels. The strip chart recording system was rectilinear (Beckman Type R612 Dynograph); total system bandwidth (position and velocity) was 0–100 Hz. Data were digitzed with 12-bit resolution using a DT2801 Data Translation board. The data were sampled at a frequency of 400 Hz and stored in a format compatible with ASYST software routines for later analysis.

Afferent stimulation

Either of two different afferent stimuli, suprathreshold vibration or electrical stimulation, were applied to the forehead (ophthalmic division of the trigeminal nerve) or the neck (over the upper insertion of sternocleidomastoid muscle) to study their effects on CN. Vibration at a frequency of ~ 100 Hz was applied using a cordless vibrator specially suited for stimulating specific points (AcuVibe, Vibrex Industries, Inc.). Electrical stimulation was applied using a Transcutaneous Electrical Nerve Stimulation (TENS) unit (EPIX XL TENS System). The stimulation was in the form of charge-balanced, biphasic pulses at a frequency of 100 Hz. The unit had two separate channels, one for the forehead and the other for the neck. The subject was asked to adjust the stimulation intensity so that he could feel it and was set at the maximum level before it became uncomfortable. Prickling sensations were minimized during stimulation by the use of specially constructed, concentric, bipolar surface electrodes (a 6.4 mm center electrode surrounded by a 1.6 mm thick ring with a 19.2 mm outer diameter).

Protocol

The subject was seated at the center of a 5 ft radius arc containing LED targets. The head was stabilized in primary position and the subject was instructed to move only the eyes to view each target as it was turned on. The i.r. signal from each eye was calibrated with the other eye behind cover to obtain accurate position information and document small tropias and phorias hidden by the nystagmus. Thirteen CN subjects participated in this study (2F/11M). They ranged in age from 8 to 49 years. The subjects were stimulated with both methods at both sites (hence four different paradigms) for a duration of approx. 5 sec. In 8 subjects, we also investigated the cumulative effects of afferent stimulation by stimulating for two 2–4 sec durations (with an interval of about 4 sec in between). Three CN patients included in this study came to the laboratory for diagnosis of their ocular motor disorder; only vibratory stimulation was applied in these cases.

Analysis

Data analysis (and filtering, if required), statistical computation of means and standard deviations, and graphical presentation were performed on an Everex 486 computer using the ASYST software for scientific computing. Digitized eye position data were differentiated using a 2-point, central-difference algorithm to obtain eye velocities (cut-off frequency of ~23 Hz). Data analysis of the variables and functions of interest was performed in 2-sec data segments, with overlapping 1-sec arrays. Foveation periods were defined as those periods of the CN cycle which lay within the "foveation window", consisting of eye velocities within ±4°/sec and positions within ±0.5° of the target (Dell'Osso & Leigh, 1992a). To calculate the average foveation time per cycle, the eye-position and eye-velocity arrays were analyzed for all points when both the ±0.5° and ±4°/sec limits of the predefined foveation window were satisfied. The effects of afferent stimulation on waveform variables associated with acuity were assessed by independent, one-tailed *t*-tests for significance at the 0.05 level.

Nystagmus Acuity Functions (NAF and NAFP)

Foveation periods play a major role in determining visual acuity in CN patients. There are three possible variables in the foveation period that could affect visual acuity:

(1) The duration of a foveation period (Tf), which may be the most important factor detemining visual acuity (Dell'Osso & Daroff, 1975; Dickinson & Abadi, 1985; Abadi & Dickinson, 1986).

(2) Accuracy of foveation from cycle to cycle (Abadi *et al.*, 1991; Bedell, White & Abplanalp, 1989; Dell'Osso, Van der Steen, Steinman & Collewijn, 1992), which is obtained from the standard deviation of foveation positions from zero (*SDp*).

(3) Velocities during the foveation periods, an indication of which can be obtained from the standard deviation of foveation velocities from zero (*SDv*) (Dell'Osso *et al.*, 1992).

In order to assess the effects of afferent stimulation on visual acuity in the CN subjects, it was necessary to develop a function that would be an accurate indicator of the subject's visual acuity. A Nystagmus Foveation Function (NFF), previously developed for detecting the CN null region, has been used as an indicator of acuity (Dell'Osso *et al.*, 1992). It is given by:

$$\mathrm{NFF} = \frac{Tfs}{(SDp)(SDv)},$$

where *Tfs* is the foveation time per second. This function has the following drawbacks when used as an indicator of acuity: (1) It does not exhibit a saturation with extended foveation time, i.e. the NFF function ever-increases for increasing values of *Tfs*, even though the visual acuity does not do so beyond a certain time interval. (2) If one of the standard deviations becomes zero, the function is undefined, even though acuity has a maximum limit. (3) The function may be too sensitive to variations in standard deviations. Preliminary analysis showed that this function was a poor indicator of acuity at higher levels. A better predictor of acuity must saturate to reasonable values for large values of *Tf* and small values of *SDp* and *SDv*.

As a first possibility, consider a Nystagmus Acuity Function (NAF), defined as:

$$\mathrm{NAF} = (1 - \sigma_{\mathrm{pv}})(1 - \mathrm{e}^{-Tf/\tau}),$$

where

$$\sigma^2_{\mathrm{pv}} = \frac{SDp^2 + SDv'^2}{2},\ SDv' = 0.125(SDv), \text{ and}$$

$$\tau = 33.3 \text{ msec.}$$

The function shows the expected saturating characteristic for *Tf*, since acuity cannot continue to increase as *Tf* increases. Acuity studies on normal subjects have shown that visual acuity continues to increase with exposure duration, approaching the maximum possible acuity at approx. 100 msec, and saturating at higher durations (Graham & Cook, 1937; Keesey, 1960). This implies that in CN patients, foveation period durations (*Tf*) of ~100 msec would result in a Snellen acuity close to 20/20 (Dell'Osso, 1982) and that, beyond that duration, the visual acuity would show very little improvement. This relationship between Snellen acuity and *Tf* can be represented by an exponentially increasing curve with a time constant τ of 33.3 msec, i.e. 3 time constants of the exponential curve would be 100 msec. σ_{pv} is the pooled estimator of both position and velocity variances, and gives a combined estimate of *SDp* and *SDv*. *SDv* is multiplied by a "position factor" to convert it to an equivalent position value (*SDv'*). This was necessary to have both position and velocity standard deviations in the same units (degrees), thus enabling the calculation of a pooled estimator. The value of the position factor was obtained using the "foveation window", i.e. 0.5°/4°/sec or 0.125 sec.

A simplified version of the NAF, the NAFP (Nystagmus Acuity Function for Position only), may be represented as:

$$\mathrm{NAFP} = (1 - SDp)(1 - \mathrm{e}^{-Tf/\tau}).$$

This function is an indicator of acuity based on the assumption that within the foveation window, the acuity is not strongly dependent on velocity, i.e. visual acuity for higher spatial frequencies is relatively unaffected by velocities below 4°/sec. This function is consistent with findings in normals (Westheimer & McKee, 1975; Barnes & Smith, 1981; Burr & Ross, 1982) that showed negligible detrimental effects on acuity with velocities up to about 4°/sec. It is clear that NAFP exponentially increases with increasing *Tf* and linearly decreases with increasing *SDp*. In order to use CN waveform criteria to predict visual acuity, the visual acuity in each CN subject should be limited *only* by the CN, i.e. in the absence of nystagmus, their best corrected acuity is assumed to be normal (20/20). In some individuals, the anxiety of

testing visual acuity causes a marked increase in the intensity of the CN. In such cases, the predicted values of acuity will exceed the measured values.

Certain assumptions are included in this function. They are: (1) Of the three variables (*Tf*, *SDp* and *SDv*), *Tf* is the dominant factor determining visual acuity. (2) The curve of visual acuity vs foveation time per cycle can be approximated by an exponential curve with a time constant of approx 33.3 msec. (3) The NAF(P) is a better indicator of visual acuity for CN patients that any of the individual variables or other functions. (4) The NAF(P) curve is proportional to acuity, and hence is a reasonably good indicator of the effect on acuity during the stimulation study. We investigated the validity of these assumptions before using the functions to assess the effects of afferent stimulation on acuity.

RESULTS

Acuity functions

Of the 13 subjects tested, two had significant afferent defects that limited their acuity and two had CN waveforms that substantially worsened to clinical observation while reading a Snellen chart. Their data were not used to correlate the functions derived from eye movement data during fixation of an LED in the dark and visual acuity on a Snellen chart during normal illumination. For the remaining 9 subjects, the means of the 3 variables (*Tf*, *SDp*, and *SDv*) and 3 functions (NFF, NAF, and NFAP), during fixation at primary position (without any stimulation), were plotted against the respective Snellen acuities (expressed as decimals).

Of the three variables, the standard deviations (*SDp* and *SDv*) were similar for these subjects and did not provide a useful measure of acuity. *SDp* values, for all subjects, lay between 0.21 and 0.27° and *SDv* values, for all subjects but one, were between 1.6 and 1.9°/sec. Tf exhibited an exponentially increasing function saturating in the region of 100 msec [see Fig. 1(a)]. This relationship between acuity and *Tf* agrees with previous studies (Abadi & Pascal, 1991; Abadi & Worfolk, 1989), in which the correlation between acuity (expressed as the log of the minimal angle of resolution) and the percentage of time of each slow phase that the velocities were $\leqslant 10°$/sec was found to be statistically significant.

We considered three candidate acuity functions, progressively including *Tf*, *SDp*, and *SDv*:

$$A_1 = f(Tf), \text{ where } f(Tf) = 1 - e^{-Tf/\tau};$$

$$A_2 = k(\text{NAF}), \text{ where NAF} = (1 - \sigma_{pv})(1 - 3^{-Tf/\tau});$$

and

$$A_3 = k(\text{NAFP}), \text{ where NAFP} = (1 - SDp)(1 - e^{-Tf/\tau}).$$

These functions were fit to the Snellen acuities using a non-linear, iterative, least-squares method. The resulting values of k, τ, the sum-squared residuals of the fit (SSE), and the correlation coefficient of the predicted and measured acuities (r^2) are listed in Table 1.

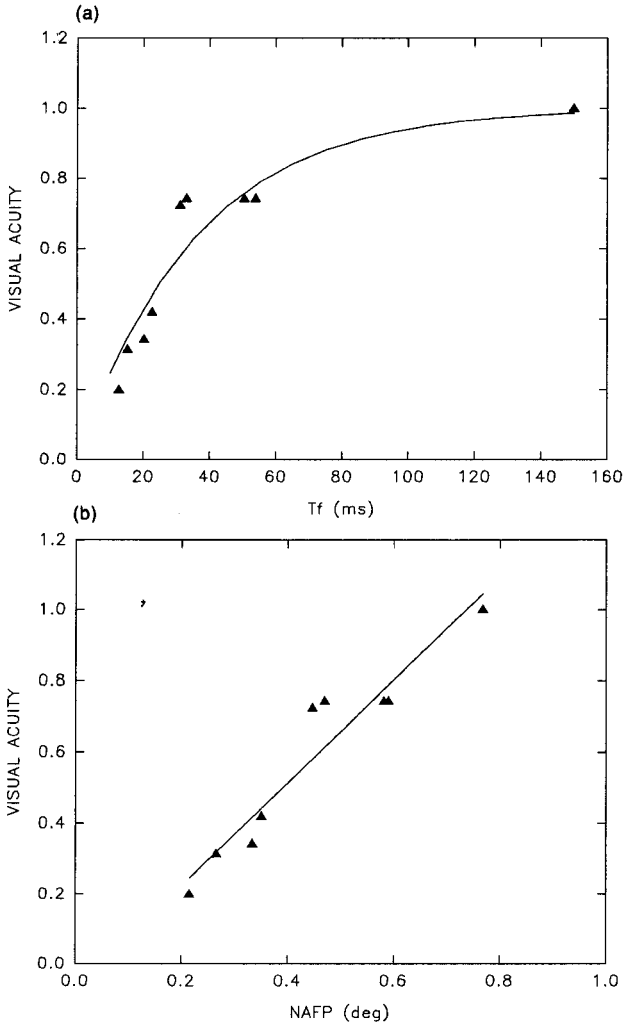

FIGURE 1. The relationship between acuity and both *Tf* (a) and NAFP (b). *Tf* is the foveation time per cycle in msec and NAFP is the Nystagmus Acuity Function for Position. Shown are the best-fitted curves:

$$\text{VISUAL ACUITY} = (1 - e^{-Tf/35.4}), \text{ for (a); and}$$
$$\text{VISUAL ACUITY} = 1.44(\text{NAFP}) - 0.065, \text{ for (b).}$$

The finding that the first function (A_1), which incorporates only the variable *Tf*, accounts for 90% of the acuity varience ($r^2 = 0.90$), suggests that the foveation time-per-cycle is the major contributor to visual acuity. Alternatively, it may only reflect the low *SDp*'s and *SDv*'s of our subjects. Also, the values of the time constants calculated independently for each function are close to the initially chosen value of 33.3 msec, predicted

TABLE 1. Regression results

	SSE	τ (±SD)	k	r^2
$f(Tf)$	0.0626	35.4 (±3.4)	1.00	0.90
NAF	0.0534	35.7 (±6.6)	1.31	0.91
NAFP	0.0548	36.5 (±6.8)	1.32	0.91

SSE: sum-squared errors.
$f(Tf)$: exponential function of foveation time with k fixed at 1.00.
NAF; NAFP: Nystagmus Acuity Functions.
τ, k: best-fit values in respective equations.
r^2: measure of linearity between function and Snellen acuity.
Refer to text for further details.

from earlier acuity studies. Thus, the first two assumptions inherent in the NAF and NAFP are justified for the group of subjects studied.

From the above analysis, the NAF and NAFP emerge as better indicators of acuity than any of the 3 variables or of NFF; they also are proportional to acuity [see Fig. 1(b)]. This justifies assumptions (3) and (4) presented in Methods. As is evident from Table 1, the inclusion of the standard deviations does improve the SSE values as well as the linearity. Although the NAF functions are only slightly better than *Tf* alone for these subjects, in subjects with more variable SD's, the NAF and NAFP should provide more accurate measures of acuity and be more generally applicable to the CN population.

For the group of subjects studied, the inclusion of the *SDv* term, i.e. the NAF function, gives approximately the same SSE values as the NAFP for the non-linear, least-squares fit of the functions to the data and, more importantly, they correlate equally well with acuity, as indicated by the r^2 values. The NAF and NAFP, therefore, are equivalent in their capacities to indicate changes in acuity in these subjects. Thus, for the purpose of this study, the NAFP was used as an indicator of acuity, using the best fit of the value of τ (36.5 msec) for these nine subjects, and was used for analyzing the effects of afferent stimulation on these subjects.

It is noteworthy that for NAFP (and NAF), the value of k obtained as a result of the non-linear, least-squares fit is about 1.32, i.e. $A = 1.32$(NAFP). Therefore, this equation predicts a maximum Snellen acuity (for a large value of τ and small *SDp*) of 1.32, i.e. 20/15, which agrees with the upper limit of clinically observed acuities (Glaser & Goodwin, 1990).

Afferent stimulation

Qualitatively, from eye-movement recordings, various effects were observed due to afferent stimulation. These have been categorized as positive and negative, depending upon the effects on the variables in relation to acuity.

Positive effects. The following three types of positive effects were observed, either alone or in combination with each other (refer to Fig. 2):

(1) decreased nystagmus amplitude with increased *Tf* [Fig. 2(a)];
(2) increased *Tf* [Fig. 2(b)]; and
(3) decreased *SDp* [Fig. 2(c)].

Negative effects. The following negative effects were observed as a result of afferent stimulation (refer to Fig. 3):

(1) increased amplitude with decreased *Tf* [Fig. 3(a)];
(2) decreased *Tf* [Fig. 3(b, c)]; and
(3) increased *SDp* [Fig. 3(d)].

Figure 3(c) has been included to illustrate that, in this case, even though the amplitude *decreased* during stimulation, there was a negative effect because *Tf* also decreased during stimulation. This shows that amplitude reduction *alone* is not sufficient to cause an improvement in acuity.

Quantitative results

The purpose of this study was to find out how afferent stimulation affects CN waveform characteristics at any given time, irrespective of what the absolute values of these variables were at the time of stimulation. CN patients show variability in waveform characteristics, and hence visual acuity. Figure 4 shows the idiosyncratic variation of NAFP with time over a 20-sec fixation period (without any stimulation) for three of our subjects. Figure 4(a) shows a subject with little variation, Fig. 4(b) shows a subject with larger variation, and Fig. 4(c) shows a subject whose NAFP tends to decrease with time. Therefore, statistical comparisons were made to assess the effects of afferent stimulation. Each of the stimulation trials was considered an independent event, without any effects on the next trial or from the previous trial.

The effects of afferent stimulation on two factors responsible for the visual acuity in CN subjects, i.e. foveation time per cycle and standard deviation of foveation position, were studied individually. For foveation time per cycle (*Tf*), a statistically significant (see below) increase during stimulation was defined as a positive effect and a significant decrease, as a negative effect. For standard deviation of position (*SDp*), a significant decrease during stimulation was defined as a positive effect and a significant increase, as a negative effect. Finally, to predict the effects of afferent stimulation on the visual acuity of the CN subjects, a significant increase in NAFP during stimulation was defined as a positive effect and a significant decrease, as a negative effect.

For the classification of effects of stimulation into positive, negative or no effects, one-tailed independent t-tests were performed on the respective quantities (*Tf*, *SDp*, NAFP) for the majority of trials (80%) at a probability level of 0.05. In order to carry out a statistical comparison, it is necessary to have sufficient data for each variable being tested, both before and during stimulation. In 20% of the trials, only qualitative comparisons could be made since: (1) the CN waveforms showed little or no foveation periods either during stimulation, before stimulation or both, and could not be statistically analysed (or only one value was available for intervals prior to or during stimulation, which is insufficient for performing statistical analysis), or (2) either of the intervals (prior to stimulation or during stimulation) had a duration which was too short to allow more than one value of the variable to be calculated. In these cases, the effects were determined from the changes in waveforms (if any) and from the available calculated variables.

The effects of afferent stimulation on *Tf* and NAFP are shown in Tables 2 and 3. They contain the combined effects obtained from both the above methods. Table 2 shows that 9 of 13 subjects showed a positive effect on *Tf* in response to at least one kind of stimulation.

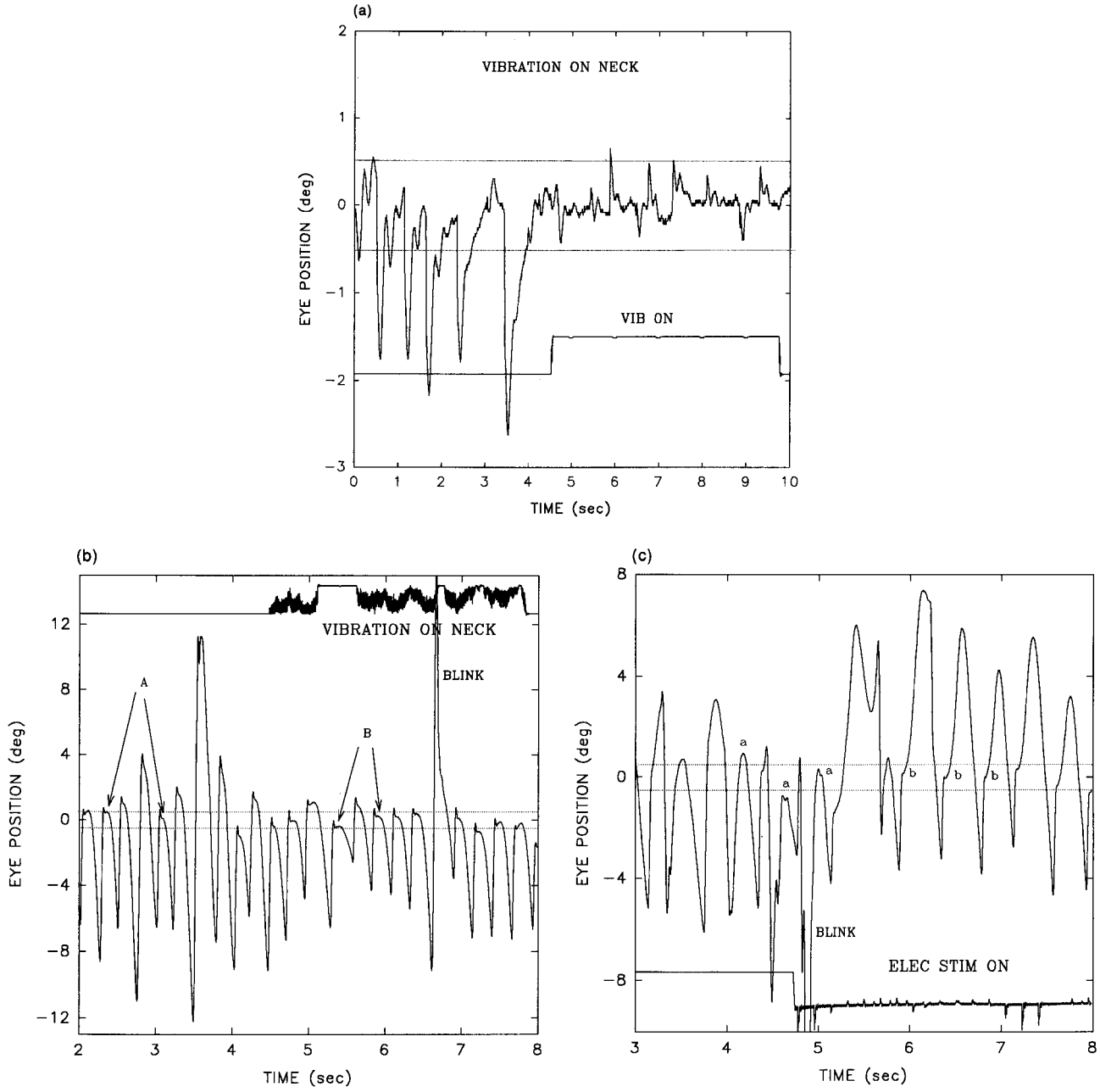

FIGURE 2. Positive effects of afferent stimulation showing (a) the reduction of amplitude of the nystagmus (from ~2–3° to ~0.2–0.5° peak-to-peak) and longer foveation period durations during vibration on the neck, and (b) an increase in the duration of the foveation periods during stimulation, but without much change in amplitude. Compare durations of foveation periods marked "A" (before stimulation) with those marked "B" (during stimulation). An effect of decreased variability in the positions of the foveation periods during stimulation is shown in (c). Compare the alignment of the foveation periods marked "a" (before stimulation) with those marked "b" (during stimulation). In this and Fig. 3, the stimulus traces indicate only the intervals of stimulation and not the stimulus signals. Noise in the vibration traces resulted from the effects of the vibration on the resistive contact responsible for this signal.

Negative effects, though less frequent across all trials, were also observed in 8 subjects. Except for two subjects during vibration on the forehead, all the effects were mutually exclusive with respect to positive or negative effects, i.e. subjects who showed a positive effect in response to a particular stimulation at a particular site did not show a negative effect with the same stimulation at the same site, although sometimes no effect was apparent. Vibration had a positive effect in a larger number of subjects (9 of 13), and with greater consistency, than electrical stimulation (4 of 10). Vibration on the neck was more consistent than vibration on the forehead.

The effects of afferent stimulation on *SDp* were fewer, and were approximately equally distributed between positive and negative effects. Vibration had a positive effect on *SDp* in 5 subjects when applied to the neck and in 2 subjects when applied to the forehead. Electrical stimulation had a positive effect on *SDp* in 3 subjects when applied to the neck and in 2 subjects when applied to the forehead.

To assess the effects of afferent stimulation on acuity, the effects on NAFP were ascertained, and are shown in Table 3. Vibration had a positive effect in 9 of 13 subjects, whereas electrical stimulation had a positive effect in 3 of 10 subjects. Vibration on the neck was more *consistently* positive than that on the forehead, even though they both had a positive effect in 5 subjects. There were fewer positive effects and more negative effects on NAFP as compared to those on *Tf*. This was due to the effects on *SDp* adding to those of *Tf*, as well as the non-linear relationship between *Tf* and NAFP. Except during vibration on the forehead for 3 subjects, the effects were mutually exclusive with respect to type and location of stimulation, i.e. they were either positive or negative for each subject. Three subjects (Nos 9, 10 and 12) responded only positively to afferent stimulation in general (i.e. they did not show any negative effects), and three subjects (Nos 3, 5 and 11) showed *only* negative effects.

In the trials involving two stimulation periods, the

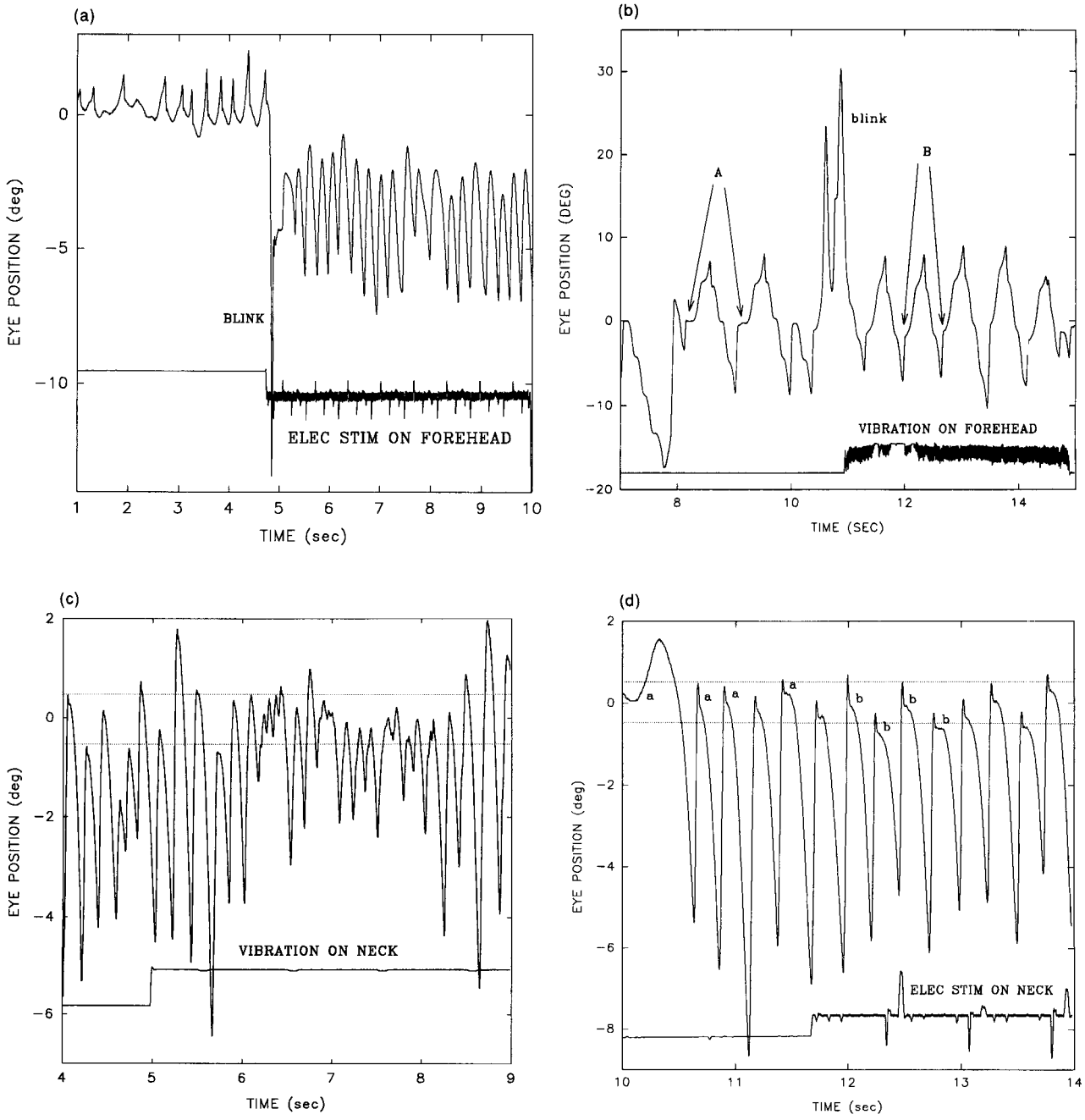

FIGURE 3. Negative effects of afferent stimulation, showing an increase in amplitude and a decrease in duration of foveation periods during stimulation (a). The slight shift in the position of the foveation periods during stimulation is probably due to a head movement in the opposite direction. (b) Decreased foveation time per cycle during stimulation. Compare the durations of the foveation periods marked "A" (before stimulation) with those marked "B" (during stimulation). The same effect, i.e. decreased foveation times during stimulation, is shown in (c). However, the amplitude *decreases* during stimulation. (d) Increased variability in the foveation positions during stimulation. Compare the alignment of the foveation periods marked "a" (before stimulation) with those marked "b" (during stimulation).

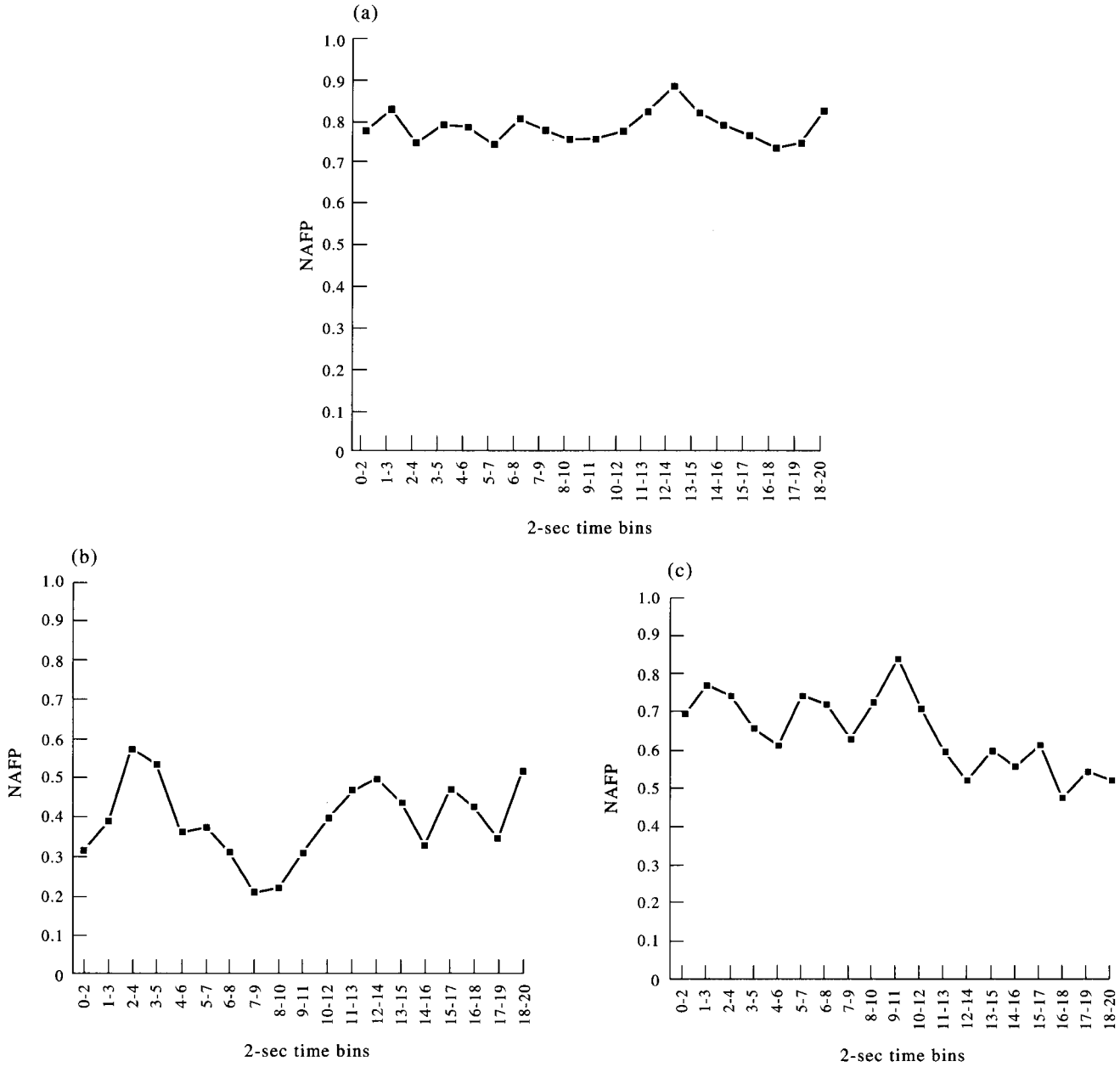

FIGURE 4. Variation of NAFP over a 20-sec period of fixation for three of the subjects participating in this study. (a) A subject with little variation. (b) A subject having larger variations. (c) A subject whose NAFP tends to decrease with time. The overlapping two-second data segments used for the NAFP calculations are shown on the abscissa.

possibility of positive effects on NAFP being cumulative was investigated. Cumulative positive effects were defined as those trials in which there were positive effects during both stimulation periods *and* a higher mean NAFP value during the second stimulation was higher than during the first. A positive cumulative effect was found in only one of 34 dual stimulation trials (Subject No. 10 during vibration on the neck).

Eight subjects were also tested for the effects of vibration while viewing a Snellen acuity chart under normal illumination conditions. Five of them showed improvements during vibration (ranging from 1 to 4 letters). All five belonged to the category of subjects who showed positive effects on the NAFP during vibration (Table 3).

DISCUSSION

The purpose of this study was to evaluate a possible treatment for CN, afferent stimulation of the forehead or neck by vibratory or electrical stimuli. Although prior studies (Ishikawa *et al.*, 1987; Dell'Osso *et al.*, 1991) suggested that such stimulation can influence CN, we wondered whether vision could be improved. Accordingly, a "Nystagmus Acuity Function" (NAFP) of the nystagmus waveform was developed that correlated well with visual acuity. We will: discuss how NAFP and it's component variables correlated with visual acuity; discuss the effects of afferent stimulation on NAFP, summarizing the positive and negative effects; and propose a hypothesis to account for these findings.

TABLE 2. Effects of afferent stimulation on *Tf*

	Positive effect				Negative effect				No effect			
	Electrical		Vibration		Electrical		Vibration		Electrical		Vibration	
Subject No.	F	N	F	N	F	N	F	N	F	N	F	N
1			1/2	1/2		1/2			1/1	1/2	1/2	1/2
2											1/1	1/1
3								1/1			1/1	
4			1/2	3/3					1/1	1/1	1/2	
5					3/3	2/3	2/3			1/3	1/3	3/3
6	1/3		2/4				1/4	1/2	2/3	1/1	1/4	1/2
7			2/3	2/3	1/3				2/3	2/2	1/3	1/3
8				2/3			2/3				1/3	1/3
9	2/3	1/3	1/3	1/3					1/3	2/3	2/3	2/3
10		1/2	1/3	3/3					3/3	1/2	2/3	
11								2/3	3/3	3/3	3/3	1/3
12		1/3		3/3					3/3	2/3	3/3	
13			1/3				1/3		3/3	3/3	1/3	3/3
Total	3/6	3/8	9/20	15/20	4/6	3/5	6/13	4/6	19/23	17/23	19/34	14/23

Effects were determined using the independent, one-tailed student's *t*-test at the 0.05 level on *Tf* values before and during stimulation, or by observation of waveform and measured values (20% of the trials).

F: Forehead; N: Neck.

The numbers in the columns indicate the number of times the corresponding stimulation paradigm had the corresponding effect out of the total number of times that paradigm was used. For example, for subject 6, "2/4" under "F" in "Vibration" under the "Positive Effects" column means that the subject had a positive effect, when stimulated by vibration on the forehead, 2 times out of 4.

The "Total" row gives an indication of the repeatability of that particular effect.

For example, "3/6" in the 1st column means that in all the subjects who showed a positive effect for electrical stimulation on the forehead at least once, they showed a positive effect three times out of 6.

Visual acuity

We found that the single variable of the nystagmus waveform that correlated best with visual acuity, was foveation duration (*Tf*). In addition to an adequate duration of the foveation period, the eye must be pointed at the target (i.e. a small standard deviation of foveation position) and must be still (i.e. a small standard deviation of foveation velocity). Although an extraretinal signal may play a part in visual perception in CN patients (Goldstein, Gottlob & Fendick, 1992), it is more likely to aid in the suppression of oscillopsia (perceived motion of the visual field) (Leigh, Dell'Osso, Yaniglos & Thurston, 1988; Dell'Osso & Leigh, 1992a, b; Bedell & Currie, 1993). Good acuity requires a stable image on the fovea, which can only occur during the foveation periods and not during the rest of the CN cycle, despite the continuous visual input. Oscillopsia suppression in CN has also been attributed to "perceptual adaptation" (Bedell, 1992). In practice, foveation periods are epochs of low velocity when the target image is on the fovea. Therefore, we expected that foveation duration would be the most important variable. A possible reason for the small contributions of *SDp* and *SDv* to acuity could be that the foveation criteria used (i.e. positions within $\pm 0.5^\circ$ and velocities within $\pm 4^\circ$/sec) were very stringent, limiting the positions and velocities of the data points to be analyzed to such small values as to not have any significant effects on acuity. If the foveation window

TABLE 3. Effects of afferent stimulation on NAFP

	Positive effect				Negative effect				No effect			
	Electrical		Vibration		Electrical		Vibration		Electrical		Vibration	
Subject No.	F	N	F	N	F	N	F	N	F	N	F	N
1			2/2			1/2			1/1	1/2		2/2
2											1/1	1/1
3								1/1			1/1	
4				3/3		1/1			1/1		2/2	
5					3/3	2/3	2/3			1/3	1/3	3/3
6			2/4				1/4	1/2	3/3	1/1	1/4	1/2
7			1/3	2/3	2/3	1/2	1/3		1/3	1/2	1/3	1/3
8				2/3			2/3				1/3	1/3
9	2/3	1/3	1/3						1/3	2/3	2/3	3/3
10		1/2		3/3					3/3	1/2	3/3	
11								2/3	3/3	3/3	3/3	1/3
12	1/3			2/3					2/3	3/3	3/3	1/3
13			1/3				1/3	1/3	3/3	3/3	1/3	2/3
Total	3/6	2/5	7/15	12/15	5/6	5/8	7/16	5/9	18/23	16/22	20/32	16/26

See Table 2 for abbreviations and explanations.

were broadened, as it must be for some individuals with CN, the effects of *SDp* and *SDv* on acuity would be more pronounced and the effects of *Tf*, reduced. For CN subjects with higher values of *Tf* (median $\simeq$ 80 msec), based on more loosely defined criteria, visual acuity was not highly correlated to foveation time in one study (Bedell & Loshin, 1991) but was in others (Abadi & Worfolk, 1989; Guo, Reinecke & Goldstein, 1990). The results of this study show that the duration of foveation required for near normal vision is in the range of 100 msec and that, beyond this range, acuity does not improve much further. The NAFP, used to correlate the CN waveform variables *Tf* and *SDp* with acuity, is given by:

$$\text{NAFP} = (1 - SDp)(1 - e^{-Tf/\tau}),$$

where *Tf* is the foveation time per cycle, *SDp* is the standard deviation of foveation position and $\tau = 33.3$ msec. Non-linear, least-squares fit of the acuity data for the 9 subjects studied gave a value of $\tau = 36.5$ msec, which supported our expected value and agreed well with the observation that there is little acuity improvement for *Tf* greater than 100 msec (Graham & Cook, 1937; Keesey, 1960). For the purpose of this study, this best-fitted value of τ (36.5 msec) was used in the NAFP equation for subsequent analysis. Linear regression analysis of NAFP vs. acuity for the 9 subjects gave an r^2 value of 0.91, demonstrating the high correlation between acuity and NAFP in these subjects, and that NAFP can be used to study the acuity effects of afferent stimulation in CN.

Afferent stimulation

In 9 of the 13 subjects, afferent stimulation induced an improvement (positive effect) in the CN waveform, and acuity, as inferred from increased NAFP values during stimulation (compared to before stimulation). Across these 9 subjects, positive effects were seen in 24/88 (27%) trials. Afferent stimulation affected one or more of the following CN waveform variables: amplitude, foveation time and the standard deviation in foveation position. The changes in these variables were judged (based on the NAFP) to be either advantageous (positive) or detrimental (negative) to visual acuity. Considering all trials across the 13 subjects, afferent stimulation caused a positive effect in 24/116 (21%) trials and a negative effect in 21/116 (19%) trials. Thus, an improvement in acuity was not a *consistent* effect of afferent stimulation. The maximum percentage of positive effects in a subject was 3/7 (43%), and the minimum percentage of positive effects was 1/12 (8%). Trials with two closely spaced stimuli demonstrated the transient nature of the effects and absence of cumulative effects.

Vibratory stimulation had a positive effect in a larger number of subjects (9 of 13) than electrical stimulation (3 of 10). In 9 subjects, positive vibratory effects occurred in 19/30 (63%) trials. In 3 subjects, positive electrical effects occurred in 5/11 (45%) trials. Thus, vibratory stimulation not only caused positive effects in a larger percent of subjects, but also caused them *more frequently*. Vibration may cause stimulation of deeper tissue and muscle, altering afferent proprioceptive signals to the nuclei of the upper spinal cord and brain stem. The forehead does not contain deep tissue; the greater effectiveness of vibration on the neck than on the forehead supports this explanation. The supra-threshold electrical stimulation may have only stimulated cutaneous afferents. One reason for the disparity in the effects from the two kinds of stimuli could be fiber differences and their neural pathways. Another possibility could be the anxiety of the subjects during the trials associated with the two kinds of stimuli. It is possible that naive subjects showed a higher level of anxiety *during* the mildly aversive electrical stimulation trials, which confounded the effects of afferent stimulation. We found no consistent differences across subjects between NAFP values prior to electrical and vibratory stimulation. This suggests that anxiety prior to stimulation was not a factor but does not rule out the negative effects of an unpleasant stimulus on the CN. Experience with electrical stimulation of patients to alleviate pain suggests that a tolerance can be built up; we expect that would reduce anxiety during stimulation and allow for more positive effects. Even though vibration applied to the two sites showed positive effects in the same number of subjects (5 of 13), these effects occurred more consistently during vibration on the neck (80%) than during vibration on the forehead (47%).

Negative effects (reduced NAFP values) were produced in 8 of the 13 subjects. However, if a positive effect was produced by a particular stimulus-site pair, a negative effect caused by the same pair was rare (only durng vibration on the forehead in three subjects). Thus, the effects were almost always either positive *or* negative (not both). The subjects sometimes showed one type of effect for a particular paradigm and a different effect for another, suggesting that the four stimulation paradigms affected each CN patient idiosyncratically. Hence, in order to assess the effects of afferent stimulation on CN patients with the aim of improving acuity, it is necessary to test each of the stimulation paradigms and consider for therapeutic intervention those that elicit a positive effect.

The positive and negative effects on NAFP are shown as Venn diagrams (Fig. 5), illustrating the contributions of each of the three variables (*Tf*, amplitude and *SDp*) as percentages of the total number of effects (positive or negative) in various combinations. A decrease in amplitude occurred in 54% of the positive effects on NAFP and 29% of the effects were caused by a positive effect on each of the three variables. A positive effect was never caused by decreased *SDp* or amplitude *alone*. However, 9% of the negative effects did occur as a result of increased *SDp* alone. Tf was involved in 100% of the positive NAFP effects, and in 91% of the negative effects; the contributions of the other two factors were smaller. This suggests that an improvement in acuity requires an increase in *Tf*.

We confirmed that a reduction in the CN amplitude *alone* is neither necessary nor sufficient to cause an improvement in acuity. Therefore, treatment of CN should be aimed more at increasing foveation time per

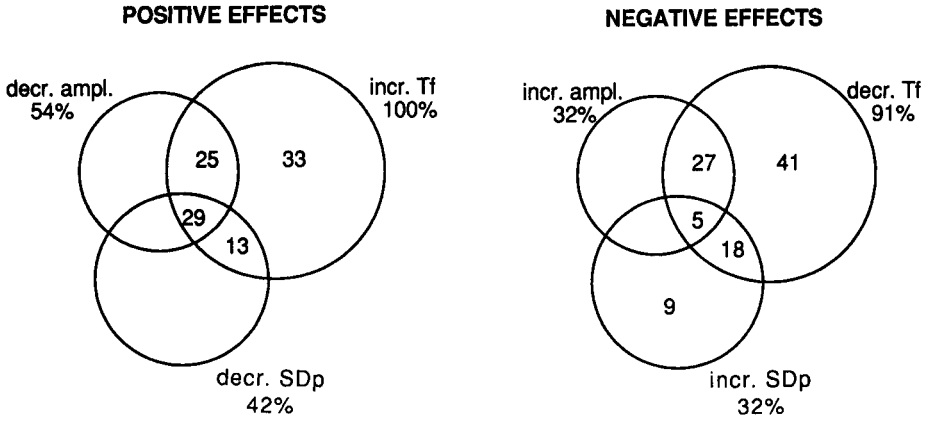

FIGURE 5. Venn diagrams of both the positive and negative effects of afferent stimulation on NAFP, illustrating the effects (as percentages of the total positive effects on NAFP) on each of the three variables amplitude, *Tf* and *SDp* (alone and in various combinations). NAFP is Nystagmus Acuity Function for Position, *Tf* is foveation duration and *SDp* is standard deviation of foveation position.

cycle than at damping the nystagmus. Eye movement recordings are necessary to accurately diagnose CN; they are also essential in determining whether afferent stimulation (or any other treatment) may be beneficial to the CN patient's acuity. Snellen-acuity improvements during vibratory stimulation (in 5 of 8 subjects) may also improve dynamic performance (pursuit, motion detection, etc.) and may benefit the subject to a greater extent than is evident by Snellen acuity measurements, which often carry with them an increase in anxiety.

Although no consistent relationship was found between the types of effects seen and the presence of gaze-angle and convergence nulls, positive effects were elicited in one subject who *lacked* both convergence and gaze-angle nulls. Therefore, afferent stimulation may provide a therapeutic benefit to patients who *cannot be helped* by exploitation of convergence or gaze-angle nulls.

In a separate study involving CN and gaze-holding failure (Dell'Osso, Weissman, Leigh, Abel & Sheth, 1993), vibration was applied on the forehead of one of the subjects, reducing CN amplitude. There was, however, no effect on the gaze-holding failure, the latter presumably due to a defective neural integrator.

Dell'Osso *et al.* (1991) reported that in one subject studied, *sub*-threshold electrical stimulation also seemed to damp the nystagmus. However, they used contact electrodes which were touched to the forehead only during the stimulation interval. We repeated this experiment using electrodes which were attached to the same subject *before* the stimulation was applied and sub-threshold stimulation was subsequently applied. No damping of the nystagmus was found in this case. Thus, the reported effect was elicited by the mechanical pressing of the electrodes on the subject's forehead to deliver the stimulus and *not* the sub-threshold electrical stimulation itself.

Mechanism

The reticular formation is responsible for regulating alertness, arousal and awareness (Role and Kelly, 1991). CN is highly dependent on these variables. This implies involvement of the reticular formation, either as a source or as a mediator of the CN oscillation. There are strong projections from the pontine reticular formation to the ocular motor nuclei (Highstein, Cohen & Matsunami, 1974; Büttner-Ennever & Büttner, 1988). There are also neurons in the reticular formation with receptive fields from both the face and neck (Darian-Smith, 1973). Afferents to the paramedian pontine reticular formation (PPRF) from the spinal trigeminal complex have been reported (Langer & Kaneko, 1984). Also, efferent pathways from PPRF to the neck musculature exist (Büttner-Ennever & Büttner, 1988) and may be responsible for the "head-nodding" frequently seen in CN patients. The fact that the afferent stimulation information from the forehead and neck is conveyed to the reticular formation and that the reticular formation innervates eye (and neck) musculature, suggests that the stimulation may be modulating the activity in the reticular system. The effects of afferent stimulation on the CN waveform could result from modulation of CN signals in the reticular formation.

In a study of three patients with left-sided neglect, vibration of the left neck muscles reduced the extent of the field neglect (Karnath, Christ & Hartje, 1993). The authors hypothesized that reduction was caused by a cortical-level shift in the egocentric frame of reference. We do not believe that our findings resulted from cortical influences since: (1) individuals with CN cannot voluntarily diminish their nystagmus; in fact, attempts to do so usually exacerbate it; (2) attempts to fixate or use the eyes worsen CN; (3) biofeedback diminishes CN by relaxing the subject; (4) we obtained positive effects on naive subjects with an anxiety-producing stimulus (electrical). Our hypothesis that an unconscious, brain stem pathway is responsible is consistent with the known characteristics of CN.

Although the exact mechanism of the effects if yet unknown, afferent stimulation can produce distinct improvements in CN waveform variables and acuity in some CN subjects, and should be considered as an alternative or an additional therapy in the treatment of CN patients. The mode of operation suggested by this study would be a transient application by the patient in instances when higher acuity is desirable. The possible

utility of long-term stimulation requires further investigation.

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