Task-Induced Stress and Motivation Decrease Foveation-Period Durations in Infantile Nystagmus Syndrome

Kwang M. Cham, Andrew J. Anderson, and Larry A. Abel

Purpose. To investigate the effect of visual demand, task-related physiological stress, and motivation on the nystagmus waveform of 19 subjects with infantile nystagmus syndrome (INS).

Methods. Subjects viewed a Landolt C of varying orientation and size, and indicated its orientation via arrow keys on a keyboard. Mental arithmetic was performed in conjunction with the visual task. Subjects then underwent a reward–penalty paradigm. Eye movements and heart rates were recorded during all experiments.

Results. Task-related physiological stress and motivation were reflected in an increase in heart rate and led to an increase in the amplitude, frequency, and intensity of the nystagmus waveform and a decrease in foveation-period durations. Changes in heart rate did not correlate with changes in waveform parameters for all experiments.

Conclusions. The results show, for the first time, the negative impact of task-induced stress and/or motivation on the characteristics of INS. This finding has important implications for individuals with INS, because stress may arise in everyday situations, such as driving or when undertaking an examination. (*Invest Ophthalmol Vis Sci.* 2008;49:2977–2984) DOI:10.1167/iovs.07-1626

Infantile nystagmus syndrome[1] (INS) is an involuntary ocular motor oscillation that manifests at or shortly after birth[2]—or, rarely, in later life[3]—and persists throughout life.[4,5] INS possesses certain characteristics that are individually imprecise but jointly, highly diagnostic. One is the often-stated observation that INS increases with fixation effort, fatigue, attention, mental concentration, and psychological factors (such as stress and anxiety).[6–8] However, only a few studies[6,7] (Wiggins et al. *IOVS* 2006:47:ARVO E-Abstract 2503) have been undertaken to assess and quantify the influence of psychological states on INS, with contradictory results.

Abadi and Dickinson[8] found that fixation effort qualitatively increased INS in eye-movement recordings, but no quantitative analyses were performed. In addition, the fixation target was a light-emitting diode (LED) that required little fixation effort. Tkalcevic and Abel[6] used a range of optotype targets and observed that INS parameters (amplitude, frequency, intensity, and foveation-period duration) did not worsen when a task was visually demanding possibly due to subjects lacking any motivational drive to perform. Nonetheless, they might have failed to induce maximum visual demand for several reasons, including unlimited viewing time of the optotypes. Also, practice trials were performed, which may have reduced stress as subjects became more familiar with the procedures. Finally, no physiological correlate of stress was used to monitor the subjects during testing.

Wiggins et al. (*IOVS* 2006:47:ARVO E-Abstract 2503) showed an increase in nystagmus intensity and skin conductance—an established indicator of physiological stress[9]—when INS subjects were stressed by an 88-dB siren. However, the foveation-period duration, which is a better predictor of visual performance than intensity,[4,10] was not reported. In addition, it would be preferable to induce stress visually or mentally rather than via an unpleasant auditory stimulus, as this would more closely parallel the everyday conditions that subjects with INS typically encounter when stressed. In a later study,[7] it was reported that increased visual demand leads to a reduction in the amplitude, frequency, and intensity of the nystagmus waveform, as well as prolonged foveation-period durations. However, task demand may have been reduced by having subjects perform the visual task in their null zones and with correction, and by not restricting viewing time. No measure of stress/arousal was used during testing. Nonetheless, both studies[6,7] are in agreement that visual demand per se does not worsen INS. In the present study, we addressed several limitations of previous studies and investigated the effect of visual demand, task-induced physiological stress, and motivation on the nystagmus waveform of INS subjects.

Methods

Our study conformed to the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the University of Melbourne, and all subjects gave written informed consent before participating. Eye-movement recordings were performed in 19 subjects with INS (8 men and 11 women, mean age 33 ± 13.2 years). The diagnosis of INS was primarily made by the referring ophthalmologist and was verified later on the basis of clinical examination and eye-movement recording analysis performed by the investigators. Sixteen subjects were classified as idiopathic, and three had associated visual disorders: One had retinitis pigmentosa, one had albinism, and one had congenital cataract and glaucoma. The subjects were free of medications and drugs. They were nonsmokers and were advised not to consume alcohol or coffee and to abstain from vigorous exercise at least 4 hours before the session. All subjects were naive with respect to the purpose of the study. Table 1 summarizes some of the relevant characteristics of the subjects. Pilot studies on normal observers ensured that the experimental paradigms used in the present study were significantly stressful or motivating to induce a significant change in heart rate.

Eye movements were recorded with a binocular infrared oculographic system (Microguide Corp., Downers Grove, IL).[11] The bandwidth was DC-100 Hz, and the sensitivity of the system was 1 min arc. Testing was performed at 1.5 m without correction and in darkness. Ten nonstrabismic subjects performed the task binocularly. The remaining nine subjects had manifest strabismus and thus undertook the experiments monocularly, with the nonstrabismic eye as the viewing eye during recordings. Head movement was minimized by cheek restraints, with residual movement monitored by a laser pointer strapped to the back of the head that then projected to a series of concentric circles, spaced approximately 1° apart at 1.85 m. The cheek restraints allowed the subjects to respond verbally without disrupting the eye-movement recordings. Eye movements were calibrated by

From the Department of Optometry and Vision Sciences, University of Melbourne, Melbourne, Victoria, Australia.

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Corresponding author: Larry A. Abel, Department of Optometry and Vision Sciences, University of Melbourne, Corner of Cardigan and Keppel Streets, Carlton, Victoria 3053, Australia; label@unimelb.edu.au.

TABLE 1. Clinical Data of 19 Subjects with INS

Subj.	Age/ Sex	Clinical Diagnosis	Distance-Corrected VA	Near Uncorrected VA	Wave.	Amp. (°)	Freq. (Hz)	Fov. (% ±2°, ≤4°/s)	Null (°)
A	22 F	Idiopathic	0.7	0.7	JL	1.79	3	66.67	0
B	22 F	Idiopathic	0.4	0.5	JL	3.76	2.5	18.55	0
C	15 F	Idiopathic	0.2	0.1	JLef	5.62	3	59.04	0
D	36 F	Idiopathic	0.8	0.8	JL	7.06	5.5	12.4	15°
E	39 M	Idiopathic	0.5	0.5	JL	1.71	3	57.75	~ −35°
F	30 M	Idiopathic	0.8	0.8	JR	2.71	5.5	12.75	~35°
G	42 M	Idiopathic	0.6	0.7	JL	2.1	4	45.43	20°
H	20 F	Idiopathic	0.3	0.3	JL	1.07	3	40.92	15°
I	52 M	Idiopathic	0.1	0.1	JLef	0.42	1.5	96.45	0
J	45 M	Idiopathic	0	0	JRef	0.9	3.5	85.81	0
K	15 F	Idiopathic	0.1	0.1	JRef	0.46	0.5	97.94	0
L	46 F	Idiopathic	0.9	0.9	JR & RPC	2.2	4	25.93	10°
M	11 F	Idiopathic	0	0	JLef	0.6	1	99.19	0
N	33 F	Idiopathic	0.6	0.7	DJL	3.22	3	19.23	0
O	16 M	Idiopathic	1.2	1.2	PPfs	4.56	2.5	39.73	0
P	13 M	Idiopathic	0.2	0.3	JR	3.34	3	52.42	−15°
Q	41 F	RP	1.5	1.5	JL	1.39	4	31.58	0
R	28 M	Albinism	0.6	0.7	RPC	6.56	4	22.07	15°
S	29 F	Cong. cataract & glaucoma	0.7	0.7	JL	3.53	3.5	40.28	0

Waveform parameters were recorded at 1.6 m. Ages are in years. VA was recorded binocularly in logMAR. Subj., subject; Cong., congenital; RP, retinitis pigmentosa; Wave., waveform; Amp., amplitude; Freq., frequency; Fov., foveation-period durations. Nystagmus waveforms were: jerk (J), dual jerk (DJ), pseudocycloid (PC), jerk with extended foveation (Jef), and pseudopendular with foveating saccades (PPfs). R and L denote right and left eyes. The null zones of subjects E and F were estimated clinically, because of the limited range of the infrared oculographic system.

consecutively presenting LEDs from −20° to +20° mounted on a 1.6-m arc in radius at 1.6 m. Fixation data were scaled with a best-fit regression line.

We selected heart rate as a physiological variable related to stress/motivation in this study, because of the ready availability of instrumentation and the ease of monitoring by noninvasive means. Heart-rate recordings were obtained with an amplifier (model 801; Neuroscientific Corp, Farmingdale, NY) that has a gain of 1000 and bandwidth of 1 to 300 Hz. Gold-capped surface electrodes with electrode cream were secured on both upper forearms with the reference electrode on the right ear. Eye position and heart-rate signals were digitized at 1000 Hz with 12-bit resolution. A baseline heart rate was obtained during the calibration trial. Subsequently, the heart rates of each subject were measured in conjunction with the eye-movement recordings for all experiments.

The present study consisted of three parts, namely the *unrestricted-viewing*, *restricted-viewing*, and the *reward-manipulation* tasks. Baseline waveform parameters were obtained by averaging over 15 s of primary gaze position during calibration at 1.6 m. In the *unrestricted-viewing* task, logMAR equivalent Landolt Cs of various orientations (up, down, left, and right) and angular size (ranging from −0.1 to 1.2 logMAR in 0.1 steps) were presented individually in the center of a 19-in. flat-screen LCD monitor of 73-cd/m^2 background luminance. Each subject was instructed to press one of four arrow keys on a computer keyboard that corresponded to the orientation of the Landolt C. The viewing time for each optotype was unlimited, though prompt responses were encouraged. Resolution thresholds were determined by a one-up/two-down staircase presentation with asymmetric step sizes (0.2-logMAR step decrement and 0.1-logMAR step increment). Landolt Cs were presented in descending order, starting with the largest optotype size (logMAR 1.2). Orientation was randomized by the computer. The trial was completed when four reversals were obtained. If the subject failed to see the largest optotype or detected the smallest optotype presented, testing was terminated.

In the *restricted-viewing* task, the experimental protocols were largely the same as for the *unrestricted-viewing* task. However, the Landolt C targets were presented for a limited time and were followed by a 100-ms visual mask, with a central red fixation cross, to eliminate any aftereffects. The subject could respond only when the visual mask disappeared, leaving the fixation cross on the screen. To increase stress, the subjects were informed only about the nature of the visual task and how to respond using the arrow keys, but not *when* to respond (unclear task difficulty). After several trials, if the subjects still failed to work out the correct sequence in responding to the optotypes, further instructions were given. As testing continued, stimulus presentation time decreased (Table 2). If the subject failed to respond within one second, it was considered a miss, and the same-sized optotype, but of random orientation, was then presented. Mental arithmetic (serial subtraction of 17 from 700) with verbalization was performed in conjunction with the visual task. Annoying verbal prompts (e.g., "please respond now, you are taking too much time") were delivered when the subject exceeded the allocated 5-second response time for the mental arithmetic task. The trial ended when 10 reversals were obtained or when the largest/smallest optotype was detected.

As our purpose was to increase the visual demand by making the task as stressful as possible, no practice runs were conducted. In addition, all subjects performed the *restricted-viewing* task first before undertaking the *unrestricted-viewing* task. We chose not to randomize the task order, as increased familiarity (analogous to giving practice runs) with the task could reduce the task-induced stress. The increase in reversals in *the restricted-viewing* task (10 vs. 4) was to keep the subjects at a near-threshold letter size for an extended period.

Subsequently, the *reward-manipulation* task was performed. The experimental protocols were the same as for the *restricted-viewing*

TABLE 2. Stimulus Presentation Time

LogMAR Acuity	Presentation Period (s)
1.2	2.000
1.1	1.500
1.0	1.000
0.9	0.631
0.8	0.562
0.7	0.501
0.6	0.447
0.5	0.398
0.4	0.355
0.3	0.316
0.2	0.282
0.1	0.251
0.0	0.224
−0.1	0.200

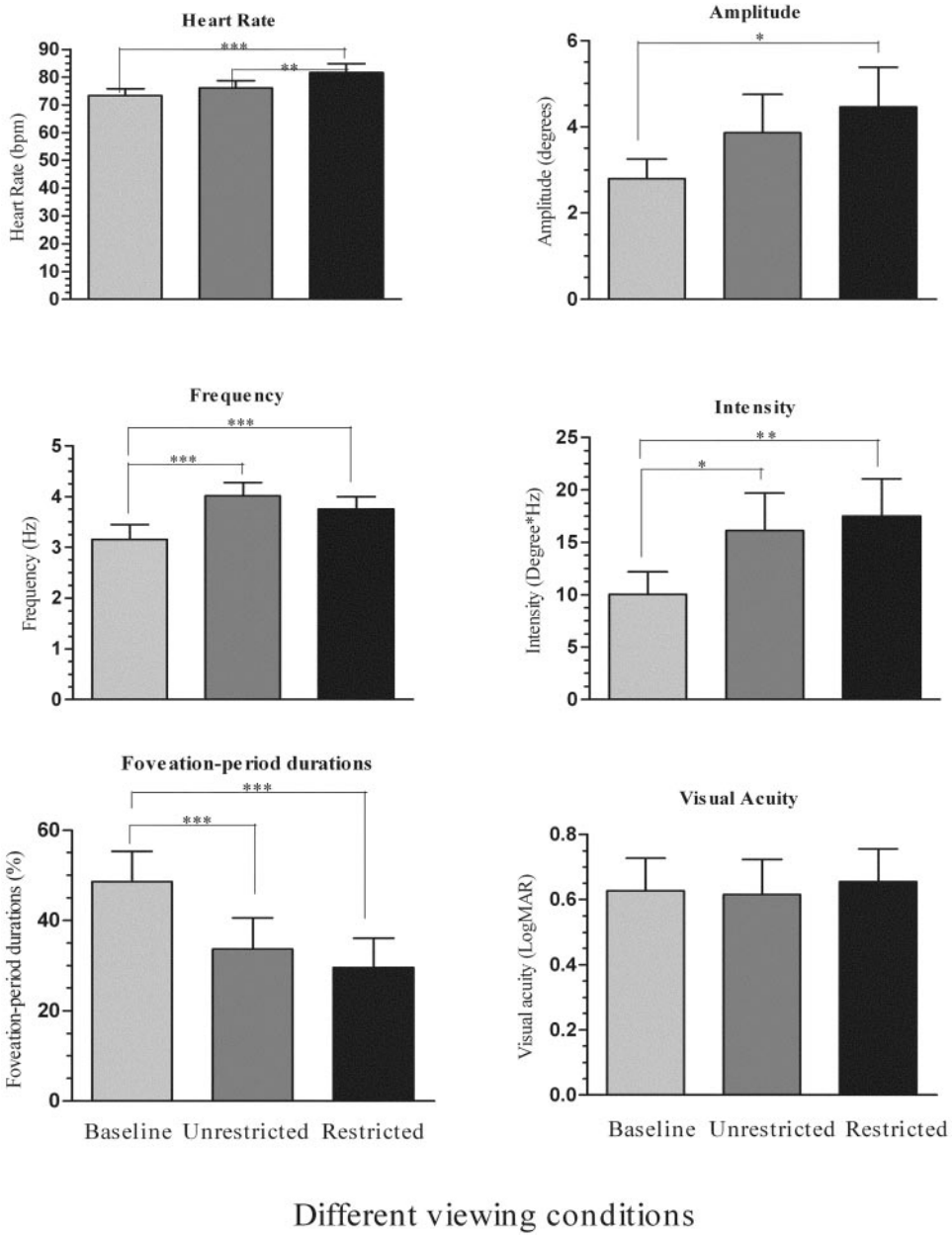

FIGURE 1. Differences in heart rate and waveform parameters among the baseline, *unrestricted-*, and *restricted-viewing* tasks. Pair-wise interactions were investigated with the Tukey multiple comparison test. $^{***}P < 0.0001$; $^{**}P < 0.001$– 0.01; $^{*}P = 0.01$–0.05. Repeated-measures 1-way ANOVA: heart rate: $F_{2,18} = 17.7$, $P < 0.0001$; amplitude: $F_{2,18} = 4.0$, $P = 0.03$; frequency: $F_{2,18} = 32.5$, $P < 0.0001$; intensity: $F_{2,18} = 7.1$, $P = 0.003$; foveation-period durations: $F_{2,18} = 25.8$, $P < 0.0001$; and visual acuity: $F_{2,17} = 0.2$, $P = 0.86$. Error bars, SE of mean.

task, except that specific instructions were delivered to the subjects, no mental arithmetic was performed, and a reward/penalty paradigm was introduced. Each subject was told that \$0.50 would be rewarded for correctly detecting two optotypes in a row. Incorrect responses would be penalized by a deduction of \$1.00 from the amount earned. No punishment was given for missed targets—that is, failing to respond to the presented optotype within 1 second. Auditory feedback was provided to inform the subjects if they had responded correctly or made an error. Contrary to this deceptive instruction, a fixed reward of \$20.00 was given to all subjects at the end of the experiment, regardless of performance. We allowed a 2-minute interval between all three tasks.

We analyzed eye-movement data for changes in the type and parameters of the waveform, in particular the foveation-period durations, during all three experiments. Any differences in heart rate were also measured. We defined foveation-period durations in which eye velocity was ≤4 °/s and eye position was inferred to be ±2° from the fixation point from cycle to cycle. This ±2° position criterion was less stringent than the typical ±0.5° position setting used in previous studies, to allow for albino subjects who lack a functional fovea.[6,12–15] Indeed, some studies did not use any position criterion when examining foveation-period durations in INS subjects; only a velocity criterion was used.[16–18] We manually estimated an average fixation position by placing a line through the beginning of as many slow phases as possible in a given fixation interval to serve as the basis for foveation calculations. Blinks and nonfixation points (e.g., times when the subject momentarily looked away from the computer screen or appeared drowsy) were excluded from analysis by visual inspection. We also rejected artifacts in the electrocardiogram waveforms (e.g., spikes due to hand movement). Subject N did not participate in the *reward-manipulation* task.

RESULTS

We compared the heart rate and waveform parameters among the baseline (from Table 1), *unrestricted-viewing*, and *restricted-viewing* tasks, with 1-way ANOVA with repeated measures. Unlike visual acuity, all other waveform parameters and heart rate differed significantly (Fig. 1).

For the *reward-manipulation* task, paired *t*-test also illustrated significant changes in heart rate and waveform parame-

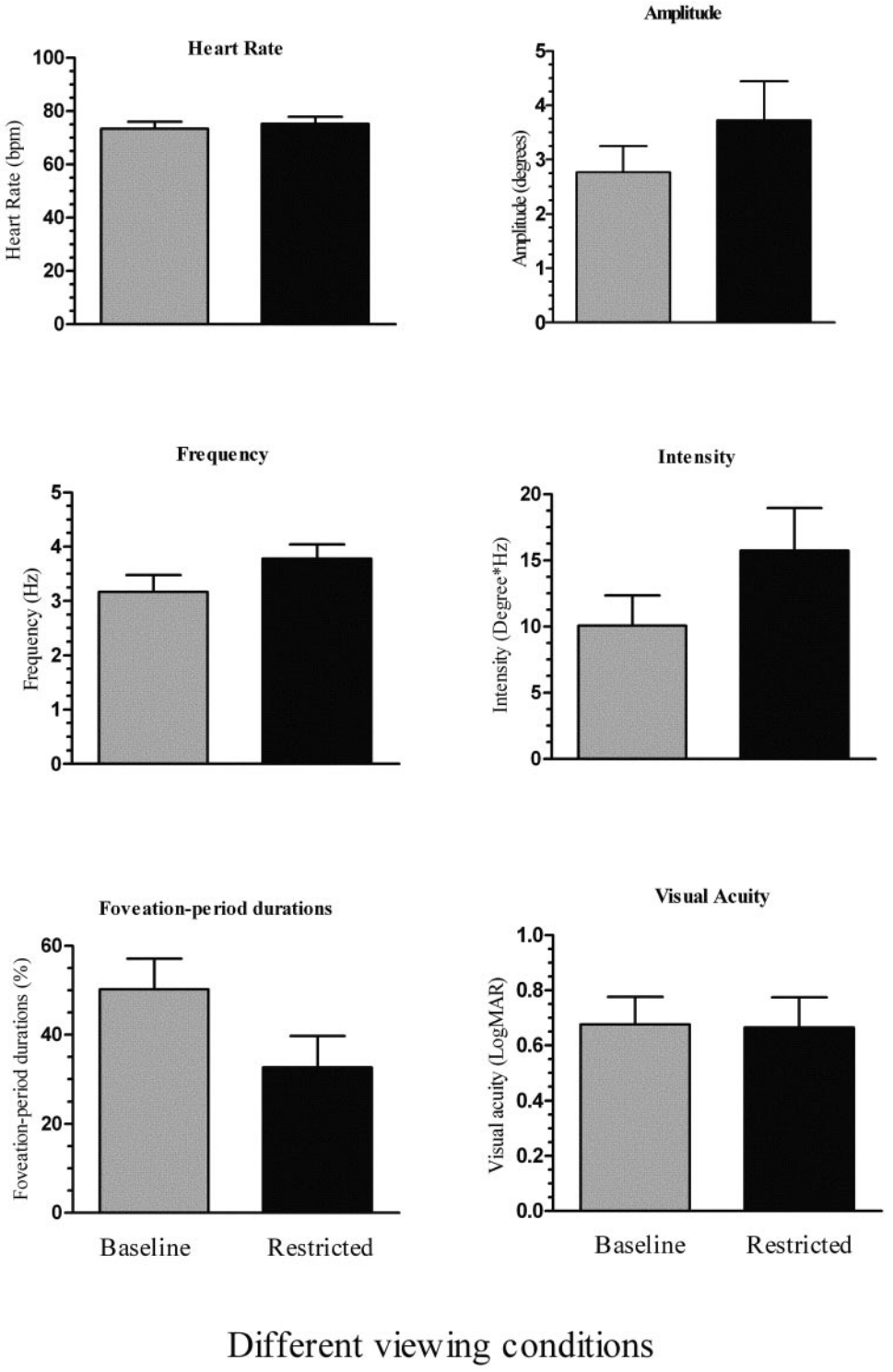

FIGURE 2. Differences in heart rate and waveform parameters between baseline and *restricted-viewing* tasks in the *reward-manipulation* paradigm. Paired *t*-test: heart rate: $t = 2.2$, $P = 0.04$; amplitude: $t = 2.2$, $P = 0.04$; frequency: $t = 4.1$, $P = 0.001$; intensity: $t = 2.9$, $P = 0.01$; foveation-period durations: $t = 4.9$, $P = 0.0001$; and visual acuity: $t = 0.2$, $P = 0.8$. Error bars, SE of mean.

ters when compared with baseline. Again, visual acuity was not significantly altered (Fig. 2).

When the heart rates and waveform parameters were examined during minimum (largest optotype read) and maximum (smallest optotype read) visual demand, significant differences were found with paired *t*-tests only for the *restricted-viewing* task, not for the *unrestricted-viewing* or the *reward-manipulation* tasks (Table 3).

The effects of increased visual demand on INS parameters (i.e., decreased—that is, improved—amplitude, frequency and, hence, intensity, as well as decreased—thus, deteriorated—foveation-period durations) and increased heart rate during the *restricted-viewing* task are shown for all subjects in Table 4, indicating considerable intersubject variability. When compared between the *restricted-viewing* and the *reward-manipulation* tasks, heart rate increased significantly more in the *restricted-viewing* task (paired *t*-test: $t = 3.64$, $P = 0.002$). Figure 3 illustrates the INS waveform of a subject at minimum and maximum visual demand during the *restricted-viewing* task.

A Pearson correlation was performed to investigate the relationship between changes in heart rate and changes in

TABLE 3. Parameter Measurements for All Three Tasks

Task	Visual Effort	Amplitude (deg)	Frequency (Hz)	Intensity (deg · Hz)	Foveation Period Durations (% ±2°, ≤4°/s)	Heart Rate (bpm)
Unrestricted viewing	Min	4.4 ± 3.5	3.6 ± 1.4	16.8 ± 14.8	33.0 ± 32.3	76.6 ± 12.1
	Max	3.6 ± 3.5, $P = 0.11$	3.9 ± 1.1, $P = 0.11$	14.9 ± 14.6, $P = 0.29$	32.0 ± 29.2, $P = 0.61$	75.8 ± 11.3, $P = 0.64$
Restricted viewing	Min	**5.8 ± 5.2**	**4.1 ± 1.2**	**23.2 ± 20.7**	**28.9 ± 31.7**	**76.4 ± 11.4**
	Max	**4.0 ± 3.1, $P = 0.02$**	**3.7 ± 1.3, $P = 0.03$**	**15.7 ± 12.4, $P = 0.02$**	**26.4 ± 29.7, $P = 0.003$**	**79.1 ± 11.3, $P = 0.04$**
Reward manipulation	Min	3.6 ± 2.4	3.9 ± 1.2	14.6 ± 9.9	36.7 ± 32.1	75.4 ± 12.0
	Max	3.1 ± 2.9, $P = 0.26$	3.6 ± 1.4, $P = 0.35$	12.9 ± 12.5, $P = 0.33$	35.6 ± 34.1, $P = 0.60$	75.4 ± 11.9, $P = 0.97$

Only changes during the restricted viewing task (shown in bold) were significant (paired *t*-test).

waveform parameters by obtaining the difference between them when responding to the smallest optotypes during the *unrestricted-* and *restricted-viewing* tasks. The correlation was performed on a subject-by-subject basis using within-subject data. Changes in heart rate did not correlate with changes in waveform parameters (amplitude, $r^2 = 0.001$, $P = 0.9$; frequency, $r^2 = 0.01$, $P = 0.7$; intensity, $r^2 = 0.0003$, $P = 1.0$; and foveation-period durations, $r^2 = 0.0001$, $P = 0.9$).

When task performance was evaluated (change from baseline heart rate versus correct response of mental arithmetic or skipped optotypes), Pearson correlation was again nonsignificant for the *restricted-viewing* (mental arithmetic, $r^2 = 0.02$, $P = 0.61$; skipped optotypes, $r^2 = 0.02$, $P = 0.61$) and the *reward-manipulation* (skipped optotypes, $r^2 = 0.0002$, $P = 0.96$) tasks. Changes in direction and predominant type of waveform were noted in seven subjects for all three tasks (Table 5).

DISCUSSION

Our study is the first to provide evidence for the negative impact of stress and/or motivation on the characteristics of the nystagmus waveform. Task-induced physiological stress, as evident by an increased in heart rate during the *restricted-viewing* task, led to an increase in the amplitude, frequency, and intensity of the nystagmus waveform and decreased foveation-period durations. The results lend quantitative support to previous observations that INS increases with psychological factors (such as stress and anxiety) that affect visual performance.[6–8]

INS is also said to intensify with fixation effort.[8,10] In contrast, we found decreased INS intensity at maximum visual demand during the *restricted-viewing* task, consistent with Wiggins et al.[7] We failed to find any significant changes in waveform type at maximum visual demand, which would otherwise explain the observed inconsistencies in INS intensity. Such intensity changes are probably functionally less important than changes in the foveation-period duration, which are a better predictor and a more direct measure of visual performance in INS.[4,10]

The findings of decreased foveation-period durations at maximum visual demand in the *restricted-viewing* task in our study contradict earlier results by Tkalcevic and Abel,[6] who found no changes in the foveation-period duration of the nystagmus waveform, and of Wiggins et al.,[7] who reported prolonged foveation-period durations. The cause of this discrepancy may be the failure of both studies to produce sufficient visual demand, as mentioned previously. This finding is supported by those for our *unrestricted-viewing* task (analogous to the task used in previous studies), which yielded no significant differences between minimum and maximum visual demands (i.e., largest versus smallest optotype). Hence, visual demand per se will exacerbate INS if the task is stressful enough.

In the present study, foveation-period durations decreased significantly during the visual tasks, while visual acuity remained relatively unchanged. This result is in contrast with those in previous studies,[4,10] in which it was found that prolonged foveation-period durations enhance visual acuity in INS. Our study was not primarily designed to measure visual acuity but rather to produce a stressful visual environment by briefly presenting optotypes with slightly blurred edges. This unconventional visual acuity task might account for the increased variability (hence, nonsignificant) in visual acuity among the visual tasks. The infrared limbus eye tracker also precluded the use of patients' spectacles for refractive error correction, thus further limiting our ability to evaluate best corrected visual acuity.

We noted a change in fast-phase direction in two of our subjects with INS when they performed tasks other than baseline fixation. This suggests that stress and/or motivation may be added to factors such as smooth pursuit, choice of fixating eye and time in the aperiodic alternating nystagmus cycle, which are already known to shift the null position in INS.

Investigators in previous studies[6,7] have proposed that the absence of rewards failed to motivate subjects, which may have influenced the findings. In the present study, we examined this assertion using the *reward-manipulation* paradigm. We observed that the reward/penalty paradigm produced a significant increase in nystagmus amplitude, frequency, intensity, and decreased foveation-period durations. Concurrently, heart rate increased, but not as much when compared with the *restricted-viewing* task. This finding reflects a greater motivational role compared to stress in the *reward-manipulation* task. We propose that the monetary reward increased motivation, and with its associated stress, increased INS significantly.

We failed to find any significant correlation between changes in the nystagmus parameters and changes in heart rate when the subjects performed different visual tasks, suggesting that, although both observed changes co-vary with stress, they do not co-vary with each other. It is possible that the variability of the data in our study results in insufficient power to illustrate the correlation, or the nature of how both changes vary cannot be demonstrated by correlation, or both. The underlying functional relationship between stress, changes in heart rate, and changes in nystagmus parameters is unknown. Furthermore, recording heart rate over a short period is a coarse measure. Being an episodic rather than a continuous measure, heart rate is less robust and less sensitive than other measures, such as galvanic skin response, for the detection of subtle changes when monitoring the psychological state of the subjects. Future studies should include additional, more continuous mea-

TABLE 4. Parameter Measurements during the *Restricted-Viewing* Task

	Amplitude (deg)		Frequency (Hz)		Intensity (Deg · Hz)		Foveation-Period Durations (% ±2 ≤4°/s)		Heart Rate (bpm)	
Subj.	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
A	1.91	0.91	3.00	3.00	5.73	2.73	66.99	63.92	87.19	80.47
B	6.29	5.13	3.50	4.50	22.02	23.09	6.40	3.89	81.10	77.56
C	16.61	11.47	3.50	3.00	58.14	34.41	13.18	14.08	75.21	87.81
D	15.77	8.42	5.00	5.00	78.85	42.10	0.90	3.54	71.31	86.80
E	3.74	2.37	4.00	4.00	14.96	9.48	19.43	12.89	58.10	58.80
F	3.67	3.49	6.25	6.00	22.94	20.94	8.11	5.82	90.25	90.27
G	3.62	3.83	5.50	6.00	19.91	22.98	6.78	6.17	82.19	84.07
H	9.85	3.14	4.00	3.00	39.40	9.42	20.48	14.78	88.82	96.66
I	2.58	0.04	3.00	2.50	7.74	0.10	85.84	84.39	62.70	64.29
J	1.39	1.38	6.00	4.50	8.34	6.21	46.38	48.55	85.71	82.35
K	1.53	0.99	3.00	2.00	4.59	1.99	85.98	82.32	81.00	83.75
L	2.57	2.12	5.00	5.00	12.85	10.60	15.52	17.88	70.45	71.43
M	1.27	1.29	2.50	1.00	3.18	1.29	90.79	75.84	95.65	94.29
N	10.81	5.60	4.00	3.50	43.24	19.60	1.95	0.18	77.41	86.64
O	15.10	7.97	3.00	3.50	45.30	27.90	6.70	8.21	64.00	65.85
P	2.85	3.18	2.50	2.00	7.13	6.36	51.00	42.35	54.70	57.59
Q	1.73	1.27	5.25	4.50	9.06	5.72	12.59	12.22	80.16	78.91
R	5.91	6.91	4.00	3.50	23.64	24.19	4.62	4.50	79.08	82.82
S	3.10	7.14	4.25	4.00	13.18	28.56	4.57	0.79	66.37	72.86
Mean ± SD	5.80 ± 5.19	4.03 ± 3.14	4.07 ± 1.15	3.71 ± 1.34	23.17 ± 20.72	15.67 ± 12.41	28.85 ± 31.66	26.44 ± 29.67	76.39 ± 11.38	79.12 ± 11.30

Group means and standard deviations (SD) are also shown for each measure.

sures to improve quantification of the psychological state of an individual.

The mechanism by which INS waveform alters with changes in stress and/or arousal remains unknown. However, it is worth considering the interactions between the brain regions that modulate emotion/motivation and the slow eye-movement (SEM) control system, which has been postulated to give rise to INS.[10,19] The amygdala is a key structure in the neural basis of emotion,[20] playing an influential role in a vast range of behavior.[21] It forms an essential connection between brain areas that process sensory information (e.g., cerebral cortex) and brain regions for eliciting emotional and motivational responses (i.e., the hypothalamus, brain stem, and striatum).[22] Complex internal circuits allow the amygdala to link autonomic responses with specific behavior.[23] Another brain region of interest is the anterior cingulate cortex (ACC), which has been linked with attention and cognitive processes,[24,25] perhaps with a motivational role.[26,27] The ACC is also known to influence emotional and affective behavior.[20] Activity in the rostral and dorsal cingulate cortices correlates with (and predicts) cardiovascular and electrodermal arousal evoked by a range of cognitive, emotional, and motivational tasks.[9,28,29] The ACC shares reciprocal connections with the amygdala. Both structures are anatomically linked with the nucleus accumbens,[30,31] which mediates the motivational effects of emotionally significant stimuli.[32,33] The posterior part of the ACC, the posterior cingulate cortex (PCC), generates eye movements by early activation of frontal ocular motor areas and through direct projections to the brain stem.[34]

Reward expectancy modulates neural activity in various brain regions, including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, ACC, premotor area, posterior parietal cortex, PCC, and caudate nucleus.[35–38] The basal ganglia are among the most significant structures in translating motivational context into ocular motor behavior.[36] Reward expectation can affect saccadic latency.[39–41] Changes in mental state (e.g., anxiety) have also been observed to increase the gain and slow-phase velocity of optokinetic nystagmus[42,43] and to prolong the time constant and increase the gain of the vestibulo-ocular reflex in normal subjects.[44,45]

In the present study, stress and/or motivation led to exacerbation of INS. Tkalcevic and Abel[6] suggested that the projections from ACC and amygdala to the brain stem could modulate activity in the vestibular nuclei, which had been postulated to be one of the structures implicated in the pathogenesis of INS.[46] Other possibly involved regions that contribute to smooth-pursuit eye movements include the subregion of the frontal eye fields,[47] supplementary eye field,[48] DLPFC,[49] anterior and posterior cingulate cortices,[50] basal ganglia,[51] and thalamus.[52] Of course, such sites are only relevant if INS is presumed to be an instability originating from the SEM control system.[10,19]

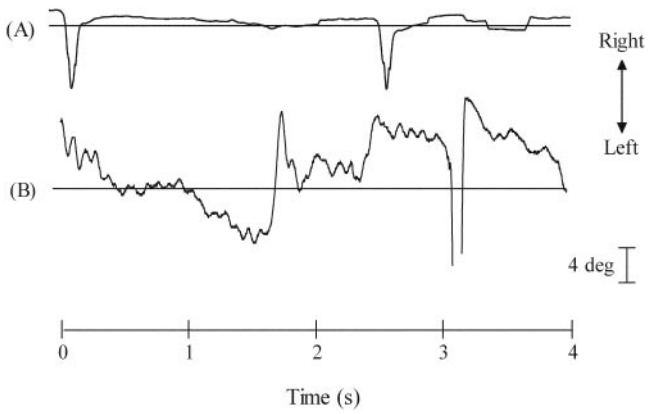

FIGURE 3. **(A)** Recording of subject M who was attempting the 1.2 logMAR equivalent optotype. This optotype required minimum visual demand. Foveation-period durations were met 91% of the time. **(B)** Recording of the same subject who was attempting the −0.1 logMAR equivalent optotype. This optotype required maximum visual demand. Foveation-period durations were met 76% of the time. *Horizontal line*: fixation. The time origin is arbitrary.

TABLE 5. Direction and Waveform Type Changes in Seven Subjects

Subject	Baseline	Unrestricted Viewing	Restricted Viewing	Reward Manipulation
A	JL	JR	DJR	DJR
D	JL	JL	JL & LPC	JL & LPC
E	JL	PPfs & BDJL	PPfs & BDJL	PPfs & BDJL
J	JRef	JRef	JR	JR
K	JRef	JRef	JR	JRef
L	JR & RPC	JR	JR	JR & BDJR
P	JR	JR	JR	JL

Bidirectional jerk, BDJ. Other abbreviations as in Table 1.

CONCLUSION

In summary, we have for the first time experimentally demonstrated the long-standing assertion that task-induced stress and/or motivation may have a negative impact on INS. They led to decreased foveation-period durations, which may affect the visual functions of INS subjects. Variations in these internal states may also lead to increased INS variability. This has important implications for individuals with INS, since stress may arise in everyday situations, such as driving or when undertaking an examination. We propose that the psychological status of individuals should be taken into consideration when they are either undergoing assessment of visual functions or when pre- and posttreatment modalities are compared. More precise manipulation of psychological behavior, such as attention, should help in extending our current knowledge of INS and how we can better assess and manage individuals with this condition.

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References

1. CEMAS Working Group. *A National Eye Institute Sponsored Workshop and Publication on the Classification Of Eye Movement Abnormalities and Strabismus* (*CEMAS*). Bethesda, MD: National Eye Institute, The National Institutes of Health; 2001.
2. Gottlob I. Infantile nystagmus development documented by eye movement recordings. *Invest Ophthalmol Vis Sci*. 1997;38:767–772.
3. Gresty MA, Bronstein AM, Page NG, Rudge P. Congenital-type nystagmus emerging in later life. *Neurology*. 1991;41:653–656.
4. Abadi RV, Bjerre A. Motor and sensory characteristics of infantile nystagmus. *Br J Ophthalmol*. 2002;86:1152–1160.
5. Dell'Osso LF. Congenital, latent and manifest latent nystagmus: similarities, differences and relation to strabismus. *Jpn J Ophthalmol*. 1985;29:351–368.
6. Tkalcevic L, Abel LA. The effects of increased visual task demand on foveation in congenital nystagmus. *Vision Res*. 2005;45:1139–1146.

7. Wiggins D, Woodhouse JM, Margrain TH, Harris CM, Erichsen JT. Infantile nystagmus adapts to visual demand. *Invest Ophthalmol Vis Sci*. 2007;48:2089–2094.
8. Abadi RV, Dickinson CM. Waveform characteristics in congenital nystagmus. *Doc Ophthalmol*. 1986;64:153–167.
9. Critchley HD. Electrodermal responses: what happens in the brain. *Neuroscientist*. 2002;8:132–142.
10. Dell'Osso LF, Daroff RB. Congenital nystagmus waveforms and foveation strategy. *Doc Ophthalmol*. 1975;39:155–182.
11. Kumar A, Krol G. Binocular infrared oculography. *Laryngoscope*. 1992;102:367–378.
12. Dell'Osso LF, Jacobs JB. An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. *Doc Ophthalmol*. 2002;104:249–276.
13. Mezawa M, Ishikawa S, Ukai K. Changes in waveform of congenital nystagmus associated with biofeedback treatment. *Brit J Ophthalmol*. 1990;74:472–476.
14. Tkalcevic L, Abel LA. Effects of stimulus size and luminance on oscillopsia in congenital nystagmus. *Vision Research*. 2003;43:2697–2705.
15. Ukwade MT, Bedell HE. Variation of congenital nystagmus with viewing distance. *Optom Vis Sci*. 1992;69:976–985.
16. Abadi RV, Worfolk R. Retinal slip velocities in congenital nystagmus. *Vision Research*. 1989;29:195–205.
17. Shallo-Hoffmann JA, Faldon M, Tusa RJ. The incidence and waveform characteristics of periodic alternating nystagmus in congenital nystagmus. *Invest Ophthal Vis Sci*. 1999;40:2546–2553.
18. Woo S, Bedell HE. Beating the beat: reading can be faster than the frequency of eye movements in persons with congenital nystagmus. *Optom Vis Sci*. 2006;83:559–571.
19. Jacobs JB, Dell'Osso LF. Congenital nystagmus: hypotheses for its genesis and complex waveforms within a behavioral ocular motor system model. *J Vision*. 2004;4:604–625.
20. Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum and prefrontal cortex. *Neurosci Behav Rev*. 2002;26:321–352.
21. Amaral DG, Price JL, Pikänen A, Carmichael ST. Anatomical organization of the primate amygdaloid complex. In: Aggleton JP, ed. *The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction.* New York: Wiley-Liss; 1992:1–66.
22. McDonald AJ. Cortical pathways to the amygdala. *Prog Neurobiol*. 1998;55:257–332.
23. Iversen S, Iversen L, Saper, CB. The autonomic nervous system and the hypothalamus. In: Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science.* New York: McGraw-Hill; 2000:960–981.
24. Davis KD, Taylor KS, Hutchison WD, et al. Human anterior cingulate cortex neurons encode cognitive and emotional demands. *J Neurosci*. 2005;25:8204–8206.
25. Posner M, Dehaene S. Attentional networks. *Trends Neurosci*. 1994;17:75–79.
26. Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci*. 2001;2:417–424.
27. Small DM, Gitelman D, Simmons K, Bloise SM, Parrish T, Mesulam MM. Monetary incentives enhance processing in brain regions mediating top-down control of attention. *Cereb Cortex*. 2005;15:1855–1865.
28. Fredrikson M, Furmark T, Olsson MT, Fischer H, Andersson J, Långström B. Functional neuroanatomical correlates of electrodermal activity: a positron emission tomographic study. *Psychophysiology*. 1998;35:179–185.
29. Gianaros PJ, May JC, Siegle GJ, Jennings JR. Is there a functional neural correlate of individual differences in cardiovascular reactivity? *Psychosom Med.* 2005;35:31–39.
30. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. *Brain*. 1995;118:279–306.
31. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*. 1992;2:435–443.
32. McDonald AJ. Topographical organization of amygdaloid projections to the caudatoputamen, nucleus accumbens, and related striatal-like areas of the rat brain. *Neuroscience*. 1991;44:14–33.
33. Parkinson JA, Cardinal RN, Everitt BJ. Limbic cortical-ventral striatal systems underlying appetitive conditioning. *Prog Brain Res*. 2000;126:263–285.
34. Gaymard B, Rivaud S, Cassarini JF. Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Exp Brain Res*. 1998;120:173–183.
35. Delgado MR, Stenger VA, Fiez JA. Motivation-dependent responses in the human caudate nucleus. *Cereb Cortex*. 2004;14:1022–1030.
36. Hikosaka O. Basal ganglia mechanisms of reward-oriented eye movement. *Ann NY Acad Sci*. 2007;1104:229–249.
37. Schultz W, Tremblay W, Hollerman JR. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb Cortex*. 2000;10:272–283.
38. Watanabe M. Role of anticipated reward in cognitive behavioral control. *Cur Opinion Neurobio*. 2007;17:213–219.
39. Lauwereyns J, Watanabe K, Coe B, Hikosaka O. A neural correlate of response bias in monkey caudate nucleus. *Nature*. 2002;418:413–417.
40. Watanabe K, Hikosaka O. Immediate changes in anticipatory activity of caudate neurons associated with reversal of position-reward contingency. *J Neurophysiol*. 2005;94:1879–1887.
41. Watanabe K, Lauwereyns J, Hikosaka O. Effects of motivational conflicts on visually guided saccades in monkeys. *Exp Brain Res*. 2003;152:361–367.
42. Goonetilleke SC, Curthoys IS, Burgess AM, MacDougall HG. Cognitive demand affects the gain of the torsional optokinetic response. *Exp Brain Res*. 2004;158:125–128.
43. Magnusson M, Pyykkö I, Jäntti V. Effect of alertness and visual attention on optokinetic nystagmus in humans. *Am J Otolaryngol*. 1985;6:419–425.
44. Matta FV, Enticott JC. The effects of state of alertness on the vestibulo-ocular reflex in normal subjects using the vestibular rotational chair. *J Vest Res*. 2004;14:387–391.
45. Yardley L, Watson S, Britton J, Lear S, Bird J. Effects of anxiety, arousal and mental stress on the vestibulo-ocular reflex. *Acta Otolaryngol* (*Stockh*). 1995;115:597–602.
46. Tusa RJ, Zee DS, Hain TC, Simonsz HJ. Voluntary control of congenital nystagmus. *Clin Vis Sci*. 1992;7:195–210.
47. Petit L, Clark VP, Ingeholm J, Haxby JV. Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *J Neurophysiol*. 1997;77:3386–3390.
48. Drew AS, van Donkelaar P. The contribution of the human FEF and SEF to smooth pursuit initiation. *Cereb Cortex*. 2007;17:2618–2624.
49. Nagel M, Sprenger A, Zapf S, et al. Parametric modulation of cortical activation during smooth pursuit with and without target blanking. an fMRI study. *Neuroimage*. 2006;29:1319–1325.
50. Schmid A, Rees G, Frith C, Barnes G. An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport*. 2001;12:1409–1414.
51. Basso MA, Pokorny JJ, Liu P. Activity of substantia nigra pars reticulata neurons during smooth pursuit eye movements in monkeys. *Eur J Neurosci*. 2005;22:448–464.
52. Tanaka M. Involvement of the central thalamus in the control of smooth pursuit eye movements. *J Neurosci*. 2005;25:5866–5876.