NAVAL MEDICAL RESEARCH INSTITUTE

Bethesda, MD 20889-5055

NMRI 90-134 December 1990

COLDEX-86: EVENT-RELATED POTENTIALS AFTER PROLONGED COLD WATER IMMERSION: POSSIBLE EVIDENCE FOR IMPAIRMENT OF COGNITIVE FUNCTION WITH MINIMAL LOWERING OF CORE TEMPERATURE

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NOTICES

TECHNICAL REVIEW AND APPROVAL

NMRI 90-134

The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCL	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution is unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) NMRI 90-134	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Naval Medical Research Institute; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION Naval Medical Command
6c. ADDRESS (City, State, and ZIP Code) 8901 Wisconsin Avenue Bethesda, MD 20814-5055	7b. ADDRESS (City, State, and ZIP Code) Department of the Navy Washington, DC 20372-5120
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) 8901 Wisconsin Avenue Bethesda, MD 20814-5044	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
63713N	M0099	.01A	0007

11. TITLE (Include Security Classification) COLDEX-86: Event-related potentials after prolonged cold water immersion: Possible evidence for impairment of cognitive function with minimal lowering of core temperature.

12. PERSONAL AUTHOR(S)
A.J. Dutka, D.J. Smith, T.J. Doubt, R.P. Weinberg, and E.T. Flynn

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical Report	FROM 04/86 TO 10/86	1990 December	26

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	evoked potentials, hypothermia

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Mild hypothermia may be associated with defects in mental performance, including changes in memory and reaction time. The P3 is an electrical response of the brain to unexpected stimuli, and the delay from stimulus to P3 occurrence (P3 latency) is related to reaction time. The P3 latency was measured in divers undergoing rewarming following extended exposure to water at 5°C and correlated with rectal temperature. There is a very significant lengthening of P3 latency related to rectal temperature in the ranges of 37 to 35°C, suggesting the possible existence of mental impairment even with minimal bodily cooling.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Regina E. Hunt, Command Editor	22b. TELEPHONE (Include Area Code) (202) 295-0198; 22c. OFFICE SYMBOL SD/RSD/NMRI

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

ACKNOWLEDGEMENTS

This study was supported by the Naval Medical Research and Development Command, Work Unit Nos. M0099.01A-0007 and M0099.01C-1515. The views, opinions, and/or assertions herein are those of the authors and should not be construed as official or reflecting the views of the Navy Department and the Naval Service at large.

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INTRODUCTION

Severe hypothermia is known to cause serious derangements in mental function (1). These changes are known to be associated with slowed background frequency and reduction in amplitude of brain waves (electroencephalogram (EEG)), and with an increase in the time needed to evoke a primary brainstem electrical response to auditory stimuli (brainstem auditory evoked response latencies) (2,3). However, obvious changes in mental function do not become apparent before the body is cooled to 32.2 °C (1), and the changes in the EEG and standard evoked responses have been measured only in severely hypothermic subjects under anesthesia (core temperatures below 32 °C). Conscious human volunteers in experimental studies often experience severe discomfort and shivering when cooled from a normal core temperature of 37 °C to 35 °C, but the limit of experimental cooling has been to 33 °C (4,5). The existence of significant changes in mental performances, EEGs, and evoked response latencies in this range of core temperatures is a subject of debate.

Hayward (6) has suggested that the decrement in mental performance associated with moderate cooling might account for unexplained diving accidents in the North Sea (6). He has supported this contention with evidence that the core temperature of divers fell despite delivery of hot water to their suits whenever they felt uncomfortable, and by laboratory studies in individuals who reported no discomfort in cold water, but nonetheless had falling core temperature (6,7,8). Coleshaw et al. (9) found that subjects with post-immersion core temperatures of 34.5 °C were able to perform at only 30% of their levels at 37 °C in tests of short-term memory, and were also impaired in tests of logical reasoning and arithmetic. Other groups have found decreases in memory, reaction time, and manual dexterity

(10,11,12), but have ascribed these changes to the distracting effect of discomfort in the cold or to direct neuromuscular effects in the cold limb. It would be useful to have a relatively objective measure of the speed of processing information in the brain (such as the EEG) so that these confounding influences of motivation and distraction could be minimized.

Standard electrical measures of brain function are, however, relatively insensitive to brain activity changes during mild hypothermia. Conscious subjects 2.5 °C below normal body temperature did not show changes in the latencies of the primary visual evoked response (4). These response latencies are a measure of the speed of impulse conduction in the nervous pathways responsible for the initial detection of the stimulus; therefore, profound changes in brain function would be expected when these are slowed. There is a daily fluctuation in the latency of the brainstem auditory evoked response that is correlated with body temperature, but it is not clear if body temperature is the cause of this change (13). The fourier-transformed power spectrum of the EEG is shifted towards lower frequency ranges at 33.5 °C, but the relationship of this derived electrical measure to mental function is unclear (4).

The brain generates a large electrical potential that is positive at the vertex several hundred milliseconds after an auditory stimulus that is both unexpected and relevant to the subject (14). This P3 wave (often known as P300) is usually elicited by rare high tones in a series of common low tones when the subject is asked to mentally count the number of high tones. Its amplitude is increased by reducing the number of rare tones in a trial, and is decreased by not specifying that the subject should attend to the stimulus (15,16). The P3 can also be elicited by asking the subject to count the number of times the stimulus is absent; it is clear from this that the response is somehow endogenously generated by the brain systems for directing attention, and is not simply dependent on the stimulus characteristics (15). The latency of this response has been linked to the reaction time in many experiments, and more specifically to the time needed to evaluate a stimulus (17). Moreover, the latency of the potential is known to increase in metabolic and disease states associated with mild changes in mental function (18). We examined the P3 latency in the cold by recording the P3 in divers with a range of core temperatures from 35 to 37 °C.

METHODS

The P3 potentials were recorded during COLDEX-86, a series of five-day saturation dives to 20 fsw. These dives were designed to test the work capacity and cold tolerance of divers exposed to 5 °C water in passive thermal protection garments for periods of up to six hours. Sixteen divers participated in the experiment after giving informed consent, and after institutional review of the protocol.

The full details of technical aspects of COLDEX-86 are given in the NMRI technical report entitled "COLDEX-86: Summary of the experimental protocol and general results." Briefly, teams of four divers were saturated at 20 fsw on air for five days at a time. Each day two divers were dressed in a thinsulate undergarment and butylated rubber dry suit, and immersed in water at 5 °C. They breathed air during exposure through a modified AGA mask, and were monitored for rectal temperature, skin temperature and heat flux at several sites, urine output, and oxygen consumption. The dives began at 1000 hours (AM dives) or 2200 hours (PM dives), and each dive team made two AM and two PM dives each under conditions of normal diets or diets rich in carbohydrates. Fifty-seven percent of attempted immersions were aborted either for equipment failures or for medical reasons, but only 8% of dives were aborted because the rectal temperature fell below 35 °C. After the dive or the abort, the divers spent 2 hours in a passive rewarming system with continued rectal temperature monitoring. The event-related potentials were recorded during the rewarming period only, and each subject had two potentials recorded during the surface training period prior to the beginning of the experimental series. During the first saturation dive the event-related potentials were recorded at the beginning and end of the rewarming, and at one hour. The later dives had records obtained only at the beginning and end of the rewarming period because the subjects did not wish to participate in a third recording.

The recordings were obtained using 10 mm gold-cup electrodes applied with conductive paste (Grass Instrument Company, Quincy, MA), after skin preparation with Omni-Prep (Weaver, Aurora, CO). Recordings were not attempted unless the combined impedance of the skin electrodes and wiring system was below 5 Kohms. The signals were carried in shielded cables to penetrate the chamber wall to an instrument room approximately 100 ft away. The Nicolet CA-1000 with P3 stimulator option (Nicolet Biomedical Instruments, Madison, WI) recorded responses and delivered the tone stimuli through earphones to both ears simultaneously. The active electrode was placed at Cz and referred to linked mastoid electrodes. The ground was placed at FPz, and the records were outputted to a 14" x 17" plotter with a positive potential at Cz giving an upward pen deflection. The bandpass was 1 to 30 Hz, the total duration of the analysis was 600 msecs, and the stimuli were delivered at a rate of 1.1 per second. The low tone accounted for 80% of the stimuli and was at 1000 Hz; the high tone occurred at random intervals 20% of the time at 2000 Hz. Both common and rare tones were delivered at a 75 dB intensity. Five hundred total stimuli were averaged for each response, and two responses were obtained at each time point to allow for certain identification of the waveform. The subjects were instructed to mentally count the total number of high tones, and were reminded repeatedly during the recording to stay awake and lie still. Their total count of high tones was compared with the total count generated by the recording system, and usually agreed nicely (no records kept).

Surface controls were obtained using the same stimulation and recording setup with the subjects supine, as they would be during the experiment. Oral temperatures were normal during surface controls, so the rectal temperature was assumed to be 37 °C for each of these trials. The actual rectal temperature was noted for each post-dive record.

The evoked potential for the common and rare tones for the two recordings at each experimental time point were displayed on the same chart record. Two conditions had to be met before the chart record was accepted for analysis: the common tones had evoked a reproducible P1-N1-P2 complex at 50-150 msecs, and the rare tone averages had to appear similar to each other. The N1 latency was taken at the lowest point of the first negative potential after the stimulus. The P3 was often broad with two or more distinct peaks well above the baseline. Therefore, following the procedure of Goodin (18), the latency was taken at the intersection of lines drawn to superimpose on the leading and trailing slopes of the peak (Figure 1). Latency and temperature were recorded separately for each waveform obtained, even if separated by only a few minutes during repetition to check for reproducibility.

The results were analyzed by linear regression with least squares fit, and the slope, intercept and variance of the lines were compared with one-way ANOVA among individuals or conditions. The number of rejected records at each temperature and the number of rejected records under each experimental

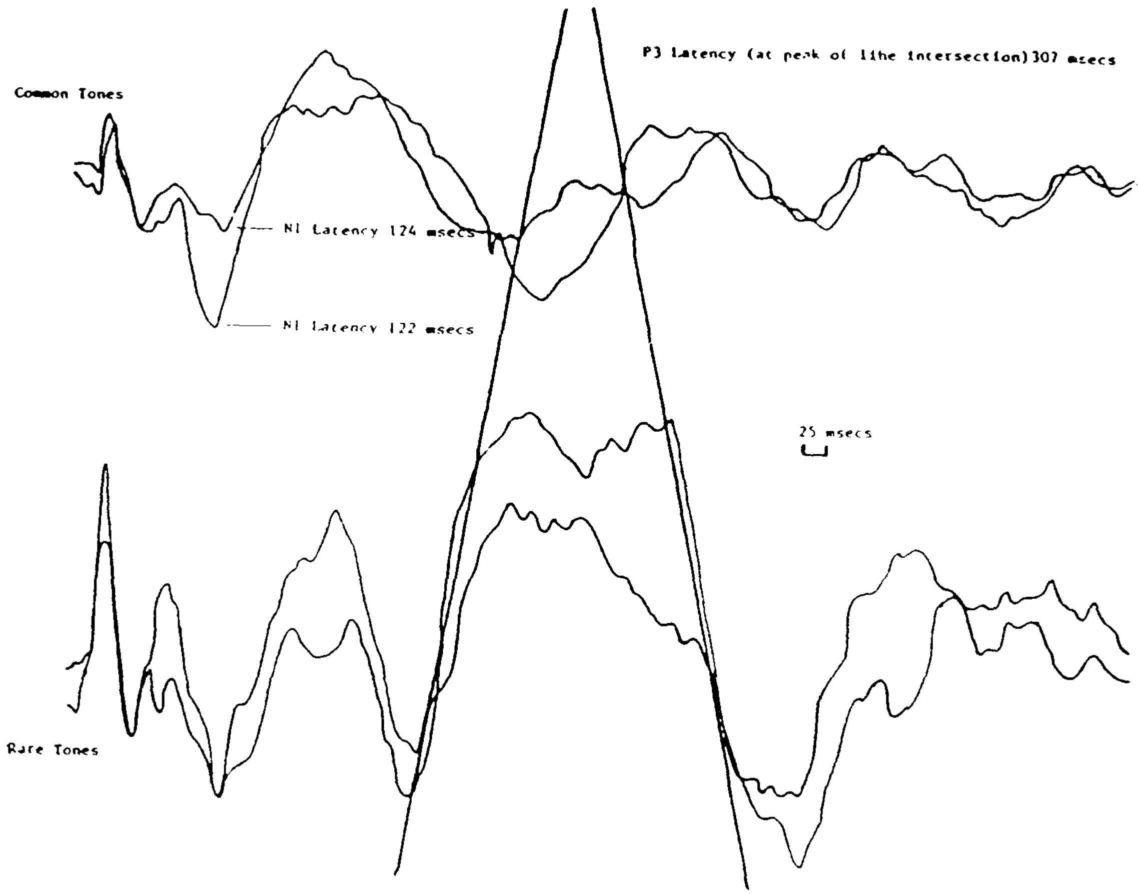

Figure 1. Recordings of common and rare tones from a control record, showing construction of lines for measurement of P3 latency.

condition were compared using the Chi-square. All average results are reported as mean ± standard error (±SE) (19).

RESULTS

The recording system could reliably detect a 0.5 microvolt (μv) test signal with minimal noise despite the long distance wiring involved.

The average age of the sixteen volunteers was 27 years, with a range of 23-33 years. Each subject had at least one surface control recorded in the warm chamber with normal oral temperatures. A total of 26 surface control recordings were obtained. The average primary auditory evoked response latency (N1 peak latency) was 95.7 ± 4.1 msecs from the start of the tracing. The average P3 latency according to our recording and measurement techniques was 295.7 ± 5.5 msecs. The surface controls do not include any rejected records since the technician had direct access to the subjects, and would do whatever was necessary to obtain readable recordings.

Two hundred and twenty-seven recordings were obtained during the rewarming period following cold water immersion for various times. A total of 84 of these records were judged unreadable according to the criteria above. The lowest temperature obtained during rewarming was 34.9 °C, and several recordings were obtained at 37.2 °C. The proportion of the recordings judged unreadable at each temperature is shown in Table 1. There is no significant difference in the number of unreadable recordings at any temperature by Chi-square (25.3 with 21 df of freedom p approximately 0.25). Fifty of 122 post-AM dive recordings were judged unreadable, and 35 of 105 post-PM dives were obscured. There is no difference in these proportions (Chi-square = 1.42, df 1, $p>0.1$).

The relationship of P3 latencies to core temperature (including the surface controls) was tested with a linear least-squares estimate. The slope,

TABLE 1

Number of Unreadable Records at Each Temperature as a Proportion of Total Records at Each Temperature

Temperature, Degrees C.	Total Number of Records	Unreadable Records
37.2	2	0
37.1	2	1
37.0*	6	3
36.9	4	2
36.8	9	6
36.7	5	2
36.6	14	3
36.5	17	5
36.4	12	6
36.3	21	7
36.2	16	6
36.1	31	15
36.0	13	2
35.9	13	2
35.8	10	4
35.7	7	3
35.6	6	1
35.5	13	4
35.4	4	1
35.3	5	3
35.2	8	2
35.1	6	4
35.0	0	0
34.9	2	0

*The data at 37 °C excludes 26 successful surface controls. The number of records reported here includes only those that happened to be 37 °C after a cold exposure.

intercept, and mean-squared error of the regression line for each subject are shown in Table 2. The lines were compared to each other using the F-max test for homogeneity of variance; an F-test compared slope and intercept to the slope and intercept obtained under the assumption that the lines did not differ. These tests showed that the regression lines for each diver were not significantly different, so that pooling of the data from all divers for the regression estimate was justified. In addition, the mean and standard deviation of the 16 estimated slopes were calculated, and this data set compared with a one- tailed t-statistic against the null hypothesis of a mean slope equal to zero with a very significant result ($t=4.13$, $p<0.001$).

Figure 2 plots the P3 latencies against temperature for all readings obtained. Figure 3 shows the regression line for these readings, along with the 95% confidence limits on the slope and intercept of the regression line. This indicates that the true regression line slope lies somewhere between those lines with a 95% probability. The equation for this line is P3 latency = -27.8(°C) + 1321.8. Figure 4 shows the regression line with the 95% prediction lines, which are the estimate of the error in estimating P3 latency from the temperature. Figure 5 shows actual recordings of P3 at 37 °C and at 35.9 °C for one subject.

The regression analysis on the pooled data from all recordings was performed for the 3 subsets of the data. There was a significant regression of P300 latency for all recordings during the rewarming period, excluding surface controls that had an assumed, unmeasured rectal temperature. Recordings done after AM or PM dives both showed significant regressions of P300 on temperature, which did not differ from that of the entire data set.

The regression line for the N1 latencies against temperature did not have a slope significantly different from zero. (N1 latency = 2.3 °C + 16.7,

TABLE 2

Calculated Regression Lines of P3 Latency versus Temperature for Each Diver

Diver #	Number of Readings	Slope	Intercept	Summed Squared Error/(N-2)
1	14	-17.8	923	715
2	7	-26.2	1287	2230
3	4	-66.0	2736	90*
4	9	-10.3	683	191
5	12	-59.8	2494	1682*
6	6	-1.3	350	613
7	12	-38.4	1727	280*
8	8	-4.7	482	288
9	10	-30.1	1422	575*
10	10	-23.0	1160	149*
11	13	-14.9	831	413
12	6	+21.8	-525	251
13	17	-15.3	859	1172
14	12	-7.5	558	787
15	16	-46.4	2018	1151*
16	13	-50.9	2133	243*

* These individual regressions are significant at $p<0.05$

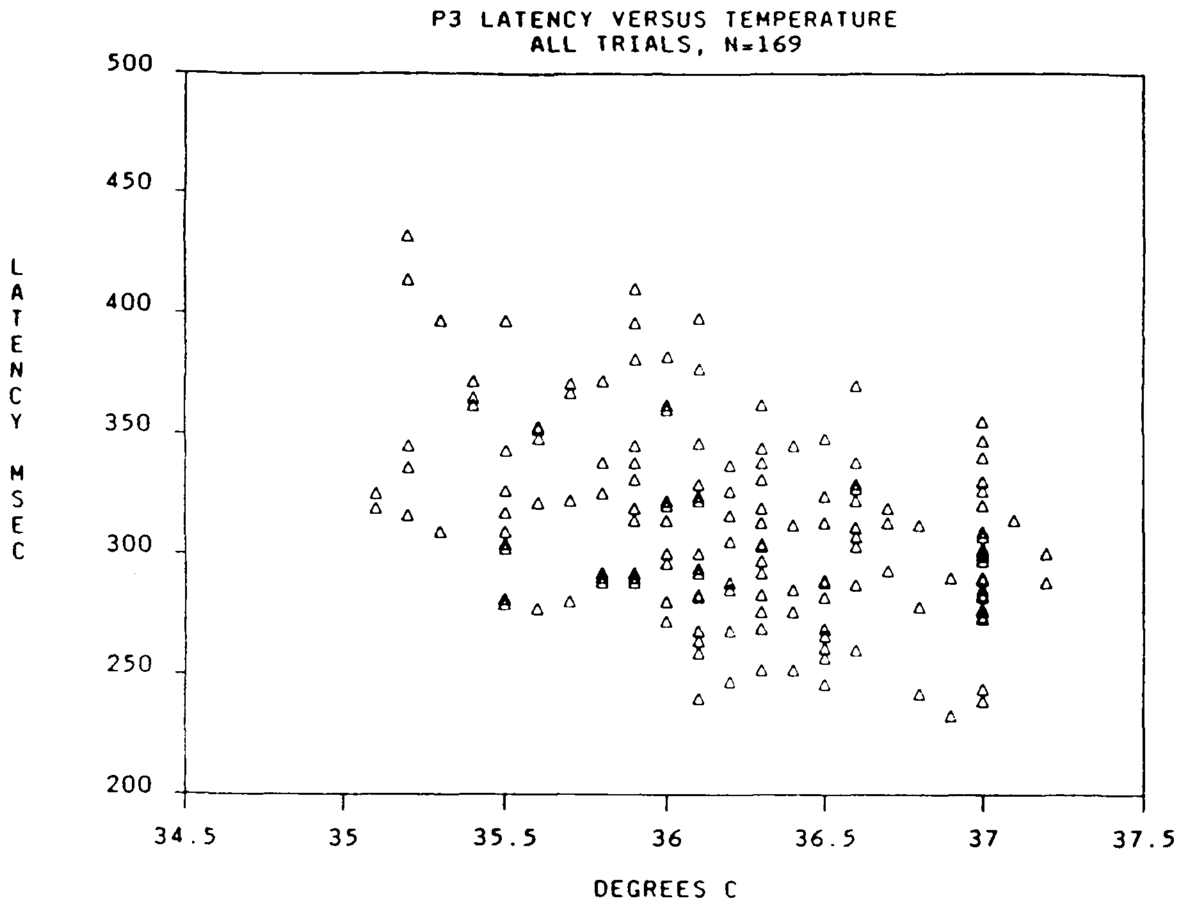

Figure 2. Graph of P3 latency, in msecs, versus temperature in degrees C for all successful recordings, N=169.

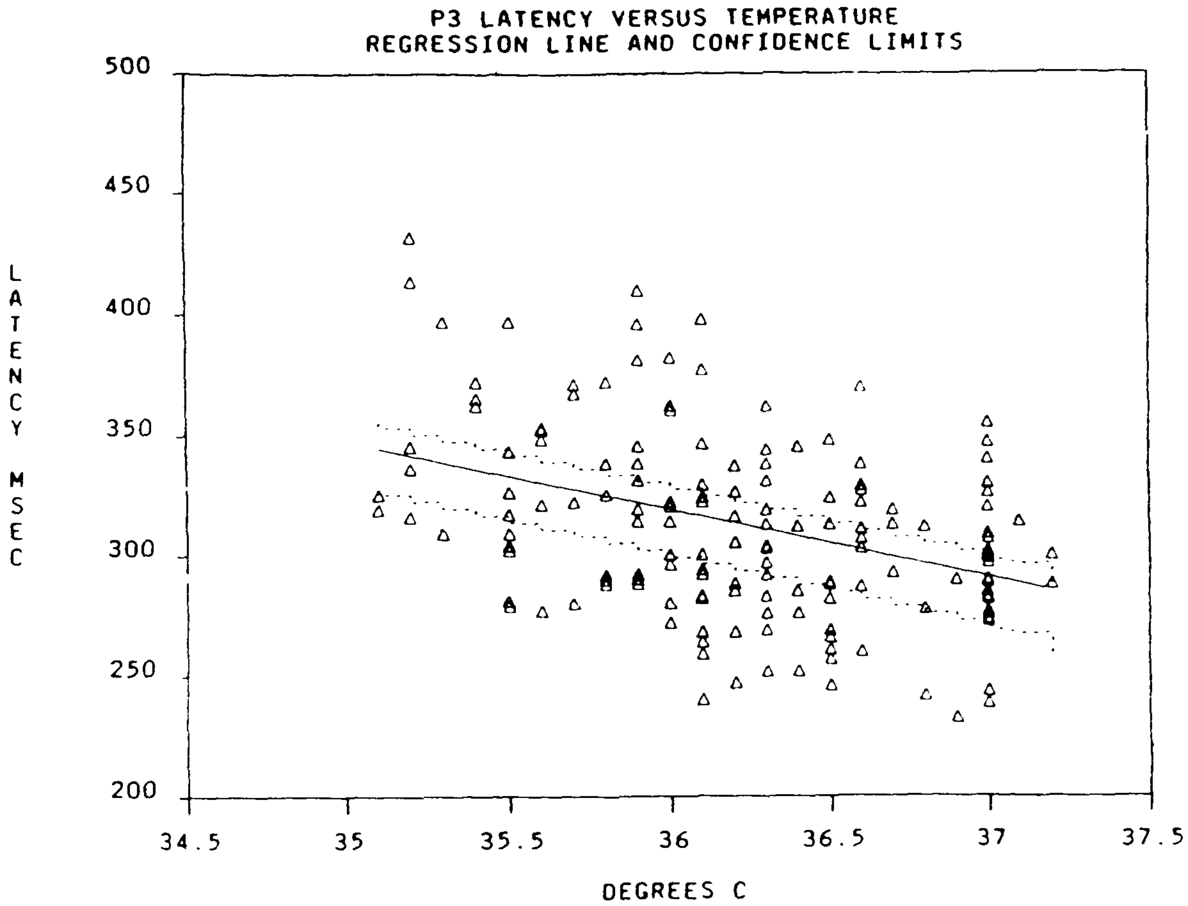

Figure 3. Calculated regression line with 95% confidence limits on the slope and intercept of the line, P3 latency versus temperature.

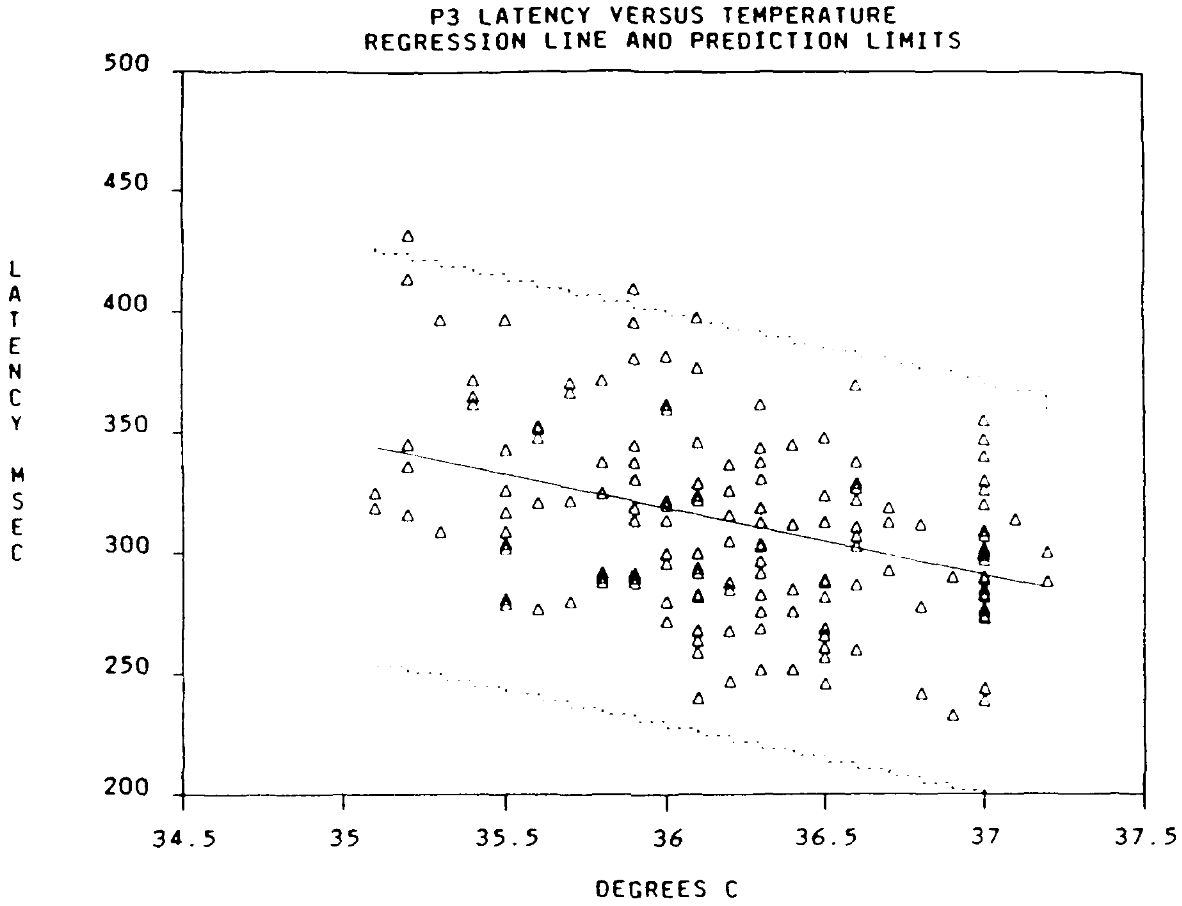

Figure 4. Calculated regression lines with 95% Y prediction limits for P3 latency given a particular temperature.

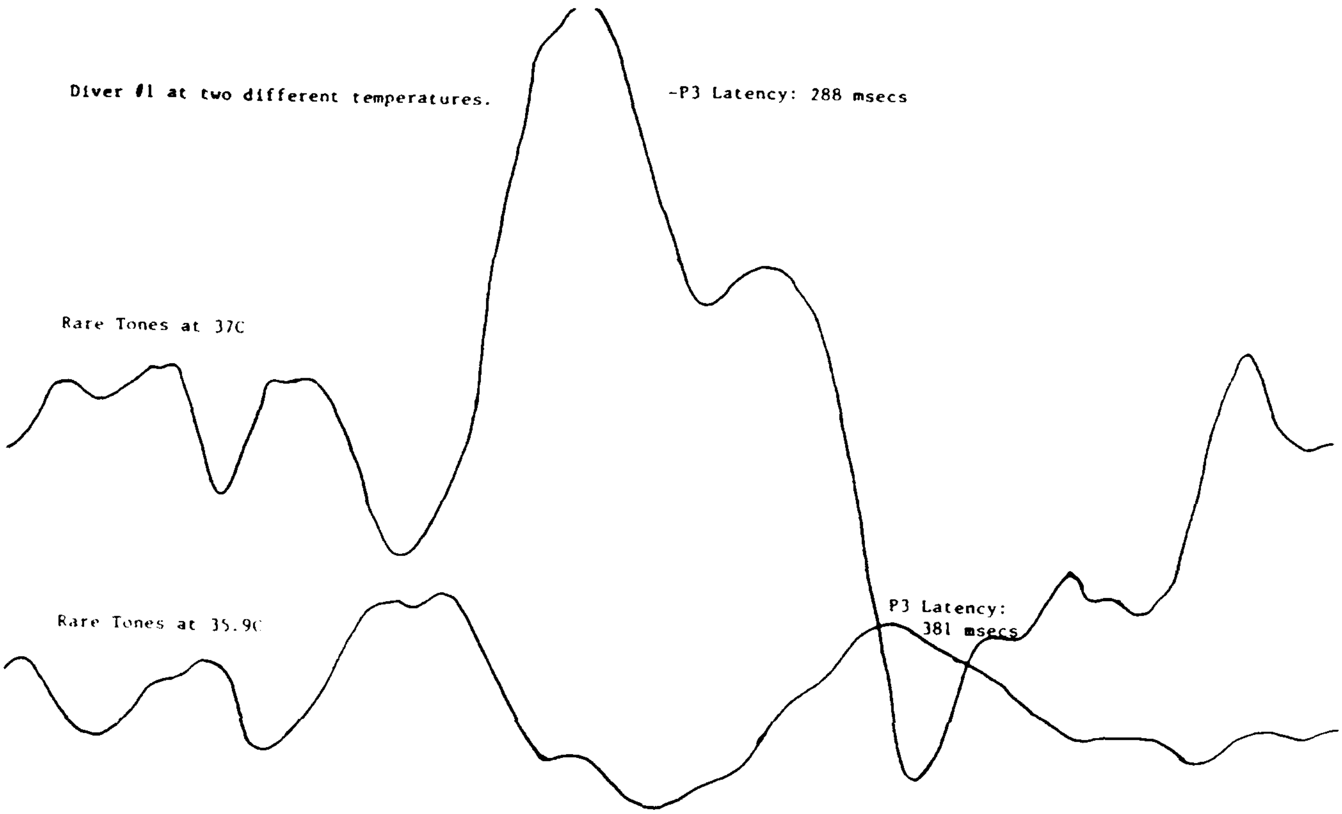

Figure 5. Evoked response to rare tones only, showing increase in latency with temperature reduction.

t = 0.689, p>0.5). The plot of N1 latencies versus temperature is shown in Figure 6.

DISCUSSION

The surface control latencies for P3 and N1 peaks agree very well with literature values for individuals in the age group studied (20,21,22). The P3 latency decreases between infancy and age 30, then increases thereafter; thus, the age range we have studied is at a minimum expected P3 latency (20). Some studies subdivided the P3 wave into P3a and P3b components, with the P3a occurring earlier and more prominently at Cz (23, 24). All of our recordings were derived from Cz and many of our recordings showed two distinct peaks on a broad positive wave, the first most probably corresponding to the P3a. The graphical measurement technique used averaged the contribution of these two waves. The P3 latency has a wide intersubject variability but is very repeatable for an individual, even when recorded on different days. Thus, our comparisons at different temperatures with control values are probably valid (25).

The lack of any temperature effect on the N1 latency is in accord with previous studies that did not show any correlation of the latency of the cortical response to visual stimulus with temperatures above 33.5 °C in a conscious man (4). The visual and auditory primary cortical evoked response both occur at approximately 100 msecs after the stimulus, and represent the electrical responses of the first cortical cells to receive the stimulus. There have been two studies that show a relationship between brainstem auditory response latencies and temperature in men (3,12). One of these studies examined men under anesthesia with deep hypothermia, and the other postulated that the diurnal variation in response latency was due to temperature. The brainstem response occurs within 10 msecs of the stimulus,

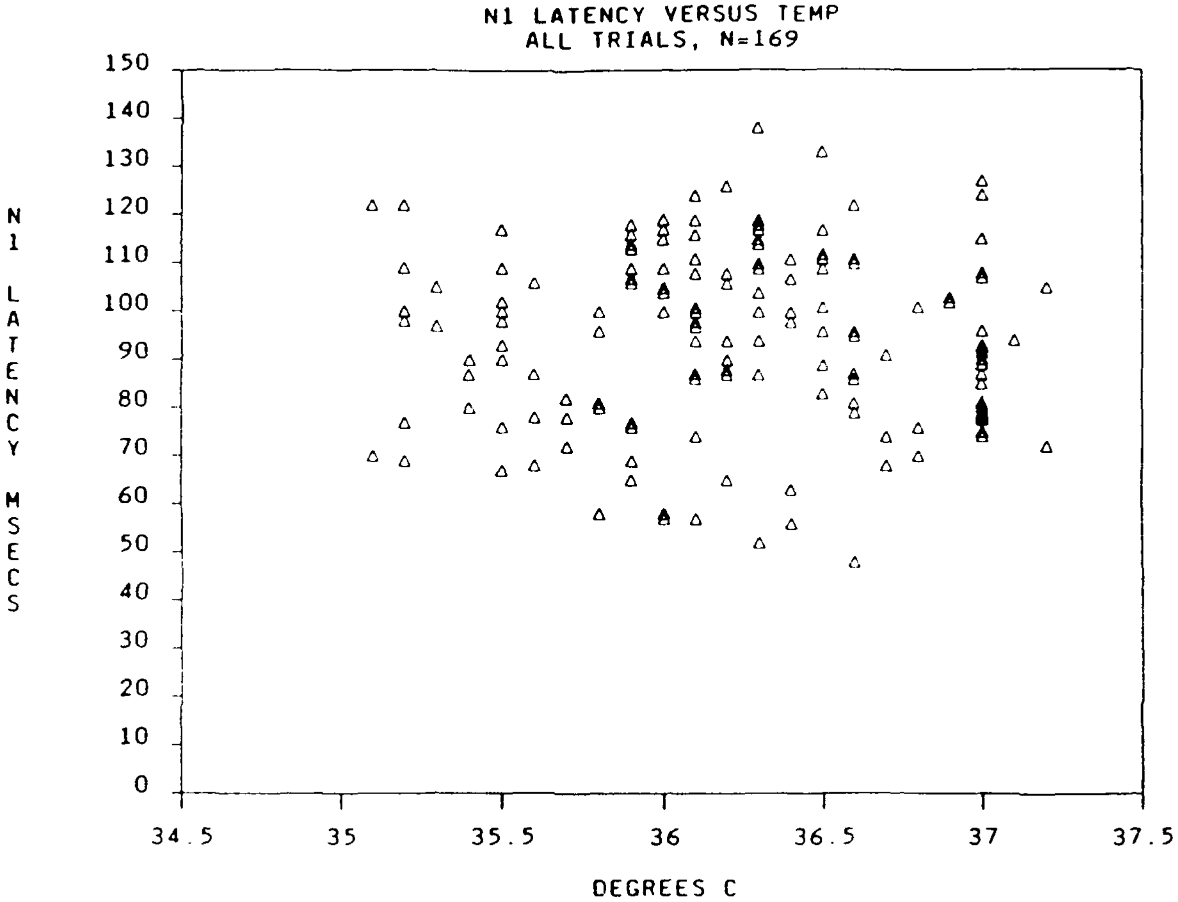

Figure 6. Graph of N1 latency versus temperature. No positive relation is evident.

and the total changes observed in the studies mentioned are on the order of tenths of msecs. These small changes would not be detectable over the 100-600 msec recording scale used for the cortical evoked responses (3).

We chose to record event-related potentials during the rewarming period mainly because of the difficulty in ensuring good recordings from an exercising, submersed diver. In addition, this procedure reduces the possibility that changes in the P3 latency are secondary to the distracting effect of cold water. Distraction due to cold discomfort, and changes in manual dexterity because of hand cooling have been postulated to account for observed changes in mental performance in the cold (10,11,12,26). Our design is similar to that of Coleshaw et al. (9), in which the tests were administered to comfortable subjects after a cool core temperature had been achieved. Thus, the relationship between temperature and P3 latency is more likely due to direct effects of brain cooling rather than secondary distraction. Most subjects in our runs were able to complete the task of mentally counting the rare tones successfully, with occasional reminders, further supporting the contention that distraction was limited. The records that were judged unreadable according to the repeatability and noise criteria were evenly distributed among all body temperatures. This would not be expected if the distraction of the subject prevented him from accomplishing the task when cold.

The P3 latency has been postulated to be a measure of the speed of processing information in the brain (17,23). The response roughly correlates with the reaction time to stimuli, and more specifically to the time needed to evaluate a stimulus for its information content (17,27). The P3 latency varies inversely with the number of digits repeated correctly, a test which is standard for estimating the attention of the subject (28,29), and with the physiologic orienting response (24). The response has been subdivided into multiple components, some reflecting the novelty of the stimulus, others more correlated with the degree of relevance to the task at hand (16,27). The scalp areas where the P3 can be recorded are numerous, suggesting that this reflects general activation of the information processing areas of the brain (30), although a voltage asymmetry reflecting hemispheric specialization for language or visuospatial tasks can be detected (31). These findings suggest that the change in P3 latency in this experiment may well be of significance to the mental performance and reaction time of the diver in the cold.

Several experiments have investigated the relationship of P3 latency to confusion and changes in reasoning in reversible and irreversible illnesses due to metabolic or degenerative changes in the brain (32). Using an "oddball" stimulus paradigm similar to that used in the present study, patients with latency increases that were between 0.75 and 2.0 standard deviations (SD) from the normal mean for their age all had abnormal mental status examinations. Most of them were frequently afflicted by memory deficits, but also had poor attention, disorientation and calculation (17). Our coldest subjects (35.2 and 35.1 °C) had an average P3 latency about 2 SD from the mean at 37 °C, suggesting possible memory and attention disturbances. This agrees well with the findings on standard performance tests that suggest that memory function is sensitive to changes in temperature (9). The P300 latency also lengthens in a dose-dependent manner when subjects breathe increasing concentrations of nitrous oxide, which produces mental alterations and slowed reaction times similar to those of narcosis (33).

This study constitutes further evidence that mild lowering of core temperature may be associated with changes in measures of mental performance. This may influence the diver's awareness and speed of evaluation of changes in his environment that constitute a threat to his survival or mission. The P3, however, seems to be a very sensitive measure of mental disturbance, which would tend to overestimate the risk of significant mental impairment. The highly motivated and trained individual may well be able to overcome these mental performance deficits, given appropriate training in and experience of the cold environment.

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