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PYRIDOSTIGMINE AND WARM WATER DIVING PROTOCOL 90-05: III COGNITIVE PERFORMANCE ASSESSMENT

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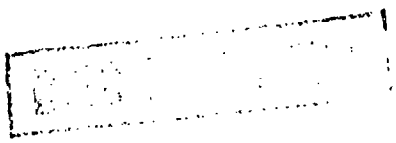

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TECHNICAL REVIEW AND APPROVAL

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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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This report describes the effects observed in cognitive performance during a study concerned with the consequences of pyridostigmine pretreatment on performance of divers during extended heat and warm water exposures. Ten U.S. Navy divers performed during two 7-hour heat and warm water tests. Each test consisted of a 4-hour predive exposure to 37.8° C air at the surface, followed by a 3-hour dive in 34.4° C water at a depth of 1.6 ATA breathing either air or 100% oxygen. Cognitive tests that measure short-term memory (Matching-to-Sample) and learning capability (Repeated Acquisition) were administered 30 min before entering the heat, after 2 and 4 h in the predive component, and immediately following the dive phase. Vision and coordination tests were conducted during the first and third hours of the predive phase and in rest periods during the dive component. A decrement in short-term

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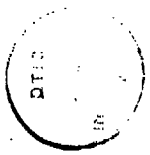
19. memory, evidenced by decline in accuracy, occurred over the 7-hour heat exposure. Accuracy declined more rapidly for the longest memory delay interval and least for the shortest memory interval. Learning of a specific sequence of responses was impaired during heat exposures in that the number of errors to learn increased during exposures. There were no observed differences of heat effects on memory or learning between pyridostigmine and placebo sessions. Also there were no systematic changes in memory or learning between post-immersion measures following air versus oxygen exposures. No differences were found in visual acuity or coordination between pyridostigmine and placebo sessions.

TABLE OF CONTENTS

	Page Numbers
Acknowledgements	iv
Introduction	1
Methods	2
Results	7
Discussion	10
References	16



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INTRODUCTION

Extended exposure to heat stress is capable of profoundly influencing cognitive performance (2,3,7,8,15), a finding of potential impact on military operations carried out in warm environments. Such findings indicate that an assessment of cognitive function is relevant to evaluating operational success of extended human performance assignments in even moderate heat environments. Additionally, studies have shown that cholinesterase inhibitors, such as pyridostigmine, may potentiate increases in core temperature when personnel are exposed to warm conditions for extended periods, and such increases may degrade cognitive performance (1,5,6,11). As it is possible that military personnel deployed in warm geographical areas may administer pyridostigmine as a prophylactic measure against organophosphate nerve agents, it is of concern to appraise the possible interactive effects of pyridostigmine on cognitive performance in a warm environment. The purpose of the present study was, as part of a research task concerned with assessing the effects of combination of pyridostigmine and warm water diving, to examine the separate and combined influence of extended heat stress exposure and administration of pyridostigmine on significant aspects of cognitive performance.

METHODS

The subjects were ten volunteer USN divers. Pertinent physical characteristics and features of the subjects may be found in a companion report by Doubt and Dutka (4). Overall methodologies related to details of experimental exposures, dive gases, and drug protocols are also described in the same report. Basically, the subjects performed during two 7-hour heat and warm water test exposures. For two days before and during one of the test exposures subjects ingested pyridostigmine, and during the other exposure the subjects ingested placebo. Each of the tests consisted of a 4-hour pre-dive exposure to 37.8°C air, followed by a 3-hour dive in 34.4°C water at a depth of 1.6 ATA breathing either air or 100% oxygen. Measures of cognitive performance were obtained at several different times throughout the test exposures as outlined below. The subjects were acclimated to 37.8°C temperature (50% humidity) in the Environmental Medicine Department climate-controlled chamber for five consecutive days prior to their first test exposure, and on alternate days between tests.

Cognitive performance during heat exposures, following immersion while breathing air or oxygen, and with administration of pyridostigmine was assessed by four different measures: 1) Delayed Matching-to-Sample, a measurement of short-term memory and recognition of spatial patterns; 2) Repeated Acquisition, a measure of learning capability and memory; 3) Visual Acuity; and 4) Mechanical Coordination. Both the Delayed Matching-to-Sample

and Repeated Acquisition tasks are part of a computer-controlled performance assessment battery (PAB) described in detail elsewhere (19).

Delayed Matching-to-Sample: A single matching task lasted for 45 trials. At the start of each trial of the task a matrix was presented as the sample stimulus. The matrix appeared in the center of a computer monitor screen. The matrix consisted of 36 cells (arranged 6 X 6) displayed in two colors, red and green. For each trial half of the cells were red and the other half green, with the cell location of the colors varied randomly. The matrix remained on the screen for two seconds and then was removed from the screen. The monitor screen remained blank for one of three delay intervals, either 2, 8, or 16 seconds. Each of the three delay intervals was programmed to occur randomly for 15 trials each during the total session of 45 trials. Following one of the three delay intervals a comparison matrix of 36 red and green cells was presented. Half of the time the matrix was the same as the sample matrix presented at the start of a trial, and the rest of the time the matrix differed from the sample matrix by the location of two cells. In the different matrix one red and one green cell appeared randomly in a different location than in the sample matrix. The subject was required to press the "1" key of the computer numeric keypad if the comparison matrix was identical to the sample matrix and to press the "3" key if the matrix was different. After the occurrence of a "same" or "different" response the screen was

blanked and the sample matrix for the next trial was presented. The accuracy and latency of matching responses were recorded separately for the three different delay intervals. Matching-to-sample tests were administered 30 minutes before entering the chamber, at two hours and four hours of the dry phase, and immediately post immersion. Subjects received ten sessions of training on the matching-to-sample task before their first exposure and two sessions of training before their second exposure.

Repeated Acquisition: During a repeated acquisition task the subject was required to learn a specific sequence of twelve responses by responding on four keys on the numeric keypad in the appropriate order. The subject was to learn which of the four keys was associated with each of twelve different squares presented on the computer monitor. The subject responded on the "2", "4", "8", and "16" keys of the numeric keypad. At the start of a trial the monitor displayed the outline of twelve blue squares on a black background. The squares were filled green, from left to right, with each successive correct response thereby indicating the progression through the sequence to the subject. At sequence completion the entire screen was green for 1.5 seconds, followed by the presentation of the twelve empty squares indicating the return to the first sequence position and the beginning of the next trial. Incorrect responses produced a one second timeout (TO) during which the screen was blanked. The screen was restored to its pre-TO state at the termination of a

TO. Responses during TO had no programmed consequence. The task lasted for 25 sequence completions (trials) or ten minutes, whichever occurred first. Data were collected in the form of response latencies from stimulus onset, keypad response, and whether the response was correct or incorrect.

During the study the response sequence for the repeated acquisition component changed each session, thereby requiring the subject to learn a new response sequence each session. The sequences were constructed with the restrictions that no response position ever repeated itself within the same sequence, that each response position appeared three times in each sequence, and that no sequence was repeated during the study. The instructions informed the subject about the basic nature of the tasks and requested that they respond as rapidly and accurately as possible. Repeated acquisition sessions were administered 30 minutes before entering the chamber (immediately following the matching to sample task), at two hours and four hours of the dry phase, and immediately following the wet phase. Subjects received ten training sessions on the repeated acquisition task prior to their first exposure and received two sessions of training prior to their second exposure.

Visual Acuity: Plastic cards with black lettering on white background were used to assess visual acuity. A series of eight letters or numbers were printed on each of seven cards. The card held three feet from the subject, plus the size of the lettering, resulted in a visual acuity of 20/40 to accurately read the card.

Acuity tests were conducted during the first and third hours of the dry phase, and during the second 10-minute rest period during immersion. At the start of each test the chamber ports were covered and all lights except one were turned off to control background lighting. Each acuity test consisted of two parts. First, a card was held three feet from the subject while ambient chamber lighting was reduced to the point where the subject could no longer discern the lettering clearly. The rheostat setting of the light was recorded as the acuity point of changing from light to dark. The second part of the test began by switching to another card and turning the rheostat setting to zero. The rheostat setting was then gradually increased until the subject could correctly identify the lettering on the card. The rheostat setting at this point was used to quantify acuity changing from dark to light conditions.

Mechanical Coordination: The coordination test required the subject to assemble twelve pairs of washers and nuts onto a 4-inch bolt as quickly as possible. The time to complete the task was recorded as the measure of overall coordination. Tests were conducted during the first and third hours of the dry phase, and during the first and third 10-minute rest periods of the wet phase (first 2 hours of immersion). During the immersed testing the tray containing the washers, nuts, and bolt was positioned underwater between the subjects.

RESULTS

Matching to Sample: Overall accuracy of matching (percent correct) was found to decline significantly across the seven-hour 37.8°C heat exposure ($p<.0001$). The lowest accuracy was obtained during the post immersion period. More important, accuracy declined more rapidly over the heat exposure for the 16-second delay interval and least for the 2-second delay (Figure 1). The data points represent the mean of all dives for the ten subjects, and the error bars indicate the standard error of the means. The first test period in Figure 1 shows accuracies obtained during test administration 30 minutes prior to entering the chamber. Test period 2 is at 2 hours and test period 3 is at 4 hours in the pre-dive heat exposure. Test period 4 indicates accuracies obtained on matching-to-sample immediately following immersion. There was a significant interaction between the length of a delay interval and exposure to heat stress ($p<.001$). Matching response latencies did not significantly change during the heat exposures, although there was a trend toward longer latencies at the post immersion measure. There were no consistent differences in matching

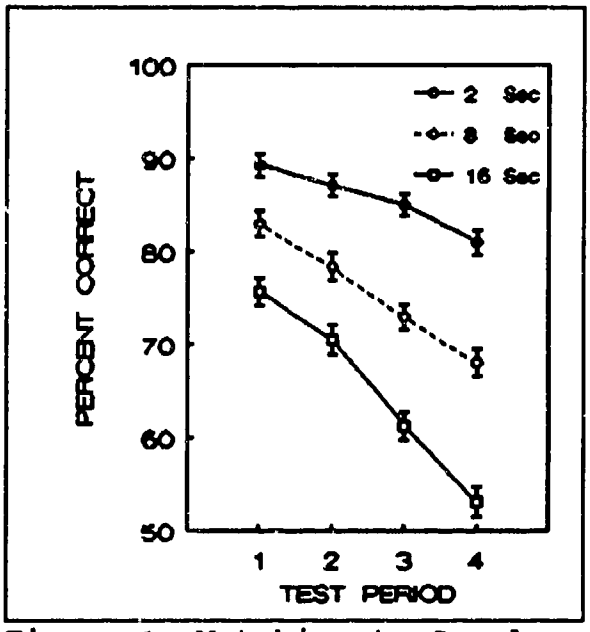

Figure 1 Matching to Sample

accuracy or latencies between pyridostigmine and placebo sessions. Likewise, there were no systematic changes in matching accuracy or latencies between post immersion measures following air versus oxygen exposures.

Repeated Acquisition: The average number of errors committed each session during the repeated acquisition procedure are presented in Figure 2. The data indicate that performance on this task deteriorated with each succeeding test period. (The test periods of Figure 2 are identical to those presented for matching-to-sample above). Analysis of these data indicate significant increases in errors ($p<.05$) between test period one (before entering the heat chamber) and both test periods three and four. The data points in Figure 2 represent the mean of all dives for the ten subjects. The error bars represent the standard error of the means. The data from all dives are combined, as no significant error differences were found between pyridostigmine and placebo conditions. Each repeated acquisition session consisted of 25 trials or 300 correct responses; therefore, the increase in the number of errors across test periods also represents an increasing proportion of incorrect

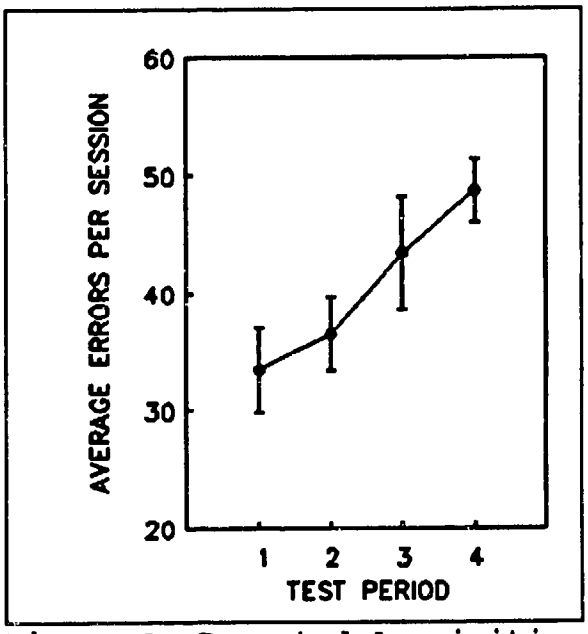

Figure 2 Repeated Acquisition

responses during successive test periods. There were no consistent effects of heat exposures or drug on latency of repeated acquisition responding.

Visual Acuity: The subjects in both drug and placebo groups had a lower threshold (in terms of chamber rheostat setting) when the illumination was lowered from light to dark than when the illumination was raised from dark to light. There were no significant differences observed between any of the obtained visual acuity measures in the pyridostigmine versus placebo comparisons.

Mechanical Coordination: The times obtained for the subjects to mount twelve washers and nuts on the bolt did not differ significantly between the placebo and drug conditions. No significant correlation of rectal temperature with the time needed to complete the coordination test could be detected (correlation coefficient: 0.0052).

DISCUSSION

The present experiment clearly demonstrates that complex cognitive performance was impaired by an extended exposure to 37.8°C, an exposure that did not increase core temperature significantly. Analysis indicated that the disruption of cognitive function as a result of a heat was unchanged by pretreatment of subjects with the cholinesterase inhibitor pyridostigmine. The fact that pyridostigmine had no effect on memory by itself or in combination with heat stress may reflect that pyridostigmine is minimally soluble in lipid membranes and does not readily cross an intact blood brain barrier (16). These data are consistent with previous reports showing that by itself, pyridostigmine is minimally behaviorally active in therapeutic dose ranges used for prophylaxis against nerve agents (3,9,10,12). It should be noted that other acetylcholinesterase inhibitors such as physostigmine, which does cross the blood brain barrier, have been shown to impair mental performance on a variety of tasks (14,17). However, these effects are fairly weak when compared to the cholinergic disruption produced by blockade of cholinergic receptors with agents such as atropine or scopolamine. The findings of behavioral deficits with physostigmine provide a benchmark from which to compare potential central anticholinesterase effects of pyridostigmine and possible effects of these agents on behavioral performance. Since there were no effects of pyridostigmine on several behavioral, neurological, and physiological indices utilized in

this study, it would appear that pyridostigmine did not cross the blood brain barrier under normal or heat stressed ambient conditions.

A clear and unequivocal finding in this study was that heat stress substantially impaired performance on the matching-to-sample and repeated acquisition tasks. A salient feature of these heat related deficits was that the magnitude of the impairment increased over the duration of exposure to the heat stress. In the matching-to-sample tasks there was an interaction between heat and delay intervals in that, relative to the performance at normal ambient temperature (test period 1), heat exposure produced less of a decrement in accuracy at the 2-second delay, a modest decrease at 8 seconds, and the largest decrease at 16 seconds. The interaction may be interpreted to indicate that heat stress selectively affected retention of information in working memory. That is, the effects of heat stress were most profound when maintenance of information over a long interval was required. The 2-second delay, less affected by the heat stress except in the fourth test session, requires only minimal temporal maintenance of information. That a slight heat-induced accuracy decrement at the 2-second delay was observed during the third and fourth test sessions indicates some impairment in acquisition of information, results which were confirmed in the repeated acquisition test at these same time points. After two hours of exposure to the dry heat a slight, but significant, decrease in memory performance at the 8- and 16-second delays was observed.

At the four hour test period performance at the longer delays dropped further and was near chance performance at the 16-second delay when subjects were tested at the fourth test period. Generally, the greatest degree of memory impairment on the matching-to-sample task was observed at the 8- and 16-second delay intervals, especially when subjects performed the task after being exposed to the warm water-exercise stress at the end of the exposure period. The severe decrement in memory performance at the long delay intervals during heat stress is indicative of a selective impairment in the maintenance of information in working memory with increasing delay.

The finding that a heat stress impaired accuracy on the matching-to-sample task supports previously reported accuracy decrements in other forms of complex cognitive performance obtained during thermal stress (18). Qualitatively, however, impairment of matching-to-sample performance observed when subjects were exposed to cold stress are quite different from those observed with heat exposure. During cold stress, impaired performance accuracy at long delays was accompanied by substantial changes in the temporal features of the tasks. In a recently published study from our laboratory we observed that response times to the sample matrix were consistently faster and comparison response times slower in subjects exposed to an environmental temperature of 2°C for 90 minutes (18). These changes in the temporal features of the response to the sample and test stimuli were generally followed by incorrect choice

responses. During exposure to heat stress in the present study impaired choice accuracy on the delayed matching-to-sample task was accompanied with slowing of response times. The demonstration of a different temporal pattern in response to stimuli during heat and cold stress suggest that while both heat and cold stress produce a similar type of performance decrement on matching-to-sample accuracy, the mechanisms underlying the impairment of memory may be distinct.

In the repeated acquisition task a gradual trend of increased errors was observed to occur across the test sessions. Repeated acquisition is a procedure that measures the ability to learn and retain new sequenced information. In the present study, exposure to heat stress for two hours increased error rate on this task. Error rate increased substantially in the third and fourth test sessions, indicating a substantial impairment in the ability to acquire a new information with extended exposure to heat stress.

Collectively, from the results of the matching-to-sample and repeated acquisitions tasks it is apparent that extended heat stress exposure can decrease the ability of personnel to learn and retain information. It is important to note that both these decrements in the ability to learn and remember information are specific in the sense that the deficits occurred under conditions in which subjects were not impaired in terms of their sensory or motor abilities. Results from this study clearly demonstrate that heat stress did not impair subjects' motor coordination on

the skilled task requiring them to mount washers and nuts on a 4-inch bolt. In addition, subjects visual acuity was not impaired by heat, a finding supported by other research (20). Although heat stress substantially impaired subjects' ability to learn and remember information, these changes in cognitive performance occurred under conditions in which subjects were able to complete the task requirements, i.e., these decrements in learning and memory were not confounded by impairment of sensor or motor abilities required to complete the task. Once again, these data are indicative of a selective effect of heat stress on specific cognitive abilities related to learning and memory.

Studies have shown that administration of pyridostigmine decreases peripheral blood flow which may potentiate the increase in core temperature when personnel are exposed to warm ambient conditions over 35°C for an extended period of time (1,5,6,11). Although this increase in core temperature could exacerbate the cognitive deficit function produced by sustained exposure to heat, there was no evidence of this in the present study.

Cognitive performance changes resulting from thermal stress have been theoretically interpreted and explained in a variety of ways. Some studies have suggested that cognitive impairments result from increased distraction, increased arousal, or possibly a direct effect of thermal changes on neural tissue (18). While the findings of the present research do not provide a direct test of possible underlying mechanisms of heat-induced cognitive impairments, they clearly indicate that the design of tasks and

equipment intended for use in even moderate heat environments should carefully consider what particular aspects of cognitive behavior are involved.

In summary, the results of the present research clearly show that a complex performance involving the ability to learn and retain new information is systematically impaired by prolonged exposure to heat stress. These deficits stemmed from a specific heat stress on learning and memory since sensory and motor performance were not impaired. Importantly, exposure to the acetylcholinesterase inhibitor pyridostigmine did not affect any behavioral or psycho-physiological component when given alone or in combination with heat stress.

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