NITROGEN NARCOSIS AND THE VISUAL EVOKED RESPONSES IN THE UNANESTHETIZED CAT

by

Raymond T. Bartus, Ph.D.

NAVAL SUBMARINE MEDICAL RESEARCH LABORATORY
REPORT NUMBER 757

Bureau of Medicine and Surgery, Navy Department
Research Work Unit MF51.524.004-9015DA5G.08

Transmitted by

Jo Ann S. Kinney, Ph.D.
Head, Vision Branch

Reviewed and Approved by:

Charles F. Gell, M.D., D.Sc.(Med)
SCIENTIFIC DIRECTOR
NavSubMedRschLab

Approved and Released by:

R. L. Sphar, CDR MC USN
OFFICER IN CHARGE
NavSubMedRschLab

SUMMARY PAGE

THE PROBLEM

To investigate the neurological locus of nitrogen narcosis in the visual system, using visual evoked responses averaged from cortical and subcortical areas of the cat.

FINDINGS

It was found that nitrogen narcosis produces significant decreases in the amplitude of cortical visual evoked responses by directly influencing normal functioning in the brain, as opposed to acting merely at peripheral sites. Furthermore, the narcosis apparently impairs neural functioning at many different levels of the brain, since it was found that neural areas both higher and lower than the primary receiving cortex were equally affected.

APPLICATION

Since nitrogen narcosis was found to affect the normal functioning of the central visual system at several functional levels, it can be expected that performance on almost any task requiring the use of visual processes will in some way be influenced while breathing hyperbaric air.

ADMINISTRATIVE INFORMATION

This investigation was conducted as part of Bureau of Medicine and Surgery Research Unit MF51.524.004-9015DA5G. The present report is Number 8 on this work unit. It was submitted for review on 30 July 1973, approved for publication on 12 September 1973 and designated as NavSubMedRschLab Report No. 757.

PUBLISHED BY THE NAVAL SUBMARINE MEDICAL RESEARCH LABORATORY

ABSTRACT

Four cats were implanted with gross, unipolar electrodes in the lateral geniculate nucleus (LGN), pretectum-superior colliculus (P-SC), primary visual cortex (VI), and secondary visual cortex (VII). After an adequate recovery period, and following preliminary testing, the cats were exposed to the sea water equivalent depth of 340 feet in a dry pressure chamber. It was found that no decrements in the amplitude of the visual evoked response occurred at the LGN, but that significant decreases did occur at all other sites. These data were interpreted as evidence that the effects of inert gas narcosis on the visual system are primarily central, and not simply peripheral in nature; that these effects are not limited to the visual cortical mantle; and that the narcosis apparently influences the neural activity of brain structures involving several anatomical levels of the brain which mediate several types of visual processes. On the basis of these conclusions, one can expect performance on almost any type of task requiring visual processing to be affected by various degress of inert gas narcosis.

NITROGEN NARCOSIS AND THE VISUAL EVOKED RESPONSE IN THE UNANESTHETIZED CAT

INTRODUCTION

When nitrogen and other physiologically inert gases are breathed under pressure, narcotic-like symptoms occur which presumably result from an interference with normal neural functioning.[1] These symptoms manifest themselves in various behavioral and neurophysiological impairments called "inert gas narcosis". When compressed air is breathed the symptoms occur quite frequently because of the existing high partial pressure of nitrogen. Although past efforts have enabled researchers to accurately predict the degree of behavioral deficit that can be expected with various pressure levels and gas mixtures, a question that remains unanswered is the manner in which the compressed gas influences normal brain functioning. Not only is little understood about the specific underlying neurophysiological and/or biochemical mechanisms that are impaired, but very little is known about the general neurological effect; that is, what specific systems or parts of systems are most seriously altered, and in what manner.

However, due to the development of signal averaging techniques, it may now be possible to test many of the major issues in this area; for example, several investigators have demonstrated recently that the amplitude of the primary components of the sensory cortical evoked response is significantly attenuated when air is breathed under pressures exceeding three atmospheres (i.e., 100 ft.)[2,3,4,5,6,7] On the other hand, no such decrements occur when the nitrogen in the air is substituted with a less narcotic gas.[3,4,6] These studies indicate therefore that the sensory systems, at least at the cortical level, are in some way influenced by the compressed gas. However, the exact nature and neuroanatomical locus of this influence remain unclear. It is obvious that to simultaneously monitor the electrical activity at several levels of a sensory system and evaluate selective changes in the averaged evoked response resulting from the effects of inert gas narcosis might be a very fruitful approach.

METHOD

Surgical Procedure

Surgery was performed on four adult cats under Penthrane anesthesia, which was administered via an endo-tracheal tube and regulated by a standard aerosol anesthetic unit. Under sterile surgical procedures, the cats were implanted with chronic gross electrodes in the primary and secondary visual cortex, lateral geniculate nucleus (LGN) and pretectum-superior colliculus complex (P-SC). The implantation procedure was a modification of the technique described by Ferris and Bartus,[8] where small, self-tapping stainless steel screws were threaded into the skull to serve as surface electrodes, while similar, but larger screws were used as assembly anchors (also, see Bartus and

Ferris[9]). The surface electrodes were positioned according to the skull landmarks over the primary visual cortex (VI), secondary visual cortex (VII), ipsilateral nasal sinus (for reference), and contralateral nasal sinus (for ground).

Depth electrodes for the LGN and P-SC were constructed of 0.25 mm diameter stainless steel wire, insulated with Epoxylite, except for a 0.5 mm recording tip. These electrodes were positioned by atlas, according to Snider and Neimer[10] and were chronically implanted using standard stereotaxic techniques. The atlas coordinates used for the P-SC were 3.50 A, 2.50 L and 4.50 D, while the coordinates for the LGN were 6.00 A, 10.50 L and 4.75 D.

Each cat was given a minimum six-week recovery period before testing was begun.

Testing Procedure

In order to facilitate the recording of visual evoked responses (VERs) from chronically prepared, unsedated cats, a specially designed head-holder, body-restrainer was used (see Bartus[11]). With their head movement limited by the head-holder, the cats were positioned so that they were facing and centered in the middle of a white, opaque hemisphere (see Fig. 1). A Grass Model P-2 Photo Stimulator was placed directly behind the cat, and the visual stimuli were produced by reflecting discrete flashes of light from the photo stimulator onto the hemisphere.

For the hyperbaric tests, the flashes were projected onto the reflecting hemisphere through a porthole in the wall of a dry-compression chamber. The photo stimulator intensity was set at 16, and a flash rate of 1.0 hz was used.

The electroencephalogram (EEG) from the four electrode locations was amplified with Grass P-511 amplifiers and recorded on FM tape for later analysis. Digital pulses, time-locked to the photo stimulator flashes, were also recorded on magnetic tape to serve as the sweep trigger for the signal averager. The EEG was averaged with a Technical Measurement Corp. Computer of Average Transients (CAT), and permanent records were written out with a Plotamatic X, Y recorder.

Before hyperbaric tests were begun, extensive recordings were taken on all cats, and it was found that if a minimum of 30 minutes of dark adaptation was given, the primary components of successive VERs varied very little as the result of repeated stimulation, or total amount of time elapsed during testing. The shapes of the averaged VERs obtained from these preparations were very similar to those reported by other researchers using cats.[3,7,12] One such record, obtained from VI, is shown in Fig. 2 and was chosen because the major components stand out particularly well.

During the preliminary recording sessions it was found that the component descriptively labeled P1 was absent almost as often as it was present, and the variability of N2, in terms of latency and amplitude often made it difficult to

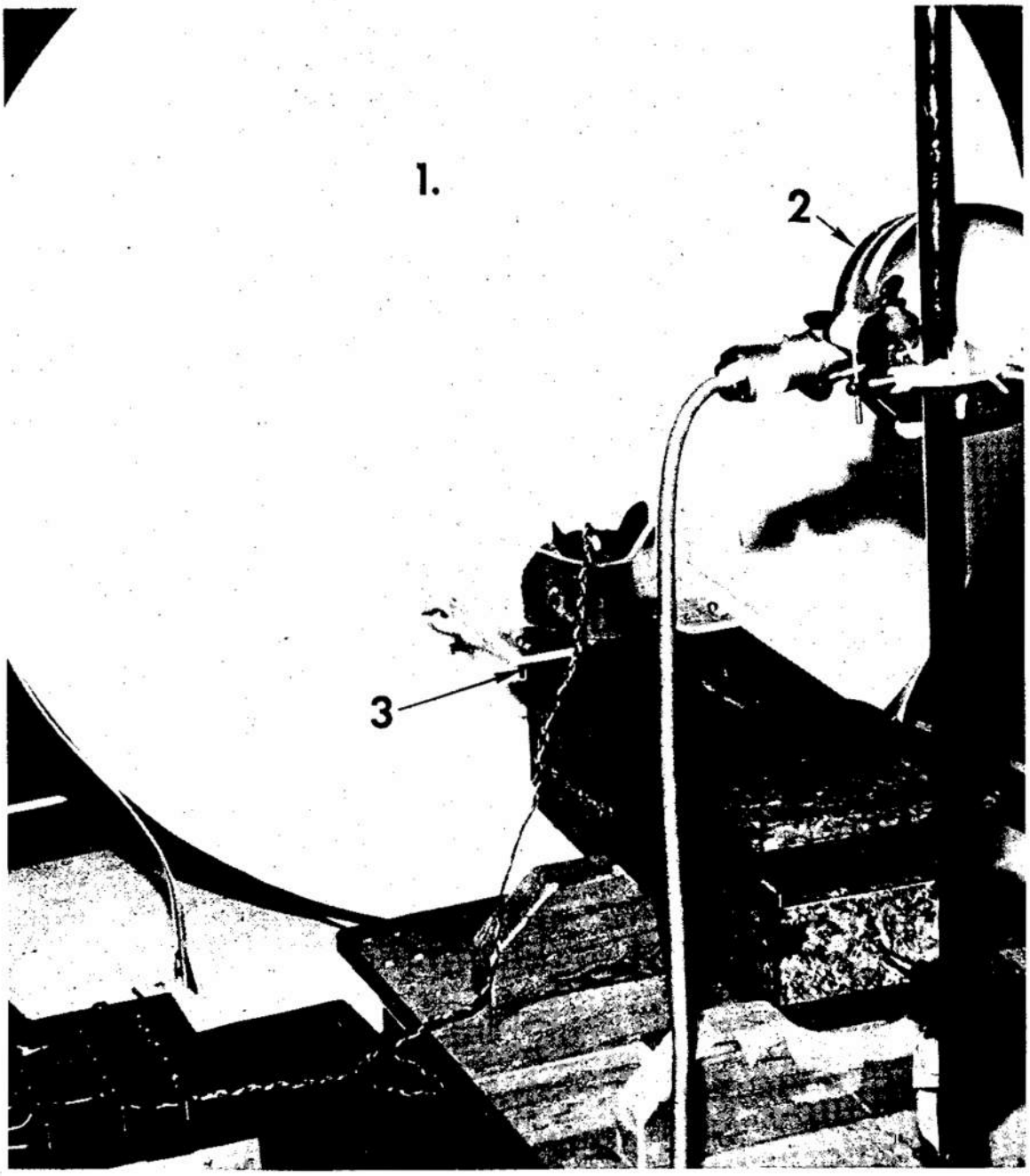

Fig. 1. Experimental arrangement showing: (1) Reflecting hemisphere, (2) Position of photo stimulator, and (3) Position of cat in head-holder and body-restrainer.

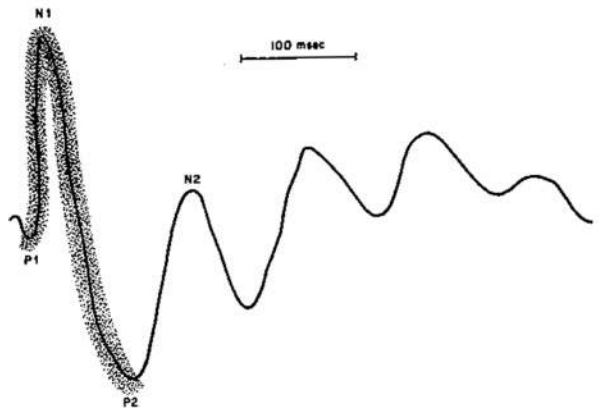

Fig. 2. Averaged evoked response from VI (area 17) of the cat.

distinguish it from later occurring components. For this reason, only the amplitude of N1 (measured peak to peak from P1 to N1) and amplitude of P2 (measured peak to peak from N1 to P2) were used to assess the effects of inert gas narcosis on the VER. The slow-wave after-discharges shown in Fig. 2 were consistently present in the records of two cats, but were virtually nonexistent in the other two cats.

EXPERIMENT 1

Three cats were used in this experiment, with each cat serving as his own control. Compression stops of two minutes each for data collection were made at 50, 200, and 300 ft. and decompression stops at 200 and 50 ft were incorporated into the decompression schedule for additional data. Testing was begun 30 seconds after reaching each pressure level, and consisted of averaging the neural responses evoked by fifty discrete flashes of light.

Results: Cortical VERs obtained at 50 feet (where past studies have shown no measurable signs of narcosis) were compared to preliminary surface VERs, and as expected, no changes were evident. The effects of narcosis on the primary VER components were evaluated by calculating the percentage change in amplitude that occurred from 50 feet to 200 feet and 300 feet. Since no consistent differences existed between changes in N1 and P2, the data for these two components were pooled.

As reported by other authors using cats,[3,7] considerable individual variability existed in the degree to which narcosis influenced the brain activity. The median percentage change in amplitude for the four brain locations is shown in Fig. 3, with the shaded area depicting the total range of change for the two primary components of each of the three cats.

The most consistent change occurred at the primary visual cortex (VI) resulting in a significant decrease in amplitude at 300 feet ($\underline{p} = .015$, Mann-Whitney U-test). Although no other changes were statistically reliable by conventional standards, the attenuation at 300 ft in VII as well as P-SC did approach significant levels ($\underline{p} = .093$ and .070, respectively). Changes at 200 ft were highly inconsistent at all electrode locations, and VERs from the LGN actually showed small, but highly inconsistent increases in amplitude at both depths.

Although it is tempting to conclude on the basis of these data that the most important effects of nitrogen narcosis in

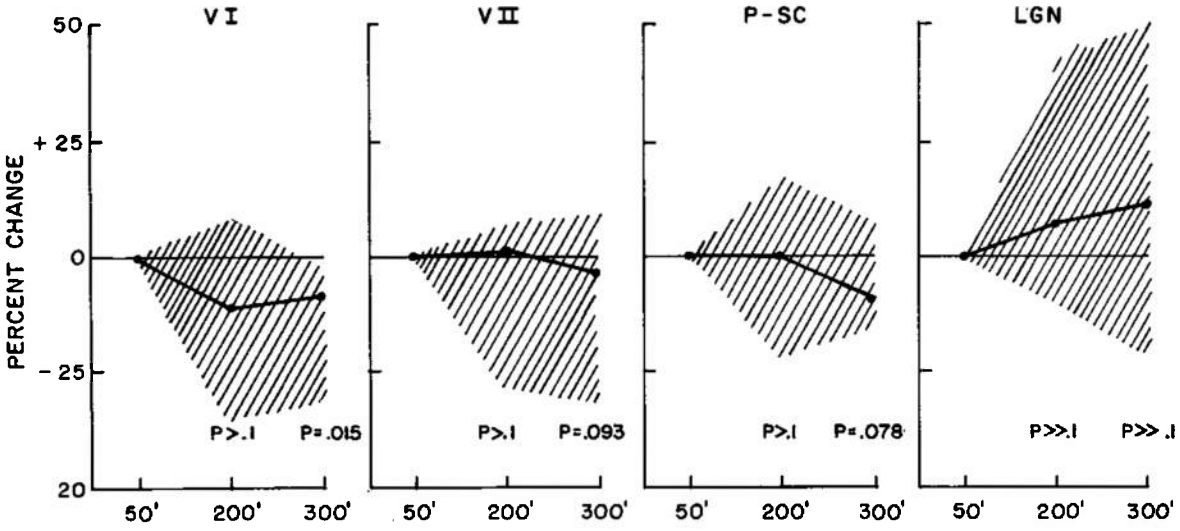

Fig. 3. Experiment #1: Percent change in amplitude of primary VER components.

the visual system occur in the primary visual cortex, such a conclusion would probably be unwarranted. For example, Bennett[3] indicated that the effects of nitrogen narcosis on the primary components of the cat's auditory evoked response (AER) are not apparent until several minutes at depth have elapsed. In fact, he noted that temporary but consistent increases in amplitude began during compression and were often still influencing the amplitude of the AER during the first few minutes after the bottom depth was reached. Since the recordings in the present study were begun after only 30 seconds had elapsed at each depth, it is not unlikely that a similar excitatory influence may be effecting the present measure of narcosis in the cortical and subcortical nucleii of the visual system. For this reason, it was decided to hyperbarically expose the cats once more, but to a depth equivalent of 340 feet and with a nine-minute waiting period occurring between the time 340 feet was reached and the time the VERs were recorded. These particular parameters were chosen on the basis of calculations estimated to give the optimal trade-off between severity of narcosis and safety for the cats during decompression.

EXPERIMENT 2

The general procedure for this experiment followed that of Experiment 1 except that the control VER was taken just before compression began and a single depth of 340 ft was used with a nine minute bottom time interval elapsing before the experimental VER was recorded. Also, a fourth implanted cat was added to the design.

Results: Figure 4 demonstrates the significant effect of narcosis in the amplitude of the averaged VERs. Once again there were no consistent differences in the change of N1 versus P2, and the data from these two components were again pooled. As can be readily seen from Fig. 4, the amplitude of the VERs in VI, VII, and P-SC all showed significant decreases at 340 ft. The size of the decrement reported is comparable to those decreases in auditory cortical evoked responses, reported by Bennett[3] for the same "bottom time" interval.

As in Experiment 1, no signs of attenuation were found in the LGN, and the percentage change was again extremely variable. Thus, the essential findings of Experiment 1 were replicated and strengthened in this second experiment.

DISCUSSION

Several points concerning the influence of nitrogen narcosis on neural functioning are evident from the data reported in these studies. Of definite importance is the finding that no significant decreases in VER amplitude occurred at the LGN. Since this nucleus is the major way-station for visual information leaving the retina and projecting to the visual cortex, this finding demonstrates that the effects of nitrogen narcosis on sensory evoked responses occur centrally and are not merely the result of peripheral influences which are simply being relayed through the visual system.

Another finding is that the effects of nitrogen narcosis are not limited to cortical sensory areas, for significant decreases also occurred in the P-SC

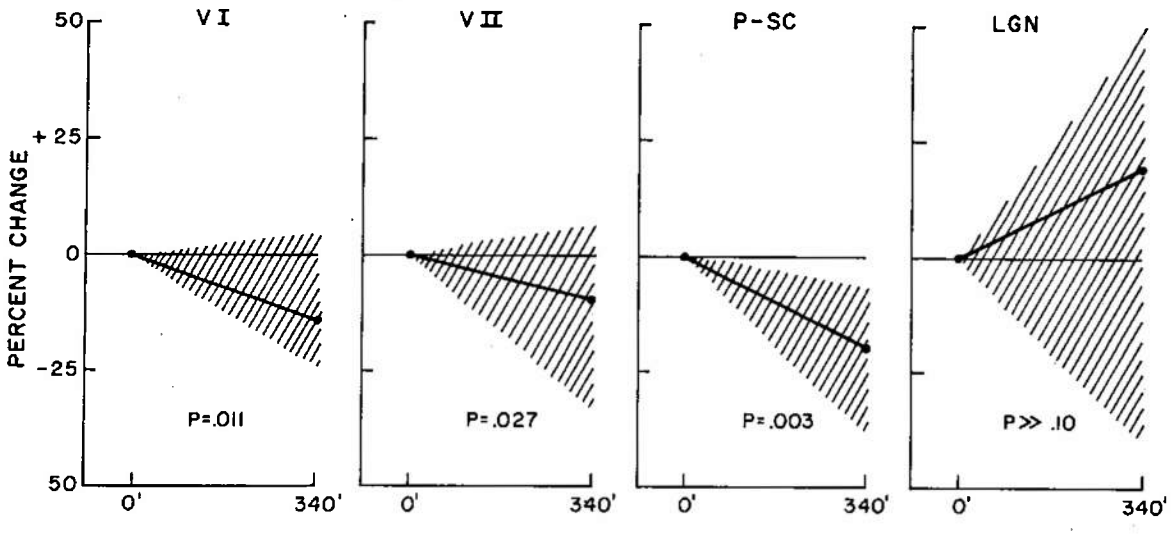

Fig. 4. Experiment #2: Percent change in amplitude of primary VER components.

area. A question which naturally follows from this is whether these effects at the P-SC are due to an actual influence of narcosis at that site, or are merely the end result of some influence at a nucleus which projects to the P-SC. One such afferent influence might be the Ascending Reticular Activating System (ARAS), for Bennett[3] has reported a significant decrease in the amplitude of AERs recorded in this region. Thus, it is possible that all sensory effects of narcosis are actually due to changes in the influence of the ARAS. Although this possibility cannot be dismissed on the basis of available data, many of our findings suggest that this is unlikely. For example, although some theorists contend that the ARAS projects to all synaptic levels of all sensory systems,[13] hard anatomical data implicating specific projections to the P-SC is lacking. Additionally, if the ARAS is somehow playing a major role in reducing the amplitude of the P-SC because of its presumed influence at all synaptic levels, then it is somewhat confusing why similar changes do not occur in the LGN. On the other hand, since direct projections are known to exist from the P-SC area (and from VI as well) to the ARAS,[14,15] it is equally likely that any attenuation observed in the ARAS is actually the result of input from these sensory sources. It should be pointed out that resolution of this issue is of more than passing interest for the etiology of nitrogen narcosis. Bennett[3] has suggested that the site of neural impairment for nitrogen narcosis is primarily limited to the "polysynaptic systems of the brain, such as those found in the reticular system and cortical mantle" (p. 394). Yet, the optic P-SC is composed of rather "primitive gray matter.. (having) short stubby dendrites," and for the most part comparatively little dentritic poliferation.[14,](p.234) If the changes observed in the P-SC are in fact the result of direct alteration in neural functioning at that site, then some modification of the hypothesized mechanism by which nitrogen narcosis affects the normal functioning of individual neurons may be necessary.

There exists yet another indirect avenue through which VERs in the P-SC area may have been attenuated. It is known that the primary visual cortex of the cat projects directly to the P-SC.[16] Furthermore, temporary depression or excitation of this cortex via topically applied chemicals respectively increases or decreases the VERs of the P-SC area to light or optic nerve stimulation.[17,18] It is therefore conceivable that the depression of the VERs in the P-SC is due merely to the depressed input from VI. If such a notion were true, however, one would have to predict that a high correlation should exist between the decrease in amplitude of VERs at both neural areas. Such a test was therefore computed, and it was found that the correlation between changes in VI and the P-SC was extremely small ($r = .17$; $p > .10$). In contrast, the correlation between changes in VI and VII (which also receives direct input from VI) was highly significant ($r = .98$, $p < .0005$). Thus, it seems extremely unlikely that the attenuation found in the P-SC area is simply the indirect effect of narcotic influences on VI. (At the same time these data further serve to decrease the likelihood that the changes in the visual cortex and P-SC result from changes in some common afferent input, such as the ARAS.) Thus, although perhaps no

definite conclusion is yet permissible, these data strongly suggest that nitrogen narcosis not only acts directly at the visual projection areas of the cortex, but at certain rudimentary, sub-cortical visual structures as well.

Another finding of some interest was that the effects of narcosis at VII were not greater than those at VI. It has been suggested that those structures involved with higher behavioral processes are more severely affected than those concerned with more elementary mechanisms.[19] On the basis of neurophysiological[20] as well as neuropsychological[21,22] evidence, it might therefore be expected that the neural activity in area VII would be most severely impaired. However, the data do not confirm this prediction. In fact, since equally robust effects occurred at the P-SC, which is generally believed to participate primarily in various reflexive and visual coordination mechanisms,[16,23] it would seem that nitrogen narcosis affects the central visual system without regard to anatomical level or function.

In conclusion, the most general findings of others using humans[2,4,5,6] and anesthetized cats,[3,7] showing that significant decreases occur in the amplitude of the primary components of cortical, sensory evoked responses have been replicated using chronically implanted, unsedated cats. Furthermore, these results have been extended by demonstrating that this effect is the result of central rather than peripheral influence, and that it occurs at levels of the brain both higher (VII) and lower (P-SC) than the primary sensory cortex. On the basis of these data one would predict that numerous visual mechanisms will be adversely affected by the narcosis (e.g., see Bartus[24]) and, therefore, that most tasks requiring almost any type of visual functioning will be, to some degree, impaired.

REFERENCES

1. Bennett, P. B. The Aetiology of Compressed Air Intoxication and Inert Gas Narcosis. New York: Pergamon Press, 1966.

2. Ackles, K. N. and Fowler, B. Cortical evoked response and inert gas in man. Aerospace Med 42: 1181-1184, 1971.

3. Bennett, P. B. The effects of high pressures on inert gases on auditory evoked potentials in cat cortex and reticular formation. EEG Clin Neurophysiol 17: 388-398, 1964.

4. Bennett, P. B., Ackles, K. N., and Cripps, V. J. Effect of hyperbaric nitrogen and oxygen on auditory evoked responses in man. Aerospace Med 40: 521-525, 1969.

5. Bevan, J. The human auditory evoked response and contingent negative variation in hyperbaric air. EEG Clin Neurophysiol 30: 198-204, 1971.

6. Kinney, J. A. S. and McKay, C. L. The visual evoked response as a measure of nitrogen narcosis in Navy divers. Naval Submarine Medical Center, Groton, Conn., Nav SubMedRschLab. Rep. No. 664, 1971.

7. Larson, C. R., Sutton, D., Taylor, E.M., and Burns, J. D. Visual

evoked potential changes in hyperbaric atmospheres. Arizona State University, Tempe, Ariz., Tech. Rep. 71-02, 1971.

8. Ferris, S. H. and Bartus, R. T. A method for recording and analyzing EEGs and VERs from rats under hyperbaric conditions. Naval Submarine Medical Center, Groton, NavSubMedRschLab Rep. No. 747, 1973.

9. Bartus, R. T. and Ferris, S. H. A modified method of implanting monopolar cortical electrodes in large laboratory animals. Naval Submarine Medical Center, Groton, Conn., NavSubMedRschLab Rep. No. 750, 1973.

10. Snider, R. S. and Niemer, W. T. A Stereotaxic Atlas of the Cat Brain. Chicago: Univ. of Chicago Press, 1961.

11. Bartus, R. T. A feline head-holder and body-restrainer for use in chronic visual electrophysiological research. Naval Submarine Medical Center, Groton, Conn., NavSubMedRschLab Rep. No. 745, 1973.

12. Thompson, R. F., Bettinger, L. A., Birch, H., and Groves, P. M. Comparison of evoked gross and unit response in association cortex of waking cat. EEG Clin Neurophysiol 27: 146-151, 1969.

13. Hernandez-Peon, R., Scherrer, H., and Jouvet, M. Modification of electric activity in cochlear nucleus during "attention" in unanesthetized cats. Science, 123: 331-332, 1956.

14. Crosby, E. C., Humphrey, T., and Lauer, E. W. Correlative Anatomy of the Nervous System. New York: The MacMillan Co., 1962.

15. French, J. D. The reticular formation. In Field, J., Magoun, H. W., Hall, V. E. (Eds.) Handbook of Physiology Vol. II. Washington, D.C.: Amer. Physiological Society, 1281-1305, 1960.

16. Creutzfeldt, O. and Sakmann, B. Neurophysiology of Vision, Ann Rev Physiol 31: 499-544, 1969.

17. Jassik-Gerschenfeld, D., Ascher, P., and Guevara, J. A. Influence of the geniculo-cortical system on visual responses of the superior colliculus. Arch Ital Biol 14: 30-49, 1960.

18. Meulders, M. and Colle, J. Influence de cortex visuel sur l'activité evoquée dan le voies optiques souscorticales. EEG Clin Neurophysiol 20: 475-484, 1966.

19. Keissling, R. J. and Maag, C. H. Performance impairment as a function of nitrogen narcosis. J Appl Psychol 46: 91-95, 1962.

20. Hubel, D. H. and Wiesel, T. N. Receptive fields, binocular interaction and functional architecture in the cat's visual center. J Physiol 160: 106-154, 1962.

21. Mishkin, M. Visual mechanisms beyond the striate cortex. In Fron-

tiers in Physiological Psychology, Russell, R. (Ed.) New York: Academic Press, 93-119, 1966.

22. Mishkin, M. Cortical visual areas and their interactions. In Brain and Human Behavior, Karczmar, A. G. and Eccles, J. C. (Eds.) Heidelberg: Springer-Verlag, pp. 187-208, 1972.

23. Gordon, B. The superior colliculus of the brain. Sci Amer 227: 72-82, 1972.

24. Bartus, R. T. Behavioral effects of nitrogen narcosis in the Rhesus monkey. Naval Submarine Medical Center, Groton, Conn., NavSub MedRschLab Rep. No. 755, 1973.

UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author) NAVAL SUBMARINE MEDICAL RESEARCH LABORATORY, Naval Submarine Medical Center	2a. REPORT SECURITY CLASSIFICATION Unclassified 2b. GROUP

3. REPORT TITLE
NITROGEN NARCOSIS AND VISUAL EVOKED RESPONSES IN THE UNANESTHETIZED CAT

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)
Interim report

5. AUTHOR(S) (First name, middle initial, last name)
Raymond T. BARTUS, Ph. D.

6. REPORT DATE 12 September 1973	7a. TOTAL NO. OF PAGES 10	7b. NO. OF REFS 24
8a. CONTRACT OR GRANT NO. b. PROJECT NO. MF51.524.004-9015DA5G c. d.	9a. ORIGINATOR'S REPORT NUMBER(S) NSMRL Report No. 757 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)	

10. DISTRIBUTION STATEMENT
Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Naval Submarine Medical Center Box 600 Naval Submarine Base Groton, Connecticut 06340

13. ABSTRACT

Four cats were chronically implanted with gross, monopolar electrodes in the lateral geniculate nucleus (LGN), pretectum-superior colliculus (P-SC), primary visual cortex (VI), and secondary visual cortex (VII). After an adequate recovery period, and following preliminary testing, the cats were exposed to the sea water equivalent of 340 feet in a dry pressure chamber. It was found that no decrements in the amplitude of the visual evoked response occurred at the LGN, but that significant decreases did occur at all other sites. These data were interpreted as evidence that the effects of inert gas narcosis on the visual system are primarily central, and not simply peripheral in nature; that these effects are not limited to the visual cortical mantle; and that the narcosis apparently influences the neural activity of brain structures involving several anatomical levels of the brain which mediate several types of visual processes. On the basis of these conclusions, one can expect performance on almost any type of task requiring visual processing to be affected by various degress of nitrogen narcosis.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Nitrogen narcosis						
Electrophysiology						
Visual evoked responses (VERs)						
Vision						
Animal research						