Neurobiological investigations of adaptive neural networks were initiated using the classically conditioned nictitating membrane response (NM CR) of rabbit. One experimental approach involved recording from single brain neurons from awake, behaving animals for the purpose of determining the loci and characteristics of neurons with activity correlated with the NM CR or its inhibition. A second approach involved the use of discrete brain lesions that selectively eliminate the NM CR while at the same time sparing the basic reflex pathway. A third approach employed fiber-tracing anatomical techniques designed to clarify the interconnectivity among brain regions essential for the NM CR. These regions include discrete portions of the cerebellum and brain stem. Information from physiological studies has been incorporated into mathematical models of learning used by adaptive network researchers, and anatomical findings have guided the development of related neuronal models.
BIOLOGICAL INVESTIGATIONS OF ADAPTIVE NETWORKS:
NEURONAL CONTROL OF CONDITIONED RESPONDING

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I Summary

Neurobiological investigations of adaptive neural networks were initiated using the classically conditioned nictitating membrane response (NM CR) of rabbit, a widely used model system for studies of learning. One experimental approach involved recording from single brain neurons from awake, behaving animals for the purpose of determining the loci and characteristics of neurons with activity correlated with the NM CR or its inhibition. A second approach involved the use of discrete brain lesions that selectively eliminate the NM CR while at the same time sparing the basic reflex pathway. A third approach employed fiber-tracing anatomical techniques designed to clarify the interconnectivity among brain regions essential for the NM CR. These regions include discrete portions of the cerebellum and brain stem. Information from physiological studies has been incorporated into mathematical models of learning used by adaptive network researchers, and anatomical findings have guided the development of related neuronal models.
II Research Objectives

A. Overview. The primary objective for the reporting period was to initiate neurobiological studies relevant to adaptive networks using the classically conditioned nictitating membrane (NM) response as a model system. In addition to procuring apparatus and developing methodologies, a number of studies were begun. These are listed in Section II B, and their status is reviewed in Section III.

Behavioral/biological studies of learning using the rabbit NM preparation have implications for adaptive network research because they can guide and validate assumptions about learning. Models arising from computational studies of adaptive networks, developed by Drs. R. S. Sutton and A. G. Barto of the Department of Computer and Information Sciences (COINS), appear to have implications for behavioral/biological studies. John E. Desmond and Dr. N. E. Berthier have developed variants of these models that can predict patterns of neural firing and response topographies typically observed in the rabbit NM preparation. Thus, a class of learning theories with applicability to learning in an AI context can also be applied to animal learning and its physiological correlates. An important goal is to develop more fully the connection between learning algorithms and physiological data.

The classically conditioned NM response (NM CR) in rabbit has been widely adopted as a model system for behavioral, neurobiological, and theoretical studies of mammalian associative learning. It is now generally held that many brain regions contribute the NM CR and that these regions act in parallel with the basic reflex pathway subserving the unconditioned response (UR). Neural circuits responsible for the CR converge, on the response side, among motoneuron pools that retract the eyeball, principally the accessory abducens nucleus (AAN). On the stimulus side, rostral elements of the sensory trigeminal complex subserve the unconditioned stimulus (US). A comparatively simple dysynaptic reflex arc completes the circuit between stimulation of the eye and defensive retraction of the globe. NM extension is a passive consequence of eyeball retraction. Circuits mediating the NM CR parallel the reflex pathway and include discrete portions of the cerebellum and reticular information and their links to other brain regions. Certain of these regions modulate the rate of CR acquisition, inhibition, and CR topography. These include the septo-hippocampal complex and poorly differentiated regions of the midbrain.
Briefly, our physiological studies involve single or multiple-unit extracellular recording from brains of awake, behaving animals. Their purpose is to determine the precise loci and firing pattern of neurons with activity related to the CR or its inhibition. This information is crucial for understanding, not only which brain regions and structures are involved in a particular aspect of the CR, but how these regions and structures interact to perform their designated tasks. Neuronal representations of these processes in the form of connectionistic schemas can be viewed as models of parallel cooperative computation.

B. Purpose of Specific Studies. Specific studies initiated during the reporting period fall into four main categories.

1. Electrophysiological: Design and assemble a computer-assisted laboratory for single-unit neuronal recording concurrent with behavioral testing for the purpose of investigating the relationship between neuronal activity and the NM CR.

2. Anatomical: Investigate the interconnectivity of brain structures essential for the NM CR, especially the anatomical relationships among the accessory abducen nucleus, supratrigeminal reticular formation, and red nucleus.


4. Theoretical: Apply information from the behavioral and physiological domains to the formulation of computational models of learning and assess their validity by testing their implications for CR topography and neuronal activity in a variety of training paradigms.

III Status of Research

A. Electrophysiological Studies. Two studies were initiated under this heading.

1. Single-Unit Investigations of Supratrigeminal Reticular Formation and the NM CR. This study is an outgrowth of John E. Desmond's anatomical, lesion, and multiple-unit studies of pontine reticular formation and the NM CR. The current project is part of Desmond's dissertation research.
Extracellular recording from single neurons are obtained during behavioral training. Sampled neurons that show activity patterns related to the NM CR are subjected to extensive off-line analyses. These analyses quantify how well the firing pattern of a given neuron predicts the form of the NM CR and the elapsed time between the neuronal "prediction" of the CR and the CR as observed peripherally.

Two main types of CR-related neuronal activity have been observed. On-cells increase their activity so as to mirror aspects of CR topography such as recruitment and amplitude. These neurons form a template of the CR as much as 100 msec. before the CR begins. Such neurons are either causally related to the CR or else they reflect processing and representation within a parallel system, as portrayed in previously published neuronal models. A subset of neurons with CR-related activity with the pontine reticular formation decrease their firing rates in relation to the NM CR. Too few cases of off-responses are available at this time to form an impression regarding their possible role in the NM CR. A sufficiently large number of high-quality recordings for submission of a report to a relevant peer-review journal should be on hand within the next twelve months.

2. Multiple-Unit Correlates of Conditioned Inhibition. This study is part of Michael Vigorito's dissertation project. Its methodology resembles that employed in the preceding study, except that multiple-unit recordings are the rule and single-units an exception. Certain theoretical models assume that conditioned inhibition involves learning in a distinct system that parallels whatever systems generate the CR. Inhibition of a CR arises because of interactions between these two systems. Lesions studies support the idea that brain systems which subserve the CR are different from those that underly inhibition. By recording from brain regions thought to be important for conditioned inhibition, e.g., lateral septal nuclei and parvocellular red nucleus, Vigorito has confirmed the existence of neurons that increase their firing rate as the CR is actively suppressed. A published report on this work should be available within the next twelve months.

B. Anatomical Studies. Interconnectivity among brain regions implicated in the NM CR were initiated using routine HRP and WGA-HRP as markers.
Because unilateral lesions of magnocellular red nucleus and its projections eliminate the NM CR on the side opposite to the lesion, it is important to determine the trajectory of two of the primary input/output fiber systems to magnocellular red nucleus: the brachium conjunctivum, which conveys information from nucleus interpositus of the contralateral cerebellar hemisphere; the rubrobulbar tract, which carries information from red nucleus to the region of the accessory abducens nucleus on the contralateral side of the brain stem. Two preliminary reports of this work are in press. A report of this work suitable for the anatomical literature awaits additional data.

In addition to fiber-tracing studies of red nucleus, we are repeating previously reported HRP studies of the accessory abducens and supratrigeminal nucleus (Desmond et al., Brain Research Bulletin, 10: 747-763, 1983) using WGA-HRP (TMB) in place of HRP (TMB). WGA-HRP provides a higher signal-to-noise ratio (fewer false negatives), while at the same time reducing the fiber-uptake problem (fewer false positives) than does older HRP histochemistry. This aspect of the project should be in publishable form within the next twelve months.

C. Lesion Studies.

1. Lesions of Brachium Conjunctivum and Rubrobulbar. Unilateral lesions of these two fibers eliminate the NM CR but not UR. Other lesions of the dorsolateral pons caudal to the abducens nerve have no effect on behavior. The study reinforced our earlier conclusion that the supratrigeminal region is also essential for the NM CR. A description of this work has been submitted for publication.

2. Bilateral Lesions of Hypothalamus Do Not Impair Conditioned Inhibition. Diana Blazis conducted this study. Theoretical considerations and earlier lesion studies by Moore and his collaborators here and in London suggested the possibility of hypothalamic involvement in conditioned inhibition. Whereas, bilateral hypothalamic lesions did not affect the NM CR or its inhibition, lesions of certain midbrain regions did impair conditioned inhibition. However, conditioned inhibition recovered gradually over repeated post-lesion training sessions. A report of this work will be submitted for publication within the next eight months.
3. Lesions That Disrupt The NM CR Do Not Affect The UR. Unilateral lesions of cerebellar nucleus interpositus or red nucleus eliminate a previously acquired NM CR. From a variety of theoretical perspectives (see original proposal leading to the current award), the extent to which lesions that disrupt the CRs also influence the UR is an important issue. For example, certain neuronal models suggest that CR-disrupting lesions should produce a slight, but significant attenuation of the UR over a range of intensities of the eliciting stimulus. This does not appear to be the case, based on data to be presented at the Society for Neuroscience meetings next Fall. Assessment of effects of CR-disrupting lesions on UR amplitude will be a routine part of any lesion study in the future.

D. Theoretical Studies.

1. Physiologically Constrained Sutton-Barto Learning Models. John E. Desmond, in conjunction with Drs. N. E. Berthier and R. S. Sutton, has developed a real-time computational version of the Sutton-Barto model of learning that is capable of predicting the firing pattern of neurons with CR related activity. The model also has implications for purely behavioral studies involving complex protocols of training, e.g., those with multiple CSs. An NSF grant that began 1 March 1984 has enabled us to acquire a remote terminal to the VAXEN network of computers available to COINS researchers. This enhanced computational power will facilitate simulation experiments.

2. Physiologically Constrained Attentional Models. As a dissertation project, Nestor Schmajuk has been developing real-time computational models derived from contemporary animal learning theory. These models provide alternatives against which to assess models derived from Sutton-Barto. Comprehensive simulation studies are underway.

3. Implications of Models for Single-Unit Recording Studies. This represents a redirection of effort from the original proposal, and we are only now proceeding toward this objective. Our current plan is to focus attention on those neurons that appear, on the basis of lesion and physiological studies, to be causally related to the NM CR. Supra-trigeminal on-cells, mentioned above under III A 1, are one candidate.
Purkinje cells of cerebellar cortex are another candidate. Dr. N. E. Berthier has been perfecting techniques for recording from cerebellar Purkinje cells during behavioral testing.

IV Technical Reports


Other articles stemming from this grant during the reporting period include two chapters to appear in forthcoming volumes. Moore and his collaborators produced an additional four research reports, prepared two additional chapters, and one abstract. The latter work was based primarily on research conducted prior to the reporting period.

The three dissertations supported by the award during the reporting period should spawn as many as six technical reports. These would be first-authored by John E. Desmond, Nestor Schmajuk, and Michael Vigorito and would be prepared for relevant peer-review journals.

Finally, a report of Diana Blazis' lesion study of conditioned inhibition, tentatively entitled "Recovery of Conditioned Inhibition following Hypothalamic and Mesencephalic Lesions," will be submitted to one of three relevant journals in the field.

V Professional Personnel

1. John W. Moore, Ph.D., Professor of Psychology (Neuroscience & Behavior) and Associated Professor of Computer and Information Science.

2. Neil E. Berthier, Ph.D., Research Associate.

Other personnel associated with research during the reporting period include doctoral candidates John E. Desmond, Nestor Schmajuk and Michael Vigorito. Diana Blazis will become a graduate student in the Fall, and A. Dovydaitis and M. E. Rosenfield are laboratory technicians with bachelor degrees.
VI Interactions

A. Formal Presentations by Moore.


3. Invited participant: Review of Air Force Sponsored Basic Research in Biomedical Sciences, UC Irvine, July 1983, on the topic "Neuronal control of conditioned responding."


5. Principal participant: Winter Conference on Neurobiology of Learning and Memory, Park City, Utah, January, 1984, on the topic "Cerebello-rubro-pathways underlying the rabbit NM CR." Organized by Dr. P. R. Solomon.


B. Informal Interactions by Moore. These include on-going interactions and consultations with Dr. A. G. Barto's group of the COINS Department. In addition, Moore consulted with colleagues at University College London on one occasion during the report period. For three weeks in the Fall of 1983 (Sept/Oct), Moore participated in physiological experiments on neuronal excitability in Dr. L. Bindman's laboratory in the Physiology Department. This was intended as a learning opportunity, as it provided Moore with hands-on experience with intracellular recording techniques. This foreign travel and associated expenses were not charged to the award.
VII New Discoveries, Etc.

A. Unanticipated Findings. There were a number of surprising discoveries during the reporting period.

1. As described in Section III A 1, the discovery of brain stem neurons that decrease their firing rate in anticipation of the NM CR constitutes a new discovery. Furthermore, the finding that some on-cells anticipate the behavioral CR by over 100 msec. is surprising. A lead-time of this duration has no parallel in the physiological literature using the rabbit NM preparation.

2. As described in Section III C 2, recovery of conditioned inhibition following midbrain lesions was unanticipated.

3. As described in Section III C 3, failure to observe any attentuation of UR following CR-disrupting lesions of cerebellum and brain stem was unanticipated.

B. Software Development. New software for analyses of the relationship between behavior, physiological data, and theoretical models were developed.

C. Applications. Where appropriate, research findings have been incorporated into neuronal schemas and computational models relevant to the project.

VIII Additional Information

The unexpected addition of Dr. N. E. Berthier to the research effort has been a tremendous plus. Dr. Berthier received his Ph.D. under my supervision. He then spent almost three years with Dr. C. H. Woody at UCLA doing intracellular neurophysiology in connection with eyeblink conditioning in cats. He brings to the project a number of technical and computational skills.

Dr. Berthier joined the project in November 1984. A good deal of his effort during the interval between then and the end of reporting period was devoted to an experiment project that, although not originally proposed, assumed high priority because of developments elsewhere in the field. Specifically, Dr. Berthier experimentally reexamined the role of extraocular muscles in the NM reflex, a crucial question for understanding the anatomical and
physiological bases of preparation. We had previously ascertained that all extraocular muscles participate in the NM reflex, (Berthier & Moore, Physiology & Behavior, 25: 667-672, 1980) and most researchers share this view. However, our conclusions were brought into question by reports from a group at the University of Iowa. Berthier's follow-up study supports our original findings. A report of his work is in press in the journal Behavioural Brain Research.
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