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Progress over the four years of the project with regard to the development of multineuronal recording systems was significant. Since this was one of the main objectives of the consortium of three laboratories it was a principal focus of research efforts throughout the project. The development has resulted in a system capable of simultaneous experimental control and acquisition of behavioral events and electrophysiological data of up to 8 experimental chambers from a single minicomputer host. Development of the DSP-based action potential waveform analyzer ("spike-sorter") allows detection and identification of up to 128 single unit waveforms recorded from any combination of 128 microwire electrodes. The use of shaped microwire arrays allowed for precise placement of electrodes in distinct anatomic regions of the brain. Development of these systems occupied the entire first two years of the project, and much of the third year as well. Much of the research effort in the final two years was directed toward completion of several studies which were in preliminary stages at the time of submission are now near completion and have been published or prepared for publication. Specifically, these include the signal detection task and the DMTS task in which complex neurophysiological analyses have revealed striking new relationships to sensory processing strategies in the hippocampus and cortex. The accompanying report summarizes these and other accomplishments throughout the period of the award.

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Multiple Neuron Recording in the Hippocampus of Freely Moving Animals

Progress Report for AFOSR-90-0092

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Progress Report

Summary

Progress was been significant over the entire period of project regarding development of multineuronal recording and systems for analysis of the multineuronal data. This was a primary objective of the three laboratory consortium, and it was the principal focus of the research efforts. The multitasking computer system was in operation in all three laboratories since the beginning of the second year of the project, and the DSP-based multineuron spike-sorter and the associated software interface for neural spike discrimination were available late in the second year. Much of the research effort in the last 2 years was directed toward implementing the spike-sorter system, collecting multineuron data, and developing the analysis strategies. Studies using the multineuron data acquisition system have revealed new relationships between the behavioral events in a delayed-match-to-sample behavioral task, and patterns of simultaneously active neurons in the hippocampus.

Research Objectives: Statement of Work

The research objectives of the first year of the award were to develop the Motorola minicomputer-based host-and-slave hardware such that multiple experiments could be independently controlled by separate, dedicated CPUs occupying a common computer backplane. Implementation of host monitor programs allowed sharing of computer storage (RAM, disk and tape) resources and control of all slave CPUs from a common console. Objectives of the second year were to implement the control and acquisition system on four experimental chambers running *tone-discrimination and delayed-match-to-sample* (DMTS) and delayed-nonmatch-to-sample (DNMTS) tasks. Electrophysiological data consisted of window-discriminated recordings from microdrive-mounted etched-tungsten electrodes, and small bundles of stainless-steel microwire electrodes. The DSP-based spike-sorter system and shaped arrays of microwires were implemented late in the second year of the project. During the third year of the award, the objectives were primarily to continue to implement the computer system for behavioral control and multiple neuron recording in hippocampus and related structures, and to utilize these techniques in sample memory tasks to determine the nature of sensory processing by the hippocampus and related structures. Objectives of the fourth (extension) year of the project were to develop analysis techniques for the multi-neuron data, and to combine electrophysiological and behavior event data with spatial tracking of the animal's position to analyze spatial as well as behavioral correlates of neuron activity in the hippocampus.

Multineuron Recording System: The first two years of the project were dedicated to development of the multineuron data acquisition and behavioral control computers. The multiuser Motorola Delta 2616 was capable of simultaneous control of up to 8 experimental chambers, with synchronous or asynchronous recording of up to 64 channels of electrophysiological data per chamber. Each of the experiments was controlled from one console terminal or separate terminals, with online reports of behavioral variables and graphic display of the electrophysiology. Software control of the programs was expanded to include a wide variety of training programs, operator alerts when specific sequences of behavioral events occur, and direct output of data to spreadsheet format for offline analysis.

A second development of this phase of the project was the translation of all Motorola-based analysis programs to machine-independent C-language programs. A principal benefit of the translation was the adaptation of Dr. J. Chapin's ANALYZE program to the Intel 80x86/MS-DOS "PC" computers, greatly increasing the speed and capacity of the analysis. Once the translation of analysis programs was completed, it became obvious that the Microsoft Windows environment for the PC was more appropriate for further development of analysis programs. As a result, the analysis programs have been extensively modified and adapted to a window-and-mouse-driven package that continues to evolve as more sophisticated analysis functions are required. Session data files transferred from the Motorola computers to PCs via "KERMIT" transfer protocols has been built into the interface programs which allow emulation of the console terminals that control the behavioral experiments. The transferred files are directly accessible on the PCs and can be analyzed by any PC running MS-Windows. This has also resulted in ready importation of data into packaged statistical analysis software such as SAS, SPSS and Statistica for multidimensional analyses.

The third focus of development has been the continued refinement of the DSP-based spike sorter programs. The MS-Windows control software was expanded to include multiple window discriminator functions, principal components analysis, cluster-cutting, activity meters, strip charts, firing rate histograms and on-screen template matching for neural spike selection. The spike-sorter instrumentation currently in use in the laboratory can now be configured to allow the 128 electrode inputs and 64 discriminator outputs to be independently assigned on one or more experimental chambers (to a maximum or 4) with independent control of the spike sorter criteria for each experiment. In combination with the patterned microwire arrays, the multichannel electrophysiological data revealed startling new data on information processing in the hippocampus during the delayed memory experiments.

Personnel:

Dr. Robert Hampson, Ph.D. Research Asst. Professor BGSM, '89-93.
Mr. Terrence Bunn, Advanced Systems Programmer, '89-93.

Information Processing and Delayed Memory Studies, Phase IV: Progress on these experiments concentrated on correlation of behavioral events with the neural activity recorded in the hippocampus during performance of these tasks. Several publications have resulted from these experiments and are listed on the last page. A brief summary of the findings from each study will be presented below.

Tone Signal Detection and Discrimination Task: Progress on this phase of the project concentrated on analyses of the hippocampal and cortical tone-evoked neural activity from the auditory signal detection and discrimination task. In particular the analysis has focussed on the transmission of information between dentate gyrus and neocortex, and the recurrent feedback of this information onto hippocampal inputs to modify hippocampal excitation on subsequent trials. The sequential dependency previously observed in auditory evoked potentials and tone-evoked single neuron discharges would thus reflect modulation of hippocampal inputs to maintain neural activity within an optimal range for processing the information represented by the input. The possible anatomic basis for this feedback is currently being investigated by a combination of multineuron recording and selective hippocampal lesions. Further directions for this study will utilize multineuron recording from sites in hippocampus, entorhinal cortex and perirhinal cortex to monitor the likely functional connections involved in the information processing loop.

Delayed Match to Sample Memory Task: The extensive analysis of single hippocampal neuron activity in the DMTS task has been reported in two publications completed in the third year. The analysis identified specific interactions of behavioral and spatial factors which influence the activity of hippocampal CA1 and CA3 complex spike cells. Numerous conjunctive influences on neural firing have been identified, including: phase of the DMTS task, lever position, and length of the delay interval. The identified response patterns suggest that combined activity of the cell types is sufficient to fully encode all features of the DMTS task. In addition, these results indicate that hippocampal neural activity does not represent purely spatial, nor purely mnemonic information, but a combination of positional and task-specific factors.

Implementation of multineuron data acquisition in the DMTS task resulted in several novel findings. Initial experiments utilized patterned arrays of microwire electrodes with pairs of electrodes simultaneously positioned in the CA3 and CA1 layers of the hippocampus. The original goal of these experiments was to identify correlated neural activity in the two layers indicative of functional anatomic projections from CA3 to CA1. The cross-correlation analyses required quite large datasets due to the large number of neural spikes required (>1000 spikes/channel), vs the relatively low firing rate of the complex spike cells (<5/sec). Acquisition and analysis of this data is still in progress, however two manuscripts are currently in preparation to report these findings. To facilitate analysis of the data, an online rate display program (ORDisp) was developed by Mr. Bunn to display the multineuron activity as a sequence of colored-coded firing patterns synchronized to behavioral events. A surprising result of this analysis was the finding that particular patterns of neural firing distributed across the CA3 and CA1 cell fields were repeated for subsequent behavioral events, but not at other times during the session. These spatiotemporal patterns reinforce the finding of conjunctive coding of spatial <u>and</u> task-relevant information in the hippocampus during behavior. These data have been presented in poster form at the Society for Neuroscience annual meetings in '92 and '93, and are being prepared for publication during the next few months.

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Ms. Katherine Alexander, Research Technician II, BGSM, '90-91.
Mr. Eric Blalock, Research Technician II, BGSM, '89-90.

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Three manuscripts are currently in preparation that are based on the DMTS and spatial exploration behavioral paradigms and many-neuron data acquisition techniques supported by this project.