1. TITLE OF PROJECT:  
Cortical Processing of Visual Motion

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT or SOLICITATION:  
X No  YES

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:  
3a. NAME (Last, first, middle)  
Newsome, William T.

3b. DEGREE(S)  
Ph.D.

3c. POSITION TITLE  
Professor

3d. MAILING ADDRESS (Street, city, state, zip code)  
Stanford University  
School of Medicine  
Department of Neurobiology  
Stanford, CA 94305-5125

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT  
Neurobiology

3f. MAJOR SUBDIVISION  
School of Medicine

3g. TELEPHONE AND FAX (Area code, number and extension)  
TEL: (650)725-5814  
FAX: (650)725-3958

4. HUMAN SUBJECTS RESEARCH:  
4a. Research Exempt If "Yes," Exemption No.  
4b. Human Subjects Assurance No.  
FWA935

4c. NIH-defined Phase III Clinical Trial  
No  Yes

4d. If "Yes," IACUC approval Date  
5/2/2002

5. VERTEBRATE ANIMALS:  
No  Yes  YES

6. DATES OF PROPOSED PERIOD OF SUPPORT (month, day, year-MM/DD/YY)  
From 07/01/03 Through 06/30/08

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD  
7a. Direct Costs ($)  
150,000  
7b. Total Costs ($)  
197,013

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT  
8a. Direct Costs ($)  
750,000  
8b. Total Costs ($)  
985,080

9. APPLICANT ORGANIZATION:  
Name  
Stanford University

Address  
Research Management Group  
1215 Welch Road, Modular A  
Stanford, CA 94305-5401

10. TYPE OF ORGANIZATION:  
Public:  
State  
Local

Private:  
Private Nonprofit

For-profit:  
General Small Business

Woman-owned:  
Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER:  
DUNS NO. (if available)  
009214214

Congressional District  
14

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE:  
Name  
Mary Palmer

Title  
Research Process Manager

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Research Management Group  
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Tel  
(650) 725-3991  
FAX  
(650) 498-5876

E-mail  
mary.palmer@stanford.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION:  
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Mary Palmer

Title  
Research Process Manager

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Stanford, CA 94305-5401

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(650) 725-3991  
FAX  
(650) 498-5876

E-mail  
mary.palmer@stanford.edu

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:  I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

15. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:  I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature of PI/PD  
W. Newsome  
DATE  
10/2/03

Signature of OFFICIAL NAMED IN 13.  
Mary Palmer  
DATE  
10/5/03
The long-term goal of this research is to understand the neural mechanisms underlying simple forms of visually based cognition, including visually based decision-making in particular. The projects will focus on a network of high-level brain structures that appears to translate perception of the visual world into plans for action. Prior studies indicate that this network includes cortical areas of the parietal and frontal lobes as well as midbrain structures such as the superior colliculus. A similar network of structures is present in humans, and the proposed research is thus likely to contribute directly to our developing knowledge of human vision, cognition, and their clinical disorders. Three specific aims will be pursued during the coming grant period:

1. Electrical microstimulation techniques will be employed to test rigorously the causal role played by each candidate neural structure in visually-based decision making.
2. Combined stimulation and recording techniques will be employed to test specific hypotheses concerning the functional circuitry that connects these areas and the information that flows between them.
3. Electrophysiological techniques will be employed to study identify and study the neural mechanisms that compute the “subjective value” that an organism places on alternative actions. Psychological and economic studies have shown that perceived value exerts an enormous influence on decision-making.

Together the proposed experiments will provide considerable impetus toward understanding the neural mechanisms underlying a simple form of cognition. The ultimate health-related value of this work will follow from an understanding of the biological basis of mental function. Neurological and psychiatric diseases that affect mental function take a massive toll on the health and well-being of our citizenry. These diseases are particularly insidious because they slowly rob the afflicted person of normal cognitive abilities - the very essence of personal identity. Understanding how brain activity gives rise to mental function in normal subjects will undoubtedly provide a deeper understanding of what goes wrong in various disease processes, and suggest useful therapeutic approaches for such diseases.

PERFORMANCE SITE(S) (organization, city, state)

Department of Neurobiology
Stanford University
Stanford, CA

KEY PERSONNEL. See instructions. Use continuation pages as needed to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Role on Project</th>
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<tbody>
<tr>
<td>Newsome, William T.</td>
<td>Stanford University</td>
<td>Principle Investigator</td>
</tr>
<tr>
<td></td>
<td>Stanford University</td>
<td>Research Associate</td>
</tr>
<tr>
<td></td>
<td>Stanford University</td>
<td>Student Research Assistant</td>
</tr>
</tbody>
</table>
The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

## RESEARCH GRANT

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### Appendix (Five collated sets. No page numbering necessary for Appendix.)

Appendices NOT PERMITTED for Phase I SBIR/STTR unless specifically solicited.

Number of publications and manuscripts accepted for publication (not to exceed 10)

Other items (list):
BUDGET JUSTIFICATION PAGE
MODULAR RESEARCH GRANT APPLICATION

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Total Direct Costs Requested for Entire Project Period: $ 750,000

Personnel:

William T. Newsome, Ph.D., Principal Investigator. Dr. Newsome will be involved in all aspects of the proposed research. He has played a major role in the conception of the experiments, and he will supervise the Research Associate and two Student Assistants as they carry out the experiments. He will also be closely involved in data analysis, interpretation, assessment of problems, design of follow-up and control experiments, and preparation of manuscripts for publication. Dr. Newsome’s salary is paid by [unspecified source] and will not be supported from this grant.

[Research Associate's name], Research Associate, will have primary responsibility for carrying out the dual microstimulation experiments described in Project #2. [Research Associate's name] has been in my laboratory as a postdoc for [number of years], and is an extremely competent physiologist. This project is technically demanding and requires the expertise and patience that [Research Associate's name] possesses. [Research Associate's name] will be supported completely from this grant.

[Student Research Assistant's name], Student Research Assistant, has performed all of the preliminary work on Project #3 as described in the Progress Report in this proposal. He is a very talented graduate student and has made excellent progress on the project already. He is the perfect person to see it through to completion. [Student Research Assistant's name] will be supported completely from this grant.

[Student Research Assistant's name], Student Research Assistant, Graduate student, is a graduate student in Electrical Engineering who has been working in my laboratory during the past year. He has performed much of the preliminary work on Project #2, including the important preliminary result illustrated in Fig. 14. [Student Research Assistant's name]’s electrical engineering training is particularly important for this project which requires substantial signal processing expertise to analyze signals recorded while electrically stimulating the brain. [Student Research Assistant's name] will be supported completely from this grant.

[Science and Engineering Associate's name], Science and Engineering Associate, The work outlined in this proposal is technically ambitious and will require fabrication of custom equipment for positioning multiple microdrives on the head, for simultaneous stimulating and recording, and for multielectrode recording. [Science and Engineering Associate's name] is an outstanding machinist who has been employed by the Department of Neurobiology at Stanford for [number of years]. He will work closely with us to design and fabricate the required custom equipment. I will support [percentage] of [Science and Engineering Associate's name]’s salary from this grant, commensurate with the amount of effort he will give to us.
7 pages redacted--biosketches omitted as requested
RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:
We have approximately 2,000 square feet of laboratory space that is solely devoted to our research. 1,400 square feet of this space is located within our laboratory. This space contains six fully-equipped experimental rigs for alert monkey behavior and physiology and an additional two rigs for monkey training. The central room is a support area for the experimental and training rooms; it contains an animal prep area, an electrode manufacture station, an electronics work bench, and a small mechanical work bench. Another 600 square feet of laboratory space is located on another floor. This space contains a computer facility for off-line data analysis, numerical simulations and software development. In addition we have access to a shared histology facility.

Clinical:
None.

Animal:
In addition to the laboratory space in the main lab building, we have a large animal room (400 square feet total), devoted to housing our monkeys. These rooms are AAALAC approved and are located on the second floor of the lab. A cage washing facility is located in the central area of the laboratory. This entire complex - laboratory, animal rooms, and cage-washing facility - is located in the same building as the laboratory space.

Sterile surgery is conducted in a designated animal surgical facility. Veterinarians and animal health technicians are available on a 24 hr. basis to address any clinical problems that may arise with the experimental animals.

Computer:
See Major Equipment below.

Office:
In addition to the laboratory space we have about 400 square feet of office space. This space contains a small private office for the P.I. and shared desk space for postdocs.

Other:
Maintains an excellent machine shop. This shop is staffed by an exceedingly talented machinist and produces very high quality work. The shop is located in the basement of the building. Thus providing for a close working relationship with the machinists' salary is subsidized by this grant.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Each of the six experimental rigs is equipped with the basic instrumentation necessary for behavioral and physiological experiments with awake, behaving monkeys. An IBM minicomputer is at the core of each experimental apparatus. The computer runs a software package developed at NIH for behavior control, stimulus control, data acquisition and data storage. Visual stimuli are created by a second IBM PC that is controlled by the first. Visual stimuli are presented on video monitors (100 Hz refresh rate). We record single unit data using a Narashige hydraulic microdrive in conjunction with a pre-amp, amplifier, and window discriminator manufactured by Bak Electronics. Neuronal signals are visually displayed on a Tektronix oscilloscope (5000 series) and are additionally fed into an audio monitor. We measure the monkeys' eye movements using a scleral search coil system composed of power oscillators, phase detectors and search coils manufactured by CNC Engineering in Seattle. Each lab also contains various custom made electronic devices such as computer interfaces, amplifiers, filters, and differentiators. All six rigs are also equipped with pulse generators and stimulus isolation units (Bak Electronics) for electrical microstimulation experiments. We have recently purchased two Plexon systems for multielectrode recording, as well as multielectrode microdrives from Thomas. We are in the process of setting up these systems, which should greatly enhance our data gathering capacities.

Our off-line computer facility is composed of Sun Ultra workstations. These machines are connected by ethernet to the laboratory PCs's and to the larger Stanford University net. They provide us with the capability for conducting numerical simulations, computation intensive data analysis, and a convenient environment for software development. Several Macintosh personal computers are available to lab members for word processing, graphics, and statistical analysis of reduced data.

This equipment is available at no direct cost to this project.
RESEARCH PLAN

A. SPECIFIC AIMS

Recent research in several laboratories has begun to elucidate neural mechanisms within the primate brain that underlie visually based decision-making. In our laboratory, such investigations have been built around the behavioral performance of rhesus monkeys on a two-alternative, forced-choice discrimination (2AFC) of motion direction. In this task monkeys discriminate between opposed directions of coherent motion in a random dot stimulus by making a saccadic eye movement to one of two visual targets aligned with the axis of stimulus motion. This behavioral context has proven particularly fecund because we and many others have accumulated a substantial base of knowledge about the neural basis of motion perception on the one hand and the neural circuits that govern oculomotor behavior on the other. Because sensory signals concerning motion direction must ultimately interact with the oculomotor system during performance on this task, we have searched initially for decision-related neural signals in brain structures that link the sensory representation of motion direction in cortical areas MT and MST to the motor structures that produce saccadic eye movements. In the course of these studies, carried out over the past several years, we and others have identified neural signals that are good candidates to participate in the underlying “decision process.” Neurons carrying such signals have been identified in the lateral intraparietal area (LIP) of the parietal lobe, in area 46 of the frontal lobe, and in the intermediate and deep layers of the superior colliculus (SC) in the midbrain.

While these results have been very encouraging, they comprise only the initial stages of an incisive investigation; substantial additional work must be performed before the biological outline of a simple decision process is actually at hand. For example, all of the results to date are merely correlative; they do not demonstrate that any of the candidate structures actually play a causal role in the formation of perceptual decisions. Thus our first specific aim:

Specific Aim 1. We will employ low-frequency microstimulation techniques to determine whether LIP, SC and specific areas of the frontal lobe (the frontal eye fields and area 46) contribute causally to the formation of perceptual decisions in the context of our 2AFC direction discrimination task.

Secondly, there has been no investigation to date of the functional circuitry between areas that represent the sensory stimulus, such as MT, and high-level oculomotor planning structures (LIP, area 46, frontal eye fields (FEF) and SC) that would be necessary to implement the associative logic of the discrimination task. In the form of the task that we employ most often, two opposed directions of motion in the visual stimulus (leftward and rightward, for example) are signaled by saccadic eye movements with corresponding directional components (e.g. leftward and rightward saccades, respectively). As detailed in Background and Significance, this logic requires a particular pattern of information flow between specific direction columns in MT and specific subregions of the saccade vector maps in structures such as the SC or the FEF. A physiological demonstration that information actually flows between MT and the SC (or FEF or LIP, etc.) in the predicted pattern would greatly strengthen the case that this circuitry implements the decision process. Thus our second specific aim:

Specific Aim 2. We will employ simultaneous microstimulation/recording experiments (two electrodes) to detect the presence or absence of information flow between identified direction columns in MT and specific subregions of the saccade vector maps in SC, FEF and LIP.

Finally, we must consider the prospective implications of successfully identifying neural circuits that mediate a simple decision process. Psychologists and economists have long known that sensory stimuli are not the only determinants of the decisions that a human or animal subject makes in a forced-choice task; behavioral “priors” such as the perceived reward “value” of the two alternatives can exert dramatic effects on choice behavior. Neural circuits that implement decisions must therefore integrate information not only from sensory processing structures (our sole preoccupation to date) but from several other sources as well, including calculations of “value” that must occur within the brain. To obtain a behavioral assay of the value a monkey assigns to each of two alternative choices, we have developed an oculomotor version of Herrnstein’s classic “matching” task in which animals choose between two alternatives with a relative frequency that is proportional to the probability
of obtaining a reward for each choice. Our third specific aim will take advantage of the behavioral assay of subjective 'value' afforded by this paradigm:

**Specific Aim 3.** We will employ electrophysiological recording techniques to determine whether single neurons in LIP and other putative decision-related structures carry signals that reflect the subjective value experienced by monkeys performing an oculomotor matching task.

Together, these three projects comprise a diverse program of investigation that should substantially advance our knowledge of the neural substrates of a simple form of visually based decision-making.

**B. BACKGROUND AND SIGNIFICANCE**

**B1. General Background**

The last five decades have witnessed steady, cumulative growth in our knowledge of the neural systems in the primate brain that mediate sensory perception on the one hand and those that govern motor behavior on the other. This foundation of knowledge has provided neurophysiologists with the opportunity to begin serious, long-term study of higher level cognitive functions that mediate the varied and complex interactions between sensory processes and the execution of behavioral responses. Notable successes have occurred in the study of attention, short-term memory, response selection, reward systems, organization of sequential movements, and some forms of learning. Cutting edge work in this emerging field typically incorporates knowledge, theoretical perspectives, and experimental techniques from the formerly separate disciplines of sensory and motor physiology.

Progress in bridging this "sensorimotor watershed" has been particularly impressive in the visual and oculomotor systems. Vision research has led the way in the study of sensory systems during the past several decades, and the central visual pathways of primates are by far the best understood of any mammalian sensory system. Similarly, the oculomotor system has proven to be highly attractive for detailed studies of motor physiology. The eyes and extraocular muscles are the simplest motor effector system in mammals, and our understanding of this system is correspondingly deeper and more extensive than for any other effector system. Not surprisingly, then, many of the highest quality studies of cognitive processes have exploited the integrated visual-oculomotor system as a platform for posing and addressing specific experimental questions about cognition. Consequently, our insights tend to be most incisive for visual attention, visual short-term memory, visually-guided response selection, etc.

The research proposed in this document falls squarely within this "cognitive neuroscience" perspective. In our ongoing studies of the sensory processing of visual motion, we have been deeply absorbed in the attempt to understand how sensory signals that we record from the cerebral cortex of monkeys mediate the psychophysical performance that we measure behaviorally on the same sets of trials (Britten et al., 1992; Britten et al., 1996; Celebrini & Newsome, 1994; Zohary et al., 1994). Formal attempts to model this relationship between sensory responses and performance led us to understand with increasing clarity that visual performance cannot be understood without specific knowledge of the decision mechanisms by which the brain evaluates sensory evidence and makes psychophysical choices (Shadlen et al., 1996). This realization led, in turn, to our efforts in the past several years to initiate direct physiological study of the decision mechanisms that link perception to behavior. These initial studies have been very encouraging (as summarized in the Progress Report), and the research proposed in this document is intended to pursue and extend these gains aggressively during the next grant period. We continue to employ the integrated visual-oculomotor system as the platform for our studies because of the considerable advantages enumerated above.

**B2. Background to Specific Aims 1 and 2.**

Figure 1 outlines the basic direction discrimination task that we have employed in numerous studies in this laboratory and will employ in the studies proposed in Specific Aims 1 and 2. Most readers of this document (all three of you!) will be familiar with this task, but we summarize it briefly for the sake of thoroughness. Rhesus monkeys are trained to fixate a point of light and discriminate between opposed directions of motion in a random dot motion display presented on a video monitor. After the monkey achieves fixation, the motion stimulus is presented for one or two seconds during which the monkey must decide which direction of motion
Figure 1

necessary for performance on this task. Each trial begins with presentation of a visual stimulus which
predominates in the visual stimulus. Following a brief delay period (1-2 sec), the fixation point dims and the
monkey indicates its decision by making a saccadic eye movement to one of two visual targets aligned with the
axis of stimulus motion. The random dot stimuli are the familiar family of "variable coherence" displays in which a
specified proportion of the dots carries the coherent, unidirectional motion signal that the monkey must
discriminate while the remaining dots flicker randomly on the screen, providing a masking motion noise. The
task can be made arbitrarily easy or difficult by varying the percentage of dots in coherent motion (i.e. the
"coherence" of the stimulus). (Ignore the “Response field” for now; this will be engaged in the Progress Report.)

The block diagram in Figure 2 illustrates how we think about the stages of neural processing that are

Figure 2

processed and encoded by the visual system, represented in the figure as "sensory systems." Following
sensory encoding, a higher level "decision process" must evaluate the sensory evidence and render a binary
judgment about the direction of coherent motion, and the output of the decision process
in turn engages motor circuitry to plan and execute the appropriate operant response.
(The requirement for a binary decision process is imposed by the logic of our 2AFC task; differently structured tasks can and do require differently structured decision processes.) In the context of our direction discrimination task, we know that columns of
direction selective neurons in cortical areas MT and MST are components of the sensory system that represents motion direction (Salzman et al., 1992; Celebrini & Newsome, 1995). In essence, the direction columns in MT produce responses that are proportional
to the amount of their "favorite motion" present in the stimulus (recall that all directions and speeds are present to some extent in the variable coherence stimuli). Similarly, we have learned in the past several decades a great deal about the motor circuits that control saccadic eye movements, the operant response on our task. Thus we are now in a unique position to ask questions about the neural substrates of the decision process—the link between sensation and action during performance of this task.

Figure 3

The block diagram in Figure 3 introduces another important element in our strategy for studying the decision process. We know that the signals that initiate performance on each trial must originate from the sensory
representation of motion direction in the visual system, including MT and MST (top line). We also know that the cascade of neural signals must ultimately influence the oculomotor circuitry that mediates the operant response (bottom line) as well as "preoculomotor" circuitry that prepares motor-related signals in advance of the actual action (3rd line). We do not know, however, whether an abstract representation of the decision process, independent of the neural systems that govern specific motor effectors, also exists within the brain (2nd line). Because stimulus motion and saccade direction are linked in a rather stereotyped manner in our task, there is certainly no necessity for such abstract representation of the
decision itself; it would be sufficient for the direction columns in MT to activate the circuits governing the associated saccades in a relatively direct manner as argued below. We elected, therefore, to begin our study of decision processes by recording from neural structures that prior studies have implicated in the oculomotor preparation or planning process—area LIP of the parietal lobe (Gnadt & Andersen, 1988; Barash et al., 1991a, 1991b; Colby et al., 1996), FEF and area 46 of the frontal lobe (Goldberg & Bruce, 1990; Funahashi et al., 1989; Schall et al., 1995), and the intermediate layers of the SC (Mays & Sparks, 1980; Glimcher & Sparks, 1992; Basso & Wurtz, 1998; Dorris & Munoz, 1998). MT projects directly although weakly to portions of LIP, FEF and SC (Maunsell & Van Essen, 1983; Fries, 1984; Ungerleider et al., 1984; Ungerleider & Desimone, 1986; Maioli et
al., 1992), but MST, a single synapse downstream from MT, projects massively to all three structures (Fries, 1984; Andersen et al., 1990; Boussaoud et al., 1990, 1992). Our decision to begin with these structures is thus supported on both conceptual and neuroanatomical grounds. (We note in passing that we are currently conducting experiments that employ a modified version of the discrimination task which substantially disrupts the stereotyped relationship between motion direction and saccade direction in order to determine whether "abstract" decision-related activity (i.e. not linked to a specific motor response) appears in the brain following training on this task. No firm conclusions are yet available from this study, and for the purposes of the present proposal, we stay with the traditional form of the task in Specific Aims 1 and 2.)

Figure 4 presents a simple, connectionist-style model of a possible decision mechanism for our task. The central notion, as suggested above, is that direction columns in MT excite pre-oculomotor circuitry selectively such that specific directions of motion elicit the specific saccadic eye movements required to report motion direction correctly. In the version of the task illustrated in Figure 1, for example, the monkey should make a leftward saccade in response to leftward motion and a rightward saccade in response to rightward motion. Thus, leftward direction columns in MT should activate portions of LIP, FEF and SC that produce leftward eye movements (black icons) and vice versa (gray icons) as illustrated in Figure 4. The logical structure of our task demands that this sort of associative logic be implemented in the brains of our monkeys and thus raises the possibility of a very precise pattern of information flow between the neural representations of motion direction and saccade direction. Neighboring columns in MT, for example, should selectively activate circuitry in different subregions of the SC, sometimes on opposite sides of the brain. It is quite possible, of course, that the circuitry operates in a "push-pull" fashion such that a leftward column in MT excites circuits that control leftward saccades and simultaneously inhibits (via interneurons) circuits that control rightward saccades.

This simple model of the decision process forms the conceptual basis for the experiments in Specific Aims 1 and 2, and it is therefore critical that we emphasize several aspects of our thinking about the model. First, we do not imply that the connections illustrated in Fig. 4 are monosynaptic. We suspect, in fact, that they are polysynaptic, but we also suspect that in our highly trained monkeys the neural circuits have been shaped so as to deliver the motion information to the saccade planning circuitry in a synaptically efficient manner. This notion is consistent with several neuroimaging studies which show that brain activation generally becomes substantially more restricted spatially as naive human subjects become familiar with a task (Raichle et al., 1994; Schacter & Buckner, 1998; Petersen et al., 1998). Second, we are not proposing that the monkeys are born with this circuitry hard-wired. Rather we believe that synaptic weights have been modified during the learning process so as to produce the pattern of information flow that generates the necessary behavior. Third, the hypothesis represented in Fig. 4 cannot be tested with neuroanatomical techniques. We presume that the web of connections between MT and the preoculomotor structures has the potential to associate any direction of motion with any saccade direction. Thus transsynaptic retrograde tracers injected into the SC, for example, are likely to label all columns in MT. Rather, the hypothesis concerns functional patterns of information flow that are likely to be mediated via differential weighting of synapses. Thus, any test of the hypothesis must be physiological. Fourth, we are not suggesting that the circuitry outlined in Fig. 4 operates automatically like a "reflex arc" through the brain. Performance on this task is motivated, purposive behavior. If the monkey is not thirsty, for example, the behavior will not emerge irrespective of activity in MT. Thus we believe that the associative circuitry in Fig. 4 must be under the control of higher level "gating" signals that bring the circuitry into a functionally active state when the behavioral context is appropriate: the monkey must be awake, in the primate chair, thirsty, fixating a point of light, and expecting a visual stimulus whose motion direction contains the key to a desired reward. If any one of these conditions does not hold, activation of the columns in MT will...
not elicit a saccadic eye movement of the predicted direction. We already know that the "gating" hypothesis is correct to some extent. In prior studies from this laboratory we have shown that electrical microstimulation of direction columns in MT influences perceptual decisions on this task and must therefore influence the oculomotor circuitry that expresses the decision. If we deliver the same train of stimulating pulses during the intertrial interval, however, or even after the monkey has achieved fixation but before the random dot stimulus appears, no eye movement results (Salzman et al., 1992; Seidemann et al., 1998). Thus the flow of information from MT to the oculomotor circuitry must be actively regulated on a fairly fast time scale as each trial unfolds in time.

If the ideas contained in Fig. 4 are roughly accurate, it becomes somewhat misguided to ask "where the decision is made" because the decision is actually implicit in the pattern of connections between the sensory and preoculomotor structures. The decision only becomes explicit in the form of single cell firing rates at the level of the preoculomotor circuit when the appropriate saccade planning networks become active (i.e. the third line in Fig. 3). One implication of this point of view is that electrical microstimulation of the preoculomotor structures themselves may causally influence the binary decision made by the monkey during the discrimination task. Thus, we would expect microstimulation to influence the choice between the two saccade targets, not simply to modify the metrics of a previously selected eye movement. Specific Aim 1 will explicitly test this hypothesis. As indicated in Research Design and Methods (section D2b), we have preliminary data suggesting that this will be a powerful approach to identifying the neural circuits that implement the decision.

The experiments outlined in Specific Aim 2 will test both the connectional logic outlined in Fig. 4 as well as the time course of the gating mechanism that governs the flow of information between MT and the preoculomotor structures. We will use a stimulating electrode to insert a few brief electrical pulses into identified direction columns in MT while recording downstream responses at precise locations within the saccade vector map in SC or FEF. The connectional hypothesis in Fig. 4 predicts that direction columns in MT should activate specific regions of the vector map (and perhaps inhibit others) depending upon the geometry of the MT receptive field, the SC response field, and the preferred direction of motion of the MT column. Furthermore, the gating hypothesis predicts that stimulating pulses in MT should have a larger effect on downstream structures when the monkey is actually using the motion information in the stimulus to make a perceptual decision. If we can demonstrate gating in this fashion, we may be able to plot the time course of the gating mechanism by delivering stimulating pulses at different points during the course of single trials. Preliminary results presented in Research Design and Methods (section D3b) demonstrate the technical feasibility of this project: we have been successful in detecting downstream responses in SC following single stimulating pulses delivered to MT, although we are only now preparing the critical experiments to test the hypotheses.

B3. Background to Specific Aim 3.

The perspective on decision processes outlined in Fig. 2 is standard for sensory scientists who are absorbed with the problem of how sensory stimuli influence decisions. Psychologists and economists, however, have long realized that adaptive behavior emerges from a milieu in which past success in achieving rewards attaches meaning, or "value", to experiences and actions. In a simple discrimination task, for example, the recent history of success and failure in achieving rewards for alternative choices can exert strong effects on decisions when the evidence from the visual stimulus itself is weak (i.e. near psychophysical threshold). This biasing effect of "perceived value" provides a powerful tool for investigating the neural basis of decision-making in the primate brain. Brain circuits that compute decision variables should reflect the effects of perceived value in an appropriate behavioral task.

A major obstacle to studying perceived value in nonhuman primates is the fact that the value or utility an animal attributes to a particular stimulus or response is an internal variable to which we lack direct access. To bring the animal's history and expectation of reward under direct experimental control, we employ a behavioral phenomenon called 'matching' to infer this internal state from an animal's ongoing choice behavior. Matching describes animals' allocation of responses among behavioral alternatives in proportion to the relative frequency with which those alternatives are reinforced. Herrnstein first reported this finding in pigeons pecking at either of two response keys for food rewards (Herrnstein, 1961) and subsequently elaborated the phenomenon into a general principle of choice behavior that he termed 'the matching law' (de Villiers & Herrnstein, 1976). Matching has since been documented in a variety of species including rhesus monkeys (Iglaur & Woods, 1974; Woolverton, 1996; Woolverton & Ailing, 1999) and applied to behavior in a variety of contexts within
psychology, foraging theory, and economics (for thorough reviews see Herrnstein, 1997; Davison & McCarthy, 1988; Stephens & Krebs, 1986).

Matching behavior is significant for our purposes because under conditions where animals match, the relative frequency of choices between two alternatives indicates the relative value ascribed to competing activities, effectively providing a continuous ‘readout’ of this internal state. Because the experimenter controls the relative frequency with which two choices are rewarded, an extended range of ‘perceived value’ can be explored under controlled conditions. We have therefore developed an oculomotor version of Herrnstein’s classic matching task (in collaboration with ----  -------- ----------  -------- and we have trained two monkeys to perform it (Sugrue, et al., 2001). We have also introduced a novel cross-correlation analysis of the behavior that allows us to quantify perceived value as it fluctuates from trial to trial while the monkey performs the task (see Progress Report, section C4). This behavioral spadework now permits us to search for neural correlates of subjective value in combined behavioral and electrophysiological experiments. Indeed, our preliminary physiological results described in Research Design and Methods (section D4b; Sugrue & Newsome, 2002), suggest strongly that subjective value is represented parametrically in LIP. The experiments outlined in Project 3 are designed to confirm this finding, to measure the dynamics of the subjective value signal on each trial, and to identify, if possible, the locus in the brain where perceived value is computed.

B4. Broader Significance

The questions we are pursuing are among the most fundamental in neuroscience: how is information processed within the brain, and how does this information processing result in organized, purposeful behavior? The visual system provides the best vehicle for investigating such issues in primates because we have an extensive knowledge base concerning its structure and function and because a very large portion of primate behavior is based on visual information. The intellectual thrust of the research, however, is directed toward fundamental issues in neural information processing that are central to understanding virtually all mental functions. The ultimate health-related value of this work will follow from an understanding of the biological basis of mental function. Neurological and psychiatric diseases that affect mental function take a massive toll on the health and well-being of our citizenry. These diseases are particularly insidious because they slowly rob the afflicted person of normal cognitive abilities - the very essence of personal identity. Understanding how brain activity gives rise to mental function in normal subjects will undoubtedly provide a deeper understanding of what goes wrong in various disease processes, and suggest useful therapeutic approaches for such diseases.

C. PROGRESS REPORT

C1. Effective dates since last competitive review: 1/1/93 to present.

C2. Grant history. This grant was recognized by NEI with a MERIT Award at the time of its last competitive review in 1992, accounting for the 10 year interval between competitive reviews. Between 1992 and mid-1997, this grant provided the sole (R01-style) financial support for this laboratory. In 1997 I was appointed an Investigator of[_________________________] and was asked by NEI to reduce substantially the funding level of this grant, which I was happy to do. I was also asked to reduce the scope of the grant correspondingly and to distinguish as clearly as possible between research that would be supported specifically by NEI as opposed to[_____.] I therefore rewrote the Specific Aims for this grant for the period of 1997-2002, restricting these aims to studies of decision mechanisms within the primate visuo-motor system. Fortunately, these studies have provided some of the most interesting and novel results to emerge from this laboratory during the past several years, and this research theme is thus continued in the present competing renewal application. The funds I am requesting in this proposal will be used nearly exclusively to provide financial support for the personnel working directly on the three proposed projects concerning decision mechanisms, plus a small portion of a machinist’s salary. Because[_________] funds laboratories, not specific projects, it is very difficult to draw rigid boundaries between[_____] and NEI supported work in my laboratory. Generally speaking, [_____] funds will completely underwrite ongoing projects in the laboratory related to color/motion interaction, speed perception, and motion transparency. [_____] funds will benefit the proposed NEI work, however, by means of general laboratory infrastructure, animal technician and computer engineer salaries, and the PI’s salary.
In the next section of the Progress Report (C3) we review specifically our work on decision mechanisms carried out over the past several years. This review provides essential background for Projects 1 & 2 unless the reader is already familiar with our recent publications on decision mechanisms (Shadlen and Newsome, 1996, 2001; Horwitz and Newsome, 1999, 2001a, 2001b). In the subsequent section of the Progress Report (C4), we present recent unpublished work that provides essential background for Project 3. Section C5 summarizes additional progress in the laboratory very briefly, and the final section of the Progress Report (C6) lists all publications from the laboratory since the last competitive renewal of this grant, including 1 edited volume, 29 primary research publications (including 3 each in Science and Nature, 11 in J. Neurosci., and 3 in Neuron), 3 major reviews, and 19 minor reviews, book chapters and commentary pieces.


My laboratory and that of have identified potential neural correlates of an oculomotor decision process for our direction discrimination task in three neural structures (LIP, area 46, SC) which contain relatively high-level neurons appropriate for planning saccadic eye movements (Shadlen & Newsome, 1996, 2001; Horwitz & Newsome, 1999; 2001a,b; see Appendix papers). We identify these neurons in preliminary screens using a delayed or remembered saccade task; the neurons begin firing when a saccade target is first presented and continue firing during an instructed delay period until the monkey receives a “go” signal to execute the saccade (e.g. Gnadt & Andersen, 1988; Mays & Sparks, 1980; Goldberg & Bruce, 1990). Although these high-level neurons are in the minority in each of these structures, they are sufficiently plentiful (20-35%) to permit a reasonable rate of progress in recording experiments. We record from these neurons during performance of the direction discrimination task as illustrated in Fig. 1. We first map the response field of the neuron using the delayed saccade task. We then set up the discrimination task so that one response target lies within the neuron’s response field (T1) while the other lies far outside the response field, usually in the opposite hemisphere (T2). The onset of a fixation point initiates each trial. After the monkey achieves fixation, the two response targets appear, followed a few hundred msec later by the random dot motion stimulus. The motion stimulus remains on for 2 sec, during which the monkey must discriminate the direction of coherent motion. Following a variable interval delay period, the fixation point disappears, and the monkey must make the appropriate saccade to acquire a liquid reward.

Figure 5, taken from Horwitz & Newsome, 2001b, illustrates the responses of a neuron that appears to carry decision-related signals during performance of the task. Data from three coherence levels are shown: a supra-threshold coherence...
(51.2%), a near-threshold coherence (12.8%) and a sub-threshold coherence (0%). Within each panel, all trials have been aligned to the onset of the visual motion stimulus (0 sec, left segment of each raster) and to saccade initiation (0 sec, right segment of each raster). Visual stimulus duration was 2 sec. The pre-stimulus firing rate of this cell was a modest 1.5 spikes/sec. Approximately 120 msec after the onset of the visual stimulus, the firing rate increased dramatically on trials that ended in a T1 choice (left column). On trials ending in T2 choices (right column), the firing rate either did not change or increased only modestly over the baseline rate. (The high-frequency motor burst immediately preceding T1-directed saccades was typical of most SC neurons we studied.) We describe this cell (and others like it) as being “choice-predictive” because its firing rate early in the trial reveals the target that the monkey will choose at the end of the trial.

Importantly, the response modulation between T1 and T2 choices (Fig. 5) does not simply reflect the influence of the sensory stimulus itself: substantial choice-predictive modulation occurred on the 0% coherence trials which contained no net motion (and on error trials as well—see Horwitz & Newsome, 2001b). Moreover, the choice-related activity persisted throughout the delay period, after the random dots were extinguished at 2 sec. Thus, some portion of the response reflects the monkey’s decision about motion direction rather than the actual motion content of the sensory stimulus. The data illustrated in Fig. 5 are typical of decision-related neural activity in the SC (Horwitz & Newsome, 2001a,b), in LIP (Shadlen & Newsome, 1996, 2001) and in area 46 of the frontal lobe (Kim & Shadlen, 1998). We have found little if any difference between these areas in the frequency of neurons with this physiological profile.

The most difficult conceptual issue for interpreting these data is the distinction between neural activity that might be involved in the actual computation of the decision, as opposed to motor preparatory activity that necessarily follows the original computation of the decision. Several aspects of our data suggest that responses like the one in Fig. 5 cannot be explained as purely motor activity. Most importantly, the activity of this neuron varied markedly as a function of stimulus coherence. On trials in which a high coherence stimulus led to a T2 choice, for example, the cell discharged only weakly (Fig. 5, top-right panel). In contrast, the cell fired moderately when a low coherence stimulus led to the same T2 choice (Fig. 5, bottom-right panel). As a result, predictive activity (in essence, the difference between the firing rates for T1 and T2 choices—see Horwitz & Newsome, 2001b) grows more rapidly and reaches higher levels as coherence increases. This physiological observation corresponds nicely to the behavioral intuition that neural activity integral to decision formation should reflect the quality of evidence in favor of a decision (i.e. the subject’s confidence level) as well as the actual outcome of the decision. This dependence of SC activity (as well as that of LIP and area 46) on coherence does not result from minor parametric variations in the operant saccades; we conducted extensive regression analyses to be certain that the effect of coherence on predictive activity was not mediated via subtle variations in saccade parameters (Horwitz & Newsome, 2001a,b; Shadlen & Newsome, 2001).

It appears, therefore, that the decision-related neural activity in SC, LIP and area 46 cannot be accounted for by strictly sensory or strictly motor influences. Rather, these signals emerge in a sensorimotor milieu that resembles, qualitatively at least, what we would expect of the decision process in this task. The predictive activity is appropriate for guiding the selection of the proper saccade target but also reflects the quality of the sensory evidence that informs target selection. Because we have not yet observed substantial differences in the predictive activity of SC, LIP and frontal lobe neurons, our working hypothesis is that neurons in all three areas function as a cooperative network in computing decision variables from the motion output of MT (and other sensory structures). Nevertheless, the data we currently have in hand are not yet compelling, and our published papers (see Appendix material) discuss some of the objections that can still be raised to this interpretation of the data. The microstimulation project outlined in Specific Aim 1, if successful, may provide definitive evidence concerning the role of SC, LIP and frontal lobe areas in the formation of perceptual decisions in the context of our behavioral task.

In addition to the discovery of decision-related activity in SC and LIP, we made a second important finding during the past grant period that bears directly on the circuitry hypothesis illustrated in Fig. 4. During the course of the SC studies, we noticed that about half of the neurons that exhibited choice-predictive activity also appeared to have a direction selective sensory response to the motion stimulus itself. In the upper left panel of Fig. 5, for example, the firing rate of the neuron decreased noticeably following the offset of the visual stimulus (2 sec), although decision-related activity continued during the delay period. This stimulus-dependent response appears to be direction selective, being present for motion toward the response field of the SC neuron and absent for equivalently strong motion away from the response field (Fig. 5, upper right panel). This association between preferred direction of the sensory response and the location of the saccadic response field is, of
course, exactly the relationship envisioned in the model in Fig. 4; each region of the saccade vector map in the SC should receive inputs from columns in MT whose combination of receptive field location and preferred direction points toward the SC response field. We therefore studied these apparent visual responses extensively during simple fixation tasks and during several control tasks designed to rule out covert motor planning as an explanation for the putative visual activity (Horwitz & Newsome, 2001a). All of the control experiments were consistent with a sensory origin for the directional signals that we observed during a simple fixation task.

This finding augurs well for the project proposed in Specific Aim 2 which is designed to test explicitly the functional circuitry hypothesis illustrated in Fig. 4. Basically, the finding suggests that the circuitry hypothesis is on the right track: the predicted association between visual motion direction and saccade direction appears to be reflected in SC physiology even under passive fixation conditions. Interestingly, our discovery of direction selective visual responses within the SC also implies that the "gating" mechanism discussed in Background and Significance is likely to reside in part within the SC itself. Because the direction selective visual activity can be evoked during a simple fixation task in which no saccadic eye movements ensue, we may infer that the "visual" activity in the intermediate layers of the SC can only engage the oculomotor circuitry in an obligatory manner during performance of the discrimination task. Thus the directional visual signals, even those present in the SC itself, must be actively linked, or "gated" to the oculomotor circuitry during task performance.

Importantly, we believe that the directional visual responses we observed in the SC result from the extensive period of behavioral training in which our monkeys learned to associate specific directions of motion with specific saccade vectors. Indeed, we have found that directional visual responses are essentially absent in a monkey that was trained on a different version of the task in which the association between visual direction and saccade direction was less stereotyped (Horwitz, Batista & Newsome, unpublished). We would make (and will eventually test) the strong prediction that monkeys trained extensively on an "antidirection" version of the discrimination task (rightward eye movements in response to leftward motion and vice versa) should generate direction selective visual responses in the SC whose preferred directions point away from the saccadic response field of the SC neuron.

C4. Research Progress: "Experienced Value".

As indicated in section B3 above, we have developed an oculomotor version of Herrnstein's classic matching task in order to measure quantitatively the 'perceived value' an animal attributes to a particular stimulus in a forced choice task. Matching has been most thoroughly documented in the setting where responses (lever presses, key pecks etc.) are reinforced on concurrent variable interval (VI) schedules. Reward availability on a VI schedule is determined by a constant rate (Poisson) process, leading to intervals between successive rewards that are distributed exponentially about a specified mean. In our oculomotor matching task, for example, eye movements to the two possible saccade targets are rewarded according to two VI schedules that run concurrently for each target (see below). A reward is made available, or 'scheduled', for a particular saccade if the VI 'clock' for that target has timed down to zero. The monkey is rewarded when it makes a saccade to a target for which a reward has been scheduled. Importantly, rewards persist over time, meaning that a reward scheduled on a particular response alternative remains available until the animal next makes that response to collect it. This latter feature makes matching the optimal response strategy in the context of concurrent VI schedules in the sense that it maximizes total return (Baum, 1981). For our task, therefore, matching is a 'rational' strategy in that it leads to the maximal overall rate of reinforcement.

Each trial begins with the onset of a fixation point (Fig. 6). Once the monkey achieves stable fixation (300 msec), two colored saccade targets appear. Fixation must then be maintained for a further delay period of 1-2 seconds at the end of which the fixation point dims—the 'go' signal for the monkey to make a saccade to one or other target. If a reward has been scheduled on the chosen target prior to this saccade (i.e. the VI clock has timed down to zero) the monkey is rewarded with a drop of juice. Irrespective of reward delivery, the monkey must hold its gaze on the chosen target until the fixation point brightens (200-300 ms)—the 'return' signal for the monkey to saccade back to the FP. When gaze returns to the fixation point the targets are redrawn, but color is randomly assigned to location. The sequence of fixation, saccade, and return then repeats, so that the monkey may execute multiple successive trials in a row provided it keeps making saccades back and forth between the fixation point and targets as cued. A series of trials is terminated when gaze deviates outside of any of three 2° spatial windows around the targets or the FP for longer than the duration of
Principal Investigator: NEWSOME, William T

Figure 6

Fixation (300 ms)

Delay (1-2 s)

LIP RF

Repeat

FP
t

FP dim: 'Go'

FP bright: 'Return'

0 100 200 300 400
Cumulative color 2 responses

0 100 200 300 400
Cumulative color 1 responses

Figure 7

Responses to each color are reinforced with identical juice rewards according to independent VI schedules. In Figure 6, for example, the mean reward rate is 10 seconds for Color 1 (C1 hereafter) and 30 seconds for Color 2 (C2 hereafter). In this scenario the monkey is 'matching' if it chooses C1 on 75% of its responses and C2 on 25%, a distribution that can yield an average of 8 rewards per minute as compared to 6 rewards per minute if the monkey chose the 'richer' target on every response. In practice, the wait times between successive rewards on a given color are drawn at random from a geometric distribution (the discrete approximation to an exponential) with a mean equal to the reciprocal of the current reward rate for that color. The overall rate of reward used in the task is constant at approximately 9 rewards per minute, while the relative rate of reward for the two colors (C1 rate/C2 rate) undergoes frequent unsignaled changes from one block (approx. 100-200 trials) to the next.

Figure 7 shows matching behavior that we obtained in a representative session. Over the course of this session the monkey was exposed to a series of 6 blocks with different programmed ratios of reward rates (1:1, 1:3, 3:1, 1:1, 1:6, 6:1, in chronological order). The monkey's choice behavior over time is described by the continuous black curve, which plots cumulative responses to C1 against cumulative responses to C2. The slope of this curve at any point represents the ratio of C1:C2 responses at that point in the session. The dashed gray lines correspond to the average ratio of C1:C2 rewards that the monkey experienced during each block of trials; the origin of each line marks the time of the unsignaled block transition where the reward rates changed. According to the matching law, the monkey matches when the ratio of C1:C2 responses equals the ratio of C1:C2 rewards, which corresponds to the gray and black curves being parallel. Two features of this plot are worthy of comment. Firstly, as predicted by the matching law, there is a close correspondence between the slopes of the gray and black curves. Secondly, at block transitions, the monkey's allocation of responses adjusts very rapidly to the change in the relative rates of reward, suggesting that the monkey bases behavioral responses on its experience of rewards within a fairly narrow time window. To assess this time window quantitatively, we computed cross-correlograms from the time series of rewards and choices. The time series of responses is string of numbers that codes C1 responses as '+1' and C2 responses as '-1', while the time series of rewards is a string of equal length that codes rewarded C1 choices as '+1', rewarded C2 choices as '-1', and unrewarded responses as '0' (recall that the monkey fails to receive a reward on the majority of trials). Like the Pearson's correlation coefficient, the crosscorrelation coefficient is a dimensionless number, bounded between -1 and +1, that measures the strength of the linear relationship between the two time series at the specified temporal offset. The cross-correlation function
relating responses to rewards thus describes how the monkey's current response relates to preceding rewards.

The gray curve in Fig. 8 shows the cross-correlogram (CCG hereafter) for the behavioral data in the experiment of Fig 7 (autocorrelograms were deconvolved to remove any effect of periodicity in the individual time series); the black curve shows the average of 296 such CCGs computed from blocks of data obtained in over 30 behavioral sessions for the same monkey. Consistent with our intuition from inspection of Fig 7, the CCG reveals that the monkey integrates information over a surprisingly short time window extending only 5-10 trials into the past (the horizontal dashed line represents the correlation expected by chance). To our knowledge, this is the first time that cross-correlation analysis has been applied to matching data, although the relevant time window for matching behavior has been a matter of controversy in the literature. We have recently obtained the same behavioral result on a second monkey as well as on rat matching data kindly provided by our collaborator.

Most important for our purposes, the average CCG in Fig. 8 can be considered as a weighting function that describes how the monkey values rewards obtained over time. We employ this weighting function to compute a metric that we term "experienced value" (EV), which quantifies from trial to trial the value that the monkey has actually experienced for the two targets. This metric, whose computation is illustrated in Fig. 9, is critical for the electrophysiological experiments proposed in Project 3. At the top of Fig. 9 is the CCG from Fig. 8, normalized to have an area of 1. Each of the three lines underneath represents a different possible reward history over the past 15 trials. Filled/empty, positive/negative tick marks symbolize rewarded/unrewarded, C1/C2 choices for each trial. To compute EV for a particular trial, we transform the history of choices and rewards for the preceding 15 trials into a string of numbers with the possible values +1 (rewarded C1 choices—filled upward tics), -1 (rewarded C2 choices—filled downward tics), or 0 (all unrewarded choices—open tics). We then multiply the assigned number for each preceding trial by the temporally corresponding value of the weighting function, measured in responses, at the top of Fig. 9. EV is the sum of the 15 values so obtained. (More formally, EV for a particular trial is simply the summed product of the normalized CCG and the vector of preceding rewards.) The outcome of this computation for each of the three example reward histories is given on the right of Fig. 9. EV is bounded between +1 and -1 for constant strings of C1 and C2 rewards, respectively—see the first two histories in Fig. 9. Negative and positive values thus indicate the degree to which recent reward history favored C1 or C2, respectively. For example, the EV of +0.37 for the third example history in Fig. 9 reflects the fact that the preceding history of choices and rewards, over the time course of interest to the monkey, leads to a higher value for a C1 choice. An EV of zero would indicate that the preceding history is entirely neutral with respect to the likelihood of a reward for either choice on the current trial. (We verified that our EV metric actually reflects the monkey's behavioral valuation of the two targets by computing the average CCG weighting function from one half of a large data set and
showing that EV computed from this weighting function accurately predicts the probability of a C1 or C2 choice in the other half of the data set—data not shown.)

The critical importance of EV is that it provides a quantitative measure of the monkey's valuation of the two targets and permits us to track changes in this valuation from trial-to-trial during the course of an experiment. Our goal in the proposed electrophysiological experiments, therefore, is to determine whether neurons in putative decision-related neural structures (LIP, SC, frontal lobe) encode EV. Our preliminary electrophysiological data, presented in section D4b below, demonstrate that some LIP neurons carry robust signals related to EV.

C5. Research Progress: Other Projects.

The laboratory has made substantial progress on several other projects during the 10 years of the MERIT Award, several of which were funded by this grant during the first 5 years of the grant period. Space limitations preclude review of each of these projects, and we must rely on the list of publications below as the primary documentation of progress. These projects include: 1) electrophysiological and modeling studies of correlated activity among sensory neurons (publications 3 & 24 below), 2) electrophysiological and modeling studies of the relationship between neuronal activity and psychophysical performance (publications 2, 6, 8, 9, 11, & 16, major review 2), 3) microstimulation studies of the “read-out” algorithm for interpreting the map of motion direction in MT (publications 4, 13 & 28), 4) electrophysiological studies of the role of MT in the perception of stereo depth perception (publications 17 & 18), 5) modeling studies of the neural code (publication 14, major review 1), 6) electrophysiological analysis of the effect of attention on MT neurons (publications 15, 7, 19), 7) electrophysiological and neuroimaging studies of the role of MT in coding the motion of chromatic stimuli (publications 22 & 23; Barberini, 2001, 2002), 8) electrophysiological analysis of speed coding in MT (publication 29). We are currently pursuing several of these projects in the laboratory with the financial support of

C6. Publications, 1993-present (period since the last competing renewal of this grant).

Edited Volume:


Primary research publications:


**Major reviews:**


**Minor reviews, book chapters, commentary:**


In addition to these publications, we have produced 36 abstracts during the 10 years since this grant was reviewed competitively, mostly brief research reports presented at the annual meetings of the Society for Neuroscience or the Association for Research in Vision and Ophthalmology.

**D. RESEARCH DESIGN AND METHODS**

**D1. General methods.** We employ conventional techniques for conducting electrophysiological and behavioral experiments in alert monkeys. The animals are prepared for experiments by surgically implanting a head holding device, recording cylinder and scleral search coil for measurement of eye movements. All surgeries are carried out under aseptic conditions in a dedicated surgical suite operated by the Veterinary Service Center at Stanford. Animal training is by operant conditioning using water or juice as a positive reward for desired behavior. Behavioral control and data acquisition during experiments are accomplished by means of a laboratory computer connected to appropriate interfaces. Visual stimuli are computed by a second computer that acts as a slave to the first. The stimuli are displayed on a video monitor positioned 57 cm in front of the monkey. Eye movements are monitored at all times during an experiment using a scleral search coil system (1 kHz sampling rate). Electrophysiological recordings are obtained from single neurons and groups of neurons using conventional tungsten microelectrodes in conjunction with appropriate amplifiers, filters and a window discriminator. Electrical microstimulation is delivered via the same microelectrodes using a pulse generator in series with a stimulus isolation unit. These standard techniques are described in more detail in the Methods sections of our published papers. We have recently purchased two multielectrode recording systems (microdrive by Thomas, Inc.; data acquisition and storage by Plexon, Inc.) and are now integrating them into our laboratory rigs. These systems will be employed for the electrophysiological experiments in Project 3.
In addition to these conventional techniques, we employ a specialized set of visual stimuli for the experiments in Specific Aims 1 and 2 (the dynamic random dot displays described briefly in section B2 above), and we use specialized behavioral techniques for measuring psychophysical responses in monkeys (the eye movement task also described in section B2 and Fig. 1 above). Using these visual displays and eye movement responses, we train rhesus monkeys to discriminate opposed directions of motion for a wide range of coherence values, including those near and below psychophysical threshold. Before experiments commence, the monkeys are trained to perform this discrimination for any axis of motion, and over a wide range of motion speeds, aperture sizes and visual field locations.

At the beginning of each experiment in Projects 1 and 2, we will employ a delayed saccade task to map the single or multiunit response field at the site of electrode placement in SC (both SC and FEF in the case of Project 1). One saccade target will be placed inside the response field and one outside as illustrated in Fig. 1. As the monkey performs the direction discrimination task, the various motion conditions (direction, coherence level) will be presented in a random sequence until a specified number of trials is obtained for each stimulus condition. Thus the animal will have no basis for anticipating the direction or strength of the motion signal from trial to trial. In the microstimulation experiments, "stimulated" trials are randomly interleaved with nonstimulated trials. Correct choices are always rewarded with a drop of water or juice. If the monkey breaks fixation prematurely or fails to indicate a choice by making an appropriate saccade, the trial will be aborted and the data discarded.

The description of the proposed experiments in Projects 1 and 2 presumes familiarity with these stimuli and procedures; the reader who desires more background information should consult the Methods section of Britten et al., 1992, and Salzman, et al., 1992. PDF files of both papers can be obtained at http://monkeybiz.stanford.edu/pubs.html.

D2. Project #1: Microstimulation of sensorimotor structures during decision-making (after Specific Aim 1).

In this project we will use subthreshold microstimulation of SC, LIP and FEF to determine whether these structures play a causal role in the formation of perceptual decisions during performance of our direction discrimination task. The technical inspiration for this experiment derives from an elegant (and underappreciated) paper by Glimcher & Sparks (1993) in which they studied the effects of "subthreshold" microstimulation of the SC on the generation of spontaneous and visually directed saccades. "Subthreshold" refers to the use of electrical stimulation parameters (10-50 μA; 20-80 Hz) that fail to evoke overt saccades in the SC. Glimcher & Sparks obtained several important results that are critical to the experiments proposed in this project: 1) Subthreshold stimulation of the SC biases the endpoints of spontaneous and visually directed saccades toward the spatial location encoded at the SC stimulation site, consistent with a vector averaging read-out mechanism for the SC. The size of the bias becomes larger with increasing current level or stimulation frequency within the subthreshold range. 2) Subthreshold stimulation does not influence saccade initiation; application of the subthreshold stimulation trains had no effect on the time interval to the next saccade. 3) Subthreshold stimulation had no effect on the choice of visual targets in a cued saccade task (the color of the fixation point cued the animal to saccade to one of two targets), even though the stimulating trains exerted measurable effects on the metrics of the saccade (amplitude, accuracy) to the chosen target. 4) The effects on saccade metrics described above were only observed if a stimulation train extended to within 40-60 msec of the time that the saccade began. Our goal is to use subthreshold microstimulation to influence the decisions that our monkeys make while performing the direction discrimination task. We know from the Glimcher and Sparks study that such stimulation will not interfere with the monkey's performance by "yanking" the eyes off the fixation point prematurely (subthreshold stimulation does not influence saccade initiation). We also know that effects on saccade metrics should occur only for stimulation trains that are temporally conjoined to the instant of saccade initiation (within 40-60 msec). We will therefore terminate all of our stimulation trains at least 100 msec prior to the "go" signal for saccade execution. One might be skeptical about the likelihood of influencing decisions in our task with subthreshold stimulation since stimulation exerted no effect on the choice of visual targets in the Glimcher & Sparks study. In that study, however, the cue to the correct target was fixation point color—a vastly suprathreshold and essentially instantaneous cue to the correct decision. As shown below, our preliminary data indicate that subthreshold stimulation in our threshold discrimination task can in fact influence target choice (i.e. the binary perceptual decision).
D2a. Experimental paradigm, part 1. The monkey will perform the direction discrimination task for a range of motion coherence levels spanning psychophysical threshold. The spatial layout of the experiment is as illustrated in Fig. 1. The monkey views a stimulus aperture presented centrally; one choice target (T1) is placed within the response field mapped at the position of the stimulating electrode (SC or LIP or FEF; we aim to do all three) while the other choice target (T2) is positioned well away from the response field, usually in the opposite hemifield. We hypothesize that subthreshold electrical stimulation will bias the monkey's binary choices in favor of the direction of motion that instructs a saccade toward the target in the response field (T1).

Figure 10 illustrates the temporal sequence of events during single trials of this experiment. Each trial begins with the monkey fixating a small point of light. After the monkey achieves fixation, three one-second-duration intervals follow: 1) a pre-period in which the monkey waits for the onset of the motion signal that will instruct its choice, 2) a visual stimulus period in which the random dots are shown, and 3) an instructed delay period during which the monkey must remember its decision until receipt of the "go" signal to make the saccade (disappearance of the fixation point). Four trial types will occur in block-random order. Microstimulation will occur on three of the trial types, during the pre-period, visual period, and delay period, respectively, while the fourth trial type will provide unstimulated control data. A full psychometric function spanning psychophysical threshold will be obtained for each trial type. We hypothesize that subthreshold function spanning psychophysical threshold will be obtained for each trial type. We hypothesize that subthreshold stimulation should exert maximal effects on the decision process during the visual stimulus period while subtle motion signals are accumulating to instruct the decision. Stimulation effects should be weaker during the pre-period (although stimulation could set up a prior "bias" state that may influence decisions for low coherence stimuli in particular) and weaker during the delay period after the monkey's decision has been formed. We also anticipate that delay period stimulation, but not pre- or visual period stimulation, may influence saccade metrics as shown by Glimcher and Sparks.

D2b. Preliminary data. We have piloted this experiment in 6 monkeys: 3 in which we stimulated the SC and 3 in which we stimulated LIP. The results were similar in the two areas: we obtained strikingly positive stimulation effects in one monkey, borderline positive effects in another, and no effect at all (on average) in the third. Figure 11 illustrates psychometric functions obtained from one SC subthreshold stimulation experiment that yielded a positive result. These data resulted from electrical stimulation during the visual stimulus period. (The data format and the fitted logistic curves are identical to those employed in our previous MT microstimulation work; Salzman et al., 1992.) The data are plotted as the proportion of T1 decisions (toward the target in the SC response field) as a function of motion coherence and direction. Positive coherences indicate motion toward the response field; negative coherences indicate motion toward the other target (T2). The psychometric function obtained on nonstimulated trials (gray line; gray symbols) shows that the monkey's behavior was under excellent experimental control: the proportion of T1 decisions varied smoothly according to the strength and direction of the motion signal. On stimulated trials, the proportion of T1 decisions increased at nearly every coherence level, resulting in a leftward shift of the psychometric function, consistent with our central hypothesis stated above. The leftward shift of the function was equivalent to a visual stimulus effect of 16% coherent dots as measured in units of the x-axis, and was
highly significant (logistic regression, \( p < .01 \)). Figure 12 shows the average stimulation effect (leftward shift of the psychometric function in units of coherence) measured across sites for the 3 monkeys in the SC series of experiments (error bars = SEM). Leftward shifts are represented by positive numbers; rightward shifts (the counter-intuitive result) by negative numbers. As in Fig. 11, all of these data are the result of stimulation during the visual stimulus period. As stated above, one monkey yielded large, statistically reliable leftward shifts of the psychometric function on average (left bar, \( t \)-test, \( p < .01 \)), one monkey yielded a significant but very small positive result (middle bar, \( t \)-test, \( p < .05 \)), and the third monkey yielded no effect on average (right bar). Results from the LIP experiments were virtually identical. For the two monkeys that yielded positive results in Fig. 12, microstimulation effects, as expected, were considerably smaller during the pre-period and the delay period (data not shown).

Because of the variability in the results among monkeys, we have not published these data. The variability could derive from one of two sources: 1) the sensorimotor circuits that comprise the decision process in our task may differ from animal to animal, or 2) the decision circuits are more distributed within the brain (i.e. SC, LIP, FEF, area 46, basal ganglia?) than are the sensory circuits that encode motion direction (MT, MST), leading to weaker and more variable effects from stimulation of one node in the network alone. We are inclined toward the latter interpretation; we feel that we are right on the edge of obtaining consistent positive results across animals. We cannot, however, rule out the former possibility at this point in time.

D2c. Experimental paradigm, part 2. Because this experiment is critically important for establishing the causal role of different neural structures in the decision process, we will perform a new set of experiments in which we use subthreshold stimulation to activate two nodes on the network simultaneously. The preliminary data in Figs. 11 & 12 are encouraging, and we believe that we will be able to obtain consistently positive results by injecting a signal into two nodes on this distributed network. The behavioral paradigm and data analysis will be the same as illustrated in Figs. 10-12. We will position stimulating electrodes in two candidate structures at points that represent a common locus in visual space (i.e. the response fields will be overlapping). In the initial experiments we will stimulate SC and FEF simultaneously because in both of these structures response fields are organized in reasonably stereotyped topographic maps that will facilitate positioning of the two microelectrodes. To speed each day's experiment, we may implant chronic electrodes at several locations in one of the structures so that we will have to search for a matching stimulation site in only one structure. This experiment will be tougher in LIP and/or area 46 because neither is known to contain an orderly topographic map of space. Our likely strategy for these structures will be to position stimulating electrodes chronically in LIP or area 46 after extensive mapping experiments, then search for spatially matching stimulation sites on a daily basis in the topographically ordered structures (SC or FEF). We will begin with stimulation parameters similar to those employed by Glimcher and Sparks for subthreshold stimulation of the SC. We are aware, of course, that we cannot apply these uncritically. Subthreshold parameters may extend to higher values in some structures (area 46; LIP); alternatively, cooperative effects from simultaneous stimulation might require that we use lower current and frequency values. We will be sensitive to this issue and adjust our procedures accordingly as we obtain more information.

D2d. Possible outcomes and interpretation. These experiments should provide a more incisive test of the role of SC, LIP and FEF in decision-making, and should provide insight into the puzzling mixed results that we obtained in our preliminary studies. For example, we will be able to compare the effects of stimulating two areas simultaneously with the effects of stimulating each area alone (trials will be randomly interleaved to eliminate any artifactual nonstationarity that might lead to different results in the various conditions). Large, consistent effects with simultaneous stimulation would support the notion that the decision process is embodied in a widely distributed network that is more effectively activated by intervention at multiple points, and would
will lean strongly toward the interpretation that the decision-making circuitry can vary from animal to animal, stored to disk for subsequent analysis of any desired aspect of the signal. The raw analog waveform from the recording electrode will be digitized (20 kHz) and our own preliminary results indicate that the approach is feasible (see D3b below). Our downstream variation relates to cognitive strategies.

D2e. Possible problems. In our judgment, this experiment has an excellent chance of success. All behavioral, stimulation, and data analytic procedures are well established in this laboratory, and the experimental design is clean. The only problem that appears potentially worrisome is any potential confusion between the effects of subthreshold stimulation on the perceptual decision per se (i.e. binary target choice) and effects on saccade metrics that might be a trivial consequence of manipulating motor circuitry. We feel confident that this will not be a serious problem for two reasons. First, Glimcher & Sparks (1993) showed that subthreshold stimulation of the SC only influences saccade metrics when the stimulating train continues to within 40-60 msec of the initiation of the saccade. Most of our stimulation trains will terminate more than a second prior to saccade initiation (Fig. 10), and even stimulation trains applied during the delay period can be terminated 100 msec prior to the saccade if desired. These numbers may vary from area to area, of course, and we will conduct appropriate controls in each area. Second, Glimcher & Sparks showed that the effects of subthreshold stimulation on the metrics of saccades to a visual target are easily recognizable. The effects are small and the final eye position is simply "pulled" modestly toward the topographic locus of the stimulation site (as in vector averaging). These small but clear effects could never be confused with an actual change of the monkey's choice between two widely separated targets. In our preliminary studies, we have in fact observed small effects on saccade metrics with delay period stimulation but not with visual period stimulation. In contrast, effects on target choice were far more pronounced for visual period stimulation (not shown). This provides a nice temporal double-dissociation between the two possible effects of subthreshold stimulation. Obviously, we are most interested in the higher order effects on decision making.

D3. Project #2: Neural circuitry underlying decision-making (after Specific Aim 2).

In this project we will test the hypothesized decision-making circuitry outlined in Fig. 4. As indicated in section B2 above, we will position a stimulating electrode in an identified direction column in MT, and a recording electrode in a downstream sensorimotor structure (SC initially because of the nice topographic map, others later). In the critical experimental manipulation, we will inject a brief train of stimulating pulses into the MT column (1-4 pulses, 20-40 μA, 500 Hz), and measure the physiological effects of MT stimulation in the downstream structure(s). Previous work from this laboratory indicates that these current levels are appropriate for stimulating single (or small clusters of) directionally specific MT columns (Salzman et al, 1992). We hypothesize that specific directional columns in MT should excite specific loci in the saccade vector map in the downstream structures according to the logic laid out in Fig. 4: rightward direction columns should generally activate loci that govern rightward saccades and vice versa for leftward direction columns. The reader should note well that our use of microstimulation in this experiment is conceptually different from our use of microstimulation in earlier experiments. Specifically, we are not seeking to change the monkey's behavior using microstimulation. Rather, we are attempting to inject a brief electrical signal that will probe the state of the neural circuitry between MT and downstream sensorimotor structures much as a voltmeter injects a modest current in order to probe the state of laboratory electronic circuitry. A potential problem with this experiment is that modest stimulation of MT may not generate a sufficiently strong signal to penetrate the (largely polysynaptic) connections between MT and the downstream structures. A few laboratories, however, have reported success with this sort of polysynaptic activation (Widener & Cheney, 1997; Holdefer et al, 2000), and our own preliminary results indicate that the approach is feasible (see D3b below). Our downstream measurements will consist of single unit recordings when possible, but we will also obtain multunit and local field potential responses. The raw analog waveform from the recording electrode will be digitized (20 kHz) and stored to disk for subsequent analysis of any desired aspect of the signal.
D3a. Experimental paradigm. In the initial round of experiments, the monkey will perform the standard direction discrimination task at a single suprathreshold coherence level (50% coherence in our preliminary study). The basic logic of the connections between MT and the downstream structures should be the same irrespective of stimulus coherence, and we can collect useful data more rapidly using a relatively easy discrimination task. The direction discrimination task will be tailored to match the information supplied by neurons at the MT stimulation site: visual stimuli will be presented within an aperture superimposed on the MT receptive, and the monkey will be required to discriminate between the preferred and null directions of motion identified for the specific MT column under study.

![Figure 13](image)

Figure 13 illustrates the sequence of events in a single trial in this experiment. After the monkey establishes fixation, three intervals follow sequentially on each trial: 1) a random duration pre-period (200-1000 msec) during which the monkey maintains fixation while awaiting onset of the visual stimulus, 2) a random duration (200-1000 msec) period containing 0% coherent dots (noise), and 3) a visual stimulus period (1000 msec) containing 50% coherent motion whose direction is toward or away from the SC response field (direction will be varied randomly from trial to trial). The trial terminates when the monkey receives the “go” signal and makes a saccade to the appropriate target. The “probe” microstimulation events (tic marks) begin after the monkey achieves fixation and are delivered every 100 msec for the duration of the trial. As indicated above, each individual probe event will consist of a brief train of stimulation pulses (1-4 pulses, 20-40 μA, 500 Hz). The exact parameters will be determined during pilot experiments in each monkey. Smaller current levels and briefer trains are best for restricting activation to a single column (or a small group of similarly directed columns), but we must also “hit” the circuitry hard enough to drive a detectable signal through to the downstream structures. Control trials in which no electrical stimulation is applied will be randomly interleaved with the test trials.

Probe stimuli will be delivered at 100 msec intervals throughout the trial for two reasons: 1) This allows us to accumulate a large number of probe events per trial. We will measure effects by averaging the downstream signal, time-locked to the probe stimulus ("probe-triggered averaging"), and the statistical power of the averaged signal is proportional to the number of probe tests that we accumulate. 2) The data so obtained will allow us to compare the downstream effects of the probe during the three intervals that occur on each trial: pre-period (no visual stimulus), 0% coherence period, and visual stimulus period (our "gating" hypothesis (section B2) makes differential predictions for the effects that should occur during the three intervals—section D3d below). A significant concern about this procedure is that each probe stimulus should effectively be an independent event; the downstream effects of one probe must dissipate completely before delivery of the next probe. Our preliminary data suggest that 100 msec is more than sufficient for this purpose (below). A secondary concern is that we want to avoid delivering a large number of electrical stimulation pulses that might alter the monkey’s behavior. Probe events delivered at 10 Hz should not change behavior (Murasugi et al., 1993), but we will be sensitive to this issue as the experiments proceed in order to detect unanticipated changes.

A primary technical challenge in this experiment is to position the two electrodes at sites in MT and SC so as to obtain a reasonable test of the circuitry hypothesis. Consider the specific example illustrated in Fig. 1. Given the location of the SC response field and the visual stimulus aperture, we can work with any MT column whose visual receptive field lies within the stimulus aperture and whose preferred direction points toward or away from the SC response field (the former should excite neurons at this SC site; the latter should fail to excite or perhaps even inhibit the same neuron(s)). We can, of course, adjust the position of the stimulus aperture to accommodate other MT receptive field locations. The key requirement is simply that the preferred direction of the column point toward or away from the SC response field. Obviously, we will have to search for MT/SC sites with the appropriate relative geometry, which will slow the experiment somewhat. But we have succeeded in obtaining appropriate geometry in pilot experiments, and we are convinced that the experiment is practical with sufficient patience.

D3b. Preliminary data. Figure 14 shows data from one experiment in which we stimulated MT while recording downstream in the SC. This experiment was not optimized to test the connectional hypothesis in Fig.
we sought merely to test the feasibility of detecting downstream effects of probe stimulation of MT. We therefore employed a large stimulating current (120 μA), and we simplified the experimental paradigm substantially: there was no 0% coherence interval, and we only applied probe stimuli during actual presentation of the 50% coherence motion stimulus. The probe stimulus in this experiment was a single biphasic pulse applied every 100 msec. The analog traces in panel A show the waveform recorded in SC following four different probe stimulation events in MT. One can easily see the large electrical stimulus artifact in each analog trace. The artifact did not saturate our electronic instruments, but it was sufficiently large to obscure any spike events that occurred in the first 3-4 msec following the probe stimulus (hereafter the “blind” interval). We are now working with electrical engineers at Stanford to develop adaptive filtering software to remove the artifact from our recordings (Widrow et al, 1975; Yelderman et al, 1983). Despite the presence of the artifact, we used a software window discriminator to identify multiunit events in the analog trace after the artifact disappeared (dots directly above the analog trace). These multiunit events are displayed in raster plots in panels B, C & D for three experimental conditions. Each horizontal line in the raster represents a single 25 msec epoch aligned to the time of the probe stimulus. The histograms show the multiunit activity averaged across 30 probe events; the gap in each raster plot and histogram corresponds to the blind interval. Data in panel B were obtained while the visual stimulus was in the receptive field of the stimulated MT column. Panel C shows data from control trials identical in all respects except that no probe pulses were applied to MT. Panel D shows another control condition in which probe pulses were applied as in panel B, but the visual stimulus was placed in the opposite hemifield well outside the the receptive field of the stimulated MT column. The different trial types in B,C & D were randomly interleaved during the experiment. The histogram in panel B shows clearly that stimulation of MT caused robust downstream responses at this recording site in the SC. The response peaked at 5 msec and effectively disappeared by 10-15 msec after the probe stimulus. The control data in panel C show that the downstream response actually resulted from electrical stimulation of MT (no response in the absence of probe stimuli), and the control data in panel D show that the downstream response is not an artifact of electrical stimulation per se (the response was highly attenuated when the visual stimulus was not superimposed on the MT receptive field even though the electrical stimulation was identical to that in panel B). We conclude, therefore, that the downstream activation evident in panel B results from synaptic activation of neural pathways that connect MT to SC. We have obtained data like this in several preliminary experiments, substantially reducing concerns about the technical feasibility of the project. We are now in the process of getting the full project underway.

**D3c. Analysis.** We collected only three complete trials for each condition in the experiment illustrated in Fig. 14. We will collect much larger numbers of trials in future experiments so as to detect weak downstream responses with the probe-triggered averaging technique. As indicated above, the downstream signals were measured will sometimes be single unit responses, sometimes multiunit responses (as in Fig. 14), and sometimes local field potentials (bandpass filtered, 10-150 Hz). Single and multiunit responses will be measured as illustrated in Fig. 14. LFP responses will be measured as root-mean-square voltage amplitude averaged across trials as a function of time after the probe stimulus. The circuitry hypothesis will be tested by comparing the
amplitude of the downstream responses when the geometry favors “excitation” between MT and SC versus “no effect” or “inhibition.” We should see larger evoked responses in the former condition and smaller responses in the latter. Because the downstream evoked responses will certainly be highly variable from experiment to experiment, we will have to accumulate a substantial data base of experiments for the two conditions to provide sufficient statistical power to test the circuitry hypothesis rigorously.

**D3d. The “gating” hypothesis.** As discussed in section B2 above, we believe that the flow of information from MT to the sensorimotor structures is under active regulation as behavior unfolds in time during each trial. We know, for example, that electrical stimulation of MT can change the monkey’s decisions (and thus the oculomotor circuitry) when applied during presentation of the visual stimulus. However, the same electrical stimulation has no effect at all on eye movements when applied to MT during the intertrial interval or during a pre-period after the monkey achieves fixation but prior to onset of the visual stimulus (Salzman et al., 1992; Seidemann et al., 1998). We infer, therefore, that information flow is “gated” during each trial, and that the circuitry between MT and the downstream sensorimotor structures becomes functionally potent during a specific interval in each trial (i.e. when the visual stimulus appears). The experimental design laid out in section D3a and Fig. 13 above will allow us to test the gating hypothesis. Probe stimuli will be delivered at 100 msec intervals during each of three intervals: the pre-period, the 0% coherence period, and the motion signal period. We believe that the functional connections between MT and SC (or LIP or FEF) will be downregulated during the intertrial interval and during the pre-period in which no visual stimulus is present, but will be upregulated to a potent state when the visual stimulus appears (0% coherence and motion signal intervals). Thus, we hypothesize that downstream signals resulting from probe stimulation of MT (like those illustrated in Fig. 14) will be stronger during the 0% coherence and motion signal intervals and weaker in the pre-period. The amplitude of the downstream responses will be assessed as described in the preceding section. Statistical significance of differences between test conditions can be assessed in several ways including permutation tests. If the gating hypothesis is confirmed, we will design subsequent experiments to measure precisely the time course of the gating mechanism. Rather than applying probe events every 100 msec, we will apply them at specific times following visual stimulus onset on different trials so as to measure the time course of the increase in signal flow between MT and SC.

**D3e. Possible outcomes and impact.** This project is the most speculative, and therefore the riskiest, of the three projects outlined in this proposal. The experiments are one-tailed in the sense that a negative result will mean little (there are several ways to fail). If the project works, however, it may well exert the most substantial intellectual and technical impact on the field of any project in this proposal. The project aims at two goals that can be accomplished in principle in the same set of experiments outlined above. The first is to demonstrate the circuitry according to the logic of Fig. 4, and the second is to demonstrate the gating of information flow between MT and downstream sensorimotor structures. To trace the intricate pattern of information flow that underlies decision-making on a perceptual discrimination task would be a salient achievement, bringing a heretofore inaccessible cognitive phenomenon into the realm of neurophysiological scrutiny. The second goal, however, is no less important. Active gating of information flow between neural structures must be a ubiquitous feature of brain function, yet neurophysiologists have made only the most tenuous steps toward rigorous study of gating. If our (stim/record) techniques succeed in measuring gating between MT and downstream structures, the techniques will certainly be applied by ourselves and others to a substantial array of similar gating phenomena in other neural systems.

**D3f. Possible problems.** Our proposed test of the gating hypothesis could be compromised by a specific technical problem. The hypothesized result—an increase in downstream stimulation-evoked activity when the visual stimulus appears—could perhaps occur trivially due to interactions in MT between visual and electrical stimulation. The hypothesized result could follow, for example, if electrical stimulation is more effective at eliciting action potentials at the stimulation site when MT neurons are partially depolarized due to simultaneous visual excitation. In this scenario, electrical stimulation effects could increase in amplitude for artifactual reasons when the visual stimulus appears, not because the neural connection is under the management of an active gating process. If we indeed obtain the hypothesized result, we will need to carry out more elaborate experiments to control for this possible artifact. For example, we could train the monkey to discriminate the direction of motion in one of two simultaneously presented patches of dots, the relevant stimulus patch being cued prior to each trial. One patch of dots will be positioned within the receptive field of the MT column, and the other will be placed in the opposite hemifield. The gating hypothesis predicts that only the circuitry appropriate for performing the task will be enabled during the trial. Probe stimuli delivered to a specific MT column should
elicit downstream responses more effectively when the monkey bases its performance on the patch of dots positioned in the receptive field of the stimulated column. If we indeed obtain this result, we can be confident that active gating occurs and is not an artifact of simultaneous visual activation which will be quite similar irrespective of which patch is attended (attention effects in MT are relatively small).

D4. Project #3: Neural correlates of experienced value (after Specific Aim 3).

We have begun our search for a neural correlate of experienced value (section C4 above) in cortical area LIP because, 1) LIP is known to play a role in conveying high level signals appropriate for guiding saccadic eye movements, 2) because prior experiments in our laboratory (summarized above) and in the laboratory of Dr. (Gold & Shadlen, 2001) have implicated LIP in decision-making, and 3) because Platt and Glimcher (1999) have found that LIP neurons are modulated by both the prior probability and the magnitude of the juice reward that an animal expects to receive for executing an instructed eye movement. Analogous modulations related to saccade probability and reward magnitude respectively have been reported in the intermediate layers of the SC (a brainstem structure to which LIP projects) and in area 46 (an eye movement center in frontal cortex to which LIP projects) (Basso and Wurtz, 1998; Leon and Shadlen, 1999). Together these results suggest that when the operant response is an eye movement, task relevant information from multiple sources, including signals related to bias and reward, may be represented within LIP.

**D4a. Experimental paradigm.** We will screen LIP for high-level neurons that fire with a sustained discharge during a delayed saccade task, as in previous studies from this laboratory. After identifying such a neuron and mapping its response field using the delayed saccade task, we will set up the matching experiment as illustrated in Fig. 6. One colored target is placed in the response field (Fig. 6, gray) and one is placed well outside the response field, usually in the opposite hemifield. The color of the target in the response field (representing the rich or lean reward schedule) will vary randomly from trial to trial. The monkey will perform the matching task illustrated in Fig. 6 while we record the activity of the LIP neuron. The experiment contains four trial types, illustrated in the 2x2 matrix in Fig. 15: the monkey may saccade to C1 or C2, either of which may be in or outside of the response field. Within each trial type, however, EV will vary widely from trial to trial depending upon the monkey’s recent history of choice and reward. We hypothesize that neuronal activity in LIP will be correlated with EV independently of target location and target color.

**D4b. Preliminary data, analysis, and interpretation.** At the time of this writing, we have recorded from 33 LIP neurons in one monkey during performance of this task. Figure 16 shows the exceedingly interesting data obtained from one such neuron. Physiological responses were considered to be the average firing rate of the neuron during the delay period prior to each saccade (Fig. 6). The neuronal response is
plotted as a function of EV of the target chosen on each trial. Four regression lines are drawn through the data points that correspond to the four conditions in Fig. 15 (all four are statistically significant, slope not equal to 0, p < .05). Choices of C1 are shown in the left panel and choices of C2 in the right panel; black and gray symbols depict saccades into and out of the response field, respectively. Plainly, the response of this LIP neuron varied markedly with EV even when the sensory context and the motor response were constant, as was the case within each trial type. When the monkey chose the target within the response field, the LIP neuron responded more vigorously as the EV of the chosen target increased, irrespective of target color (black symbols, left and right panels). When the monkey chose the target outside the response field, the response of the neuron decreased with increasing EV, irrespective of target color (gray symbols, left and right panels). Perhaps the best way to think about the data in Fig. 16 is that the neuron appears to code EV of a particular region in space which comprises its own response field. From trial to trial, EV of one target varies inversely with EV of the other target. Thus, increasing values of EV computed with respect to the chosen target outside the response field (gray symbols in Fig. 16), correspond to decreasing EV for the nonchosen target in the response field. Stated more intuitively, when the monkey chooses the target inside the response field, the neuron’s response increases with increasingly greater expectation of a reward; when the monkey chooses the target outside the response field, the neural response decreases with increasingly greater expectation of reward.

It is particularly interesting to note that the difference in neuronal response for saccades into and away from the response field is quite modest on trials in which EV favored the target that the monkey did not choose (negative EV values). In the left panel of Fig. 16, for example, rightward and leftward saccades resulted in a response difference of roughly 10 spikes/sec at an EV of 0, whereas the difference was greater than 30 spikes/sec in the delayed saccade task that we used to map the response field (data not shown). Thus, EV accounts for as much or more variance in this neuron’s firing rate as the eye movement itself. We have verified this qualitative impression with multiple regression analyses for data obtained from this and other LIP neurons.

The neuron illustrated in Fig. 16 is one of our better examples, but the basic result is confirmed in a population analysis of the 33 neurons we have recorded thus far. The slopes of the regression lines of neural response onto EV are positive across the population when the target inside the response field is chosen, and are negative across the population when the target outside the response field is chosen (Sugrue and Newsome, 2002). Pending results from a second animal (and a control analysis outlined below), we tentatively conclude that EV is reflected in the responses of LIP neurons as hypothesized above.

D4c. Possible problems. We are concerned about two possible problems relevant to the interpretation of these data. One is of a technical nature and can be addressed directly with additional data analysis. The second is conceptual and is more difficult to address rigorously.

Our interpretation that LIP activity is influenced by EV depends upon our assertion that the monkey’s eye movements to the chosen target are constant within each of the four trial types denoted in Figs. 15 & 16. We know, however, that this is not precisely true since small variations in metrics are typical of saccades to visually guided targets. A central question, therefore, is whether small variations in saccade metrics can account for the variation in neuronal response that we have attributed to EV. We have not observed any systematic variation in the saccades during experiments, but we are in the process of conducting a rigorous quantitative analysis of this issue. We store eye movement data for every experiment, and we are conducting multiple regression analyses of firing rate onto several saccade parameters (latency, amplitude, angle, accuracy, velocity) in addition to EV, exactly as we have done in prior studies of the effects of motion coherence on decision-related activity in LIP and SC (Shadlen and Newsome, 2001; Horwitz and Newsome, 2001b). Thus far we are detecting some weak but significant effects of EV on eye movement parameters, but these effects do not account for a measurable portion of the variance in the firing rates of the LIP neurons. If this result is confirmed in the completed analysis, we can rule out a trivial interpretation of the data based on eye movements.

Assuming that our basic result is correct, a thorny conceptual issue remains: can we attribute the neuronal effects in LIP directly to EV, or might the effect of EV be mediated through a second cognitive process such as attention? It would seem natural, for example, for a monkey to attend more closely to a target for which he has a high expectation of reward. We cannot rule out this possibility, but we do not consider it to be critical to the success of the proposed experiments. The critical point is that we have developed a metric based on the monkey’s weighted experience of choices and rewards over recent history that: 1) predicts accurately the probability of future choices to one or the other target, and 2) accounts for substantial variance in the firing rate of LIP neurons independently of sensory and motor aspects of the task. We cannot calculate any variable
with similar predictive power from considerations of attention alone. Even if LIP neurons are receiving EV-related information through the "lens of attention", the effects are plainly rooted in the monkey's internal valuation of possible choices as revealed in matching behavior.

Having said that, however, we must also add that we do not believe that EV is computed in LIP. We have performed a preliminary analysis of the EV population effects as a function of time during the delay period. The effects of EV are weak (if present at all) early in the delay period and increase in intensity as the delay period proceeds to the time of the saccade. Thus the representation of EV in LIP appears to be "reset" between each saccade as though LIP were receiving anew the result of a computation performed elsewhere in the brain. This is not surprising since the structure of our task requires that EV be computed with respect to target color, not with respect to spatial location. We presume that the original computation of EV in the brain must be "tagged" by target color, and that this information is transmitted to LIP after the two targets appear on each trial and the monkey knows which color (i.e. the rich or lean target) is present within the response field of each LIP neuron. Identifying the site of EV computation is a major future goal for this project.

D4d. Future experiments. The intellectual terrain embraced in this project is particularly fecund; our studies can expand in several important directions in the future. The most immediate priority is to expand our LIP data base in the current monkey, obtain a similar data set in a second monkey (the second animal is already trained on the matching task), and complete critical controls such as the eye movement analysis described above. Publications of the behavioral and electrophysiological work will follow at that point.

Our second priority is to identify the primary representation of EV in the brain. We expect this representation to be tagged by target color as described above, and we expect EV to be reflected in the tonic firing rates of the tagged neurons, although this is not the only coding mechanism that can be imagined. Our first experiments will be targeted toward the orbito-frontal cortex, which contains neurons that appear to encode the relative value of competing rewards (Rolls et al., 1996; Rolls, 2000; Tremblay and Schultz, 1999, 2000a, 2000b). Other possible recording sites include anterior cingulate cortex, which has been implicated in executive monitoring and correction of ongoing performance (e.g. Holroyd and Coles, 2002; Schall et al., 2002), and dorsal prefrontal cortex.

Our third priority is to combine "sensory" and "value" influences in a single forced-choice task to examine how these variables interact during decision making. Our published studies were primarily concerned with effects of the sensory stimulus (Shadlen and Newsome, 1996, 2001; Horwitz and Newsome, 1999, 2001a, 2001b) while our current studies are concerned exclusively with experienced value. We will ultimately combine these variables by requiring the monkey to perform a version of our direction discrimination task in which the probability of motion in one or the other direction is varied unpredictably as in the matching task. Key questions will include how the competing variables interact at the behavioral level, and how signals related to these variables are processed at the neuronal level (i.e. same or different populations of neurons?).

Another avenue for exploration concerns the influence of reward schedules and learning on choice behavior. Does the weighting function revealed by our cross-correlation analysis describe the general character of a monkey's ability to integrate reward information across time, or would the weighting function change in shape if rewards were delivered according to a different schedule? While our primary goal in the coming grant period will be to pursue the electrophysiological studies, we may also have time to pursue behavioral studies of the effect of reward schedules.

D5. Time Line

If this grant is funded, we will pursue simultaneously all three of the major projects in this proposal. We have 8 rig slots available each day, with the possibility of expansion if necessary. I will devote one rig slot to each of these projects throughout the grant period. We will train two monkeys for Project 1 during the first year of the grant period, and conduct the experiments in different combinations of cortical and subcortical areas (LIP, FEF, SC) during years 2-4. The final year will be occupied by follow-up experiments in which we assess the effects of varying the timing of stimulation pulses to the two areas (i.e. synchronous vs. asynchronous; rhythmic vs. arhythmic), assuming that the first experiments are successful. One monkey is already trained for Project 2, and another will be in training soon. Experiments will be initiated on Project 2 during year 1 and continued in years 2 and 3. It will probably take 2-3 years of work on this project to know exactly what we do or do not have. If we are indeed able to demonstrate the circuitry in these experiments and measure the time course of the gating process, we will design additional experiments to study the gating mechanism in detail, including (possibly) drug infusions to identify the transmitter systems involved. Project 3 is already underway,
and the experimental plans outlined in the preceding section will easily occupy all five years of the proposed grant period.

E. HUMAN SUBJECTS: NONE

F. VERTEBRATE ANIMALS

1. Description of proposed use of animals. The use of awake, behaving monkeys is integral to all of the experiments proposed in this document. The specific use of animals has been described in the description of each project in Research Design and Methods (sections D2, D3 and D4), and in the section on General Methods (D1). We include here brief descriptions of our surgical procedures and controlled fluid intake protocol, which are not described elsewhere in the proposal. All of our procedures, of course, conform to NIH guidelines and are approved in advance by the Institutional Animal Care and Use Committee at Stanford.

Cranial implant surgery. A mid-line incision is made from the frontal brow ridge to the occipital ridge. Skin, fascia and muscle are retracted to expose the cranium. Titanium orthopedic plates (Synthese) are fitted to the curvature of the skull and attached to the skull with titanium orthopedic screws. A head holding post is attached to the bent and raised ends of the plates using bone cement. A craniotomy is made to permit microelectrode access to target regions within the brain, and a hard plastic recording cylinder is attached to the skull by means of titanium bone screws and bone cement. A fitted plastic cap is fastened to the top of the recording cylinder and removed only for experiments or for cleansing of the cylinder. Muscle, fascia and skin are sutured so as to obtain a snug fit to the cranial implant. Wound edges are tended regularly (hair trimming, cleansing, topical antibiotic if needed) for the duration of the animal's stay in the lab.

Eye coil surgery. A scleral search coil is fitted around the perimeter of the eye globe in order to provide accurate measurements of eye position during experiments. An incision is made to disengage the conjunctiva from the limbus, and the conjunctiva is then separated from the anterior half of the globe using blunt dissection. The search coil is fitted to the globe (4-6 mm from the edge of the cornea) and tacked down with very small amounts of cyanoacrylate glue. The electrical lead from the coil is routed subcutaneously to the area of the cranial implant and soldered to an electrical plug which is then attached to the cranial implant using bone cement. Stitches are made so as to draw the conjunctiva tightly around the globe. Ophthalmic ointment is administered prophylactically to prevent infection and reduce swelling.

Controlled fluid intake. Access to fluids is controlled in order to motivate the animals to perform the behavioral tasks. Fluids are withheld overnight, and the animals work for fluid rewards during experiments. Most experiments end when the animal has obtained sufficient fluid that it is no longer motivated to perform. If an experiment is terminated prior to this point, supplemental fluids and fruit are given to bring the total up to the standard level established individually for each animal. The general health, weight and food intake of each animal on the controlled fluid protocol are closely monitored by laboratory scientists, by trained animal care technicians, and by the veterinary staff. We provide each animal with the maximum amount of fluid that is consistent with good health and with motivated performance of the behavioral tasks.

Species, ages, gender and number. All experiments will be performed on macaque monkeys (M. mulatta or M. fascicularis), male or female, ages 4-15 years. The proposed experiments will require the use of 9 monkeys (three per project) over the 5 year project period. Our procedures are not intrinsically harmful to the animals. Most of our animals remain in experimental study for several years and are euthanized ultimately because of our need for histology.

2. Justification for use of animals, choice of species, and numbers of animals. The objective of research in this laboratory is to understand how neural processing in the cortex of primates mediates visual perception and visually-based cognition. To understand the neural basis of cognition, it is essential to conduct neurophysiological experiments in awake, behaving animals. Cognitive functions such as perception, attention, decision-making, and motor planning occur only in intact, functioning nervous systems. Of the experimental approaches currently available for studying cognitive function in alert animals, the most powerful and versatile is the awake, behaving monkey, developed originally in the laboratory of Herbert Jasper and subsequently developed extensively by Edward Evarts and his colleagues at the National Institute of Mental Health. Macaque
monkeys can be trained with operant conditioning techniques to perform a wide variety of simple cognitive tasks such as perceptual discrimination, object recognition, short-term memory, attentional priming, and sequential motor planning, among others. We will use rhesus monkeys (Macaca mulatta) for most of our experiments, but may occasionally use cynomologous macaques (Macaca fascicularis) depending upon the availability of rhesus. Rhesus is our species of choice for several reasons. First, previous experiments have shown that the visual capabilities of this species and the visual pathways in its brain closely resemble those of humans. Similarities in visual acuity, color vision, stereopsis, and contrast sensitivity as well as a broad range of eye movements (saccades, smooth pursuit, optokinetic nystagmus, etc.) make it highly probable that new discoveries in this species will be directly applicable to our understanding of visual function in humans. Secondly, rhesus monkeys are ideal for experiments in which the animal's behavioral cooperation is required. They can be trained on a wide variety of visual tasks and will perform these tasks reliably in a laboratory environment. Finally, decades of research have given us a broad base of knowledge concerning the organization of the visual system of the rhesus monkey. We are therefore able to ask relatively sophisticated questions with this animal that would be impossible in a species for which more basic aspects of visual function are poorly understood. (Lower animals such as rats and mice can be employed to study certain restricted functions at which they excel, such as spatial navigation (mazes) and olfactory function. But it is exceedingly unlikely that rodents possess the full range of cognitive abilities that we wish to study.) Three monkeys per project represents the minimum number of animals required for the proposed research. Each of the three projects is highly innovative and likely to yield novel results. Truly novel results must be demonstrated in multiple animals to ensure that the data are sound and do not result from idiosyncratic aspects of individual animals.

3. Veterinary care. Our animals receive outstanding veterinary care and husbandry provided by the outstanding veterinary care and husbandry provided by the All of Stanford's animal facilities are AAALAC accredited. The veterinarians and their technical staff are experienced, well trained, and maintain the highest professional standards of their profession. The veterinary staff are experienced, well trained, and maintain the highest professional standards of their profession. employs several veterinarians, most of whom are also faculty members of the Department of Comparative Medicine. At least one veterinarian is on-call at all times, and two of the veterinarians have been designated as specialists for primate labs. The veterinary staff are very responsive and are willing to work with us in great detail to solve any problem that threatens the health of an animal. A veterinarian is typically present in my lab 2-3 times per week for general monitoring or to address a specific clinical problem with an individual animal. Daily husbandry (feeding, cage cleaning, general monitoring) is performed by trained technical personnel. In addition, my head laboratory technician oversees all special husbandry that is performed by laboratory personnel, consisting mainly of daily cleansing and care of cranial implants and recording cylinders. All animals are tested for TB four times per year, and for herpes virus B twice a year. Post-operative care is performed in the post-operative recovery suite (ICU) with the assistance of staff. The animals typically remain in the ICU overnight following surgery.

4. Procedures for ameliorating pain and distress. The primary area of concern in our procedures is the surgery to implant the cranial hardware and the search coil. We scrupulously follow the recommendations of our veterinarians for ameliorating pain and distress associated with the surgery. Animals are pre-anesthetized with ketamine hydrochloride (5-15 mg/kg, IM) and maintained under isoflurane anesthesia for the duration of the procedure (1-5%, inhaled). Postsurgical pain relief is accomplished with Torbugesic (0.02 mg/kg, IM) immediately following surgery and subsequently as needed. Daily care and cleansing of wound edges and recording cylinders is generally not painful. If an animal reacts to wound contact as though it were painful, we apply local anesthetic topically to eliminate the problem. The animals become well accustomed to the daily routine of exiting the cage, climbing on the scale for weight measurement, entering the primate chair, and performing behavioral tasks in exchange for liquid rewards. The daily behavioral routine provides opportunities for exercise, for extensive interaction with human handlers, and for behaviorally interesting “foraging” for rewards. We have an extensive program for caring for the psychological welfare of our animals, and we are now experimenting with pair housing of experimental animals. We have one stable pair who spend approximately 20 hrs/wk together, and we will begin working with a second pair in the near future.
5. **Euthanasia.** Following termination of all experiments, an animal is euthanized with an overdose of sodium pentobarbital (50 mg/kg, IV), consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. The brain is generally removed for histological study.

**G. LITERATURE CITED**


 obedient to the US Office of Naval Research and Stanford University specifies that animal care charges and services carry a separate indirect cost rate which is excluded from, and does not duplicate, Stanford University's Modified Total Direct Cost (MTDC).

4. SMOKE-FREE WORKPLACE  X  Yes  No (The response to this question has no impact on the review or funding of this application.)