1. **TITLE OF PROJECT**
   Hierarchical Processing in the Motion System

2. **RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION**
   Number: Title: 

3. **PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR**
   New Investigator: No Yes
   3a. NAME (Last, first, middle) Britten, Kenneth H.
   3b. DEGREE(S) Ph.D.
   3c. POSITION TITLE Associate Professor
   3d. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Medicine / Division of Biological Sciences
   3e. MAJOR SUBDIVISION
   3f. TELEPHONE AND FAX (Area code, number and extension) TEL: 530-754-5080 FAX: 530-757-8827

4. **HUMAN SUBJECTS**
   4a. Research Exempt: No Yes
   4b. Human Subjects Assurance No. M-1325
   4c. NIH-defined Phase III Clinical Trial: No Yes

5. **VERTEBRATE ANIMALS**
   5a. If "Yes," IACUC approval Date 6/4/04
   5b. Animal welfare assurance no A-3433-01

6. **DATES OF PROPOSED PERIOD OF SUPPORT**
   From 7/1/04 Through 6/30/09

7. **COSTS REQUESTED FOR INITIAL BUDGET PERIOD**
   7a. Direct Costs ($) 200,000
   7b. Total Costs ($) 294,839

8. **COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT**
   8a. Direct Costs ($) 1,000,000
   8b. Total Costs ($) 1,491,439

9. **APPLICANT ORGANIZATION**
   Name The Regents of the University of California
   Address OVCR, Sponsored Programs
   118 Everson Hall
   One Shields Avenue
   University of California
   Davis, CA 95616-8671

   Institutional Profile File Number (if known) 577503

10. **TYPE OF ORGANIZATION**
    Public: Yes No
    Private: No Yes
    For-profit: No Yes
    Woman-owned: No Yes
    Socially and Economically Disadvantaged: No Yes

11. **ENTITY IDENTIFICATION NUMBER**
    DUNS NO. (if available) 04-712-0084
    Congressional District 1

12. **ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE**
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14. **PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE**
    SIGNATURE OF PI/PD NAMED IN 3a.
    (In ink. "Per" signature not acceptable.) DATE 6/30/04

15. **APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE**
    SIGNATURE OF OFFICIAL NAMED IN 13.
    (In ink. "Per" signature not acceptable.) DATE Jun 23 2004
The basic "building blocks" of visual perception are starting to become reasonably well understood, and we can make a fairly good account of how simple discriminations are done. What we understand much less is how the visual system solves more realistic, everyday challenges. Visually guided navigation is a particularly good "model system" for studying real-world visual processes in the laboratory. The perception of self-motion from the pattern of motion on the retina has been studied extensively, though we still know very little about where in the brain the critical processing steps occur, and how the complex pattern of motion is converted into effective movement. The present proposal seeks to answer these open questions. First, we will seek direct evidence for the involvement of multiple cortical areas in the perception of self-motion, by using multiple, simultaneous recording techniques while our experimental animals are performing a discrimination of self-motion direction. Secondly, we will seek to ask if the parietal cortical area (the ventral intraparietal area, or VIP) is both necessary for self-motion perception and is actually used. We will do this by perturbing the pattern of activity in VIP in the context of the self-motion task, both by reversible inactivation as well as by electrical activation. These complementary methods should greatly extend our understanding of how the parietal cortex participates in self-motion perception. However, to really extend our knowledge of self-motion perception, we need to extend the inquiry into a more active context. Human-factors studies have revealed that guidance of self-motion ("steering") is a very active process, with the direction of gaze being a critical component. However, next to nothing is known about the central nervous system mechanisms used in this active task. So, we propose to establish, characterize and exploit an animal model of active locomotion to study the involvement of brain structures in this task. We will train our subject to direct their "virtual" trajectories by joystick, and characterize how their normal behavior is influenced by cues including target direction, gaze direction, gaze velocity, and visual motion information. We will then record activity in multiple cortical areas while animals are engaged in this task, and explore the signals in visual and parietal cortex to better understand brain mechanisms of visually guided navigation. This information, in the long term, might be useful in helping the disabled to navigate, and in the development of visual prosthetics for the blind.
RESEARCH GRANT

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Research Plan

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Checklist

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):

| Number | 4 |

Check if Appendix is Included
$ 200,000
$ 200,000
$ 200,000
$ 200,000
$ 200,000

Total Direct Costs Requested for Entire Project Period

Graduate students have recently become more expensive in the UC system, and their fees promise to grow substantially over the next budget period. At present, students receive annual fees of 8,406, and this figure might rise unpredictably over the next few years.
2 pages redacted--biosketches omitted as indicated in the request
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:
The P.I. has full and sole use of a modern 725 sq. ft. laboratory. It is equipped with two recording "rigs" and one monkey training station. It is fully equipped with standard electronic and computer equipment for extracellular recording and microstimulation in alert monkeys.

Clinical:

Animal:
Animal facilities at Davis are top-notch, especially for primate research. The local Primate Research Center has a large staff of trained veterinary and support staff, who assist with animal procurement, surgery, and health monitoring. Surgeries are performed in a fully equipped, dedicated surgical suite at the Primate Center, which has a full-time primate anesthesiologist/surgical technician. Once procured, the animals are housed in the vivarium. Feeding and routine care is handled by Animal Research Services, which devotes approximately a half-time staff person to the primates in use at the center.

Computer:
The lab has 6 computers dedicated to experimental control, data collection, and visual stimulus presentation. Additionally, there is a small Linux cluster for data analysis. Lastly, there are 3 Macintosh computers for word processing and graphics. The center has a full-time computer and network support staff person for software and hardware assistance.

Office:
The P.I. has a 125 sq. ft. office, and postdocs are additionally housed in floating office space. Grad students are given carrels in a large common area.

Other:

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

Each recording "rig" contains amplifiers and dual window discriminators (Bak), programmable pulse generators (A.M.P.I), stimulus isolation units (FHC), oscilloscopes (Tektronix) and audio monitors. One rig is equipped with multi-channel recording capability (Thomas Recording, Plexon). Histology facilities are available through private arrangement with local anatomy labs (Krubitzer, Usrey, and Jones).

MRI scans of nonhuman primates are available through the CNPRC.
Introduction to revised application
a. Specific Aims

While we know much about the basic mechanisms of visual processing, we know very little about how this information is used to guide effective behavior. Visually guided locomotion is an extremely important natural behavior in most species, including humans, but little is known about its sensory substrates or its immediate motor planning stages. The experiments in this proposal seek to elucidate the role of sensory and premotor areas in the perception of self-motion, and the guidance of effective motor responses. We will focus on the interface between the well-understood “motion system” of dorsal extrastriate cortex and the posterior parietal cortex, which is clearly a watershed area for sensorimotor processing. We will use a well-defined task, visually guided heading, to ask how the upper levels of the motion system and the motion-influenced areas of posterior parietal cortex contribute to the perception of self-motion and the generation of appropriate motor behavior.

Aim 1. Is VIP either necessary or used for heading perception?

Single-cell recording experiments have shown that VIP contains signals sufficient to support heading perception. To go beyond this, we wish to perturb the area in the context of a heading task. We plan to use reversible inactivation to test the necessity of VIP in heading perception and microstimulation to test for sufficiency. The results of these experiments should allow us to conclude whether or not VIP has a direct, causal, and necessary role in heading perception.

Aim 2. How do multiple areas interact to produce the perception of heading?

Heading perception, like many complex functions, is likely to depend on multiple cortical areas. We propose to evaluate quantitatively the contributions of three areas—MT, MST, and VIP—to heading perception. Single-cell and multi-electrode recordings will be made from these areas while monkeys discriminate heading, and cell activity will be analyzed for sensitivity (neurometric function analysis), choice probability, and inter-neuronal correlation. The resulting data will allow us to directly evaluate each area’s contribution to the performance of individual animals on this complex task, and how these areas interact during task performance.

Aim 3. The role of cortex in an active heading task

We have been very successful using a perceptual task to study heading, but in natural behavior, such stimuli are used to guide movement. We plan to start studying how the visual system guides more natural behavior by developing an active “steering” task. We will characterize the performance of monkeys on this behavioral task, as well as the cues that they use and how eye movements influence adaptive heading responses. We will then record the activity of dorsal stream extrastriate areas and posterior parietal areas to explore the involvement of these regions in the guidance of behavior.

b. Background and Significance

b1. General background

Motion is one of the best-understood sub-modalities of vision, but we know much less about how it is used in natural behavior. The study of the sensory aspects of motion processing has been a tremendous success story of systems neuroscience, in part because of the tight interplay between theory and experiment, and in part because of the highly specialized cortical areas that support motion processing in primates. Visual motion is used to guide and inform scene segmentation, object form and trajectory judgments, and adaptive motor responses such as eye movements and
locomotion. While physiologists have been developing a good understanding of the sensory aspects of optic flow processing, the psychophysical community has moved toward studying more natural “active vision” tasks, such as locomotion and steering. Virtually all mammals engage in visually guided locomotion, yet we know much less about the neural mechanisms for this important visuomotor behavior. However, we are tantalizingly close, since we know so much about the sensory substrates for this category of behavior. In this proposal, we include experiments that both further our understanding of the sensory aspects of the perception of self-motion, as well as develop a true sensorimotor model, which will be applicable to a wide range of natural, motion-guided behaviors.

b2. Background for Aims 1 and 2 (sensory aspects of heading)

Gibson (1950) was the first to point out that the pattern of image motion on the retina was an important source of information about where one was heading, and this sparked a large number of studies at many different levels of analysis. The study of heading has been particularly fruitful because of the tight interplay among psychophysics, theory, and physiology. However, despite a plethora of good experiments, crucial questions remain unanswered. In particular, we are still woefully ignorant of which central nervous system structures participate in the recovery of heading from optic flow. Work from many labs has produced a very good body of candidate areas, since appropriate signals are widespread. Starting in the 1980s, work in the Tanaka lab showed that area MST contains neurons selective for optic flow patterns (Saito et al., 1986; Tanaka et al., 1986; Tanaka et al., 1989; Tanaka and Saito, 1989). Guided by theory (Koenderink and van Doorn, 1987) and a natural predilection for parametric study, many physiologists (including myself) quantified the properties of neurons in MST and other areas using well-defined stimuli. A subset of possible optic flow patterns—rotation and expansion/contraction (curl and div, mathematically)—has received particularly careful scrutiny. Responses selective for such patterns have now been found in many cortical areas, including MST (Duffy and Wurtz, 1991; Graziano et al., 1994), VIP (Schaafsma and Duysens, 1996; Schaafsma et al., 1997; Bremmer et al., 2002), area 7a (Sakata et al., 1986; Siegel and Read, 1997; Phinney and Siegel, 2000), PEc (Raffi et al., 2002), and even motor cortex (Merchant et al., 2001). One important conclusion of this series of studies is that these responses clearly differentiate these higher-order areas from area MT, which is almost entirely selective for the local translational components of such patterns (Graziano et al., 1994; Lagae et al., 1994).

Yet these studies, however revealing, have certain fundamental limitations with respect to the analysis of heading. First, in most experiments, the stimuli were explicitly two-dimensional, corresponding to rotating or looming flat surfaces. While similar optic flow components can be found in the more complex, three-dimensional scenes that we normally move through, their existence does not necessarily demonstrate that these representations are adequate for supporting normal heading judgments. Psychophysicists have repeatedly emphasized the importance of depth in making heading judgments (Warren et al., 1991; Royden et al., 1992; van den Berg, 1992), but physiologists have been slow to adopt depth-varying stimuli. Only a few studies (Kim et al., 1997; Paolini et al., 2000; Upadhyay et al., 2000) have used more realistically structured stimuli. So, from all this work, we have a large suite of possibly involved areas, still waiting for the demonstration that their signals are actually involved in heading. We have begun to work on this problem (see Progress Report), but much more needs to be done. In particular, to document which areas are actually involved in heading, we need to apply what has been learned on simpler tasks. There is now a well-developed “toolkit” for exploring the relationship between cortical activity and perception (Parker and Newsome, 1998), and these tools need to be brought to bear on the problem of heading. However, we must take the hint from the physiology that the number of candidate areas is large, and thus we will need to broaden our search beyond MST.
VIP makes a particularly good candidate. First, it is anatomically well-connected to the motion areas of the dorsal stream, including MT and MST (Lewis and Van Essen, 2000). Accordingly, it has briskly directional responses to motion stimuli (Schaafsma and Duyssens, 1996; Cook and Maunsell, 2002). But, since it lies in the parietal cortex, it is also densely connected with the auditory, somatosensory, and motor systems (Lewis and Van Essen, 2000). This endows VIP with properties not seen in antecedent motion areas, which might be particularly useful in complex tasks such as heading. Heading perception is largely invariant with eye movements, and VIP has properties that correlate with this perceptual ability. Specifically, receptive fields (RFs) of VIP neurons are frequently in head-centered coordinates with respect to eye position (Duhamel et al., 1997) and with respect to eye velocity (Appendix B, Zhang et al.). Thus, we can certainly add VIP to the list of areas that might support heading, but what is still lacking is the documentation that it actually is engaged. For this, we need to measure the responses in these candidate areas while animals are actually engaged in a heading perception task, and also to perturb areas while animals are performing such tasks, to show direct involvement in perception. These are the goals of Aims 1 and 2 in this proposal.

b3. Background for Aim 3 (steering task)

The psychophysical approach we have taken is a necessary first step to understanding a complex function like self-motion, since it isolates the sensory limits on performance. But in order for this information to be useful, it needs to be integrated into a behaviorally relevant context. The normal context for heading perception is self-motion, where we control our direction of motion according to visual, somatosensory, and vestibular feedback. Among these, visual cues are probably the most important. It is possible, although very difficult, to explore the mechanisms underlying actual self-motion in monkeys (Nishijo et al., 1997; Ono and Nishijo, 1999). However, a suitable surrogate exists in the guidance of virtual trajectories. Such virtual-navigation tasks have been used extensively in the study of human performance (e.g., Rushton et al., 1999), and monkeys can be easily trained to navigate using joysticks (Washburn and Astur, 2003). Virtual navigation tasks offer the advantage of making it possible to study the contribution of visual signals in isolation. Therefore, it is a natural extension to this well-developed model system to place the monkey in an active virtual-trajectory task to study the interaction of visual motion with appropriate motor guidance. As a first step, we have trained a monkey to “steer” a virtual trajectory toward a specified goal using a joystick that controls its trajectory (see Progress Report, section c4). We have adopted a simplifying approach, studying just the horizontal dimension of heading and of trajectory control, just as has been done in much of the human psychophysics. This is ethologically justifiable for both humans and rhesus macaques as these species spend much of their time navigating across the ground surface using visual cues.

The field of steering has been engaged in a controversy over the last few years, which the proposed experiments will help to resolve. In particular, the contention concerns the extent to which optic flow cues are actually used in the guidance of self-motion under normal conditions. Gibson (Gibson, 1950), argued that the presence of such rich information about self-motion in the scene would almost necessitate that it be used. The psychophysical experiments of Banks, Warren and many others certainly show that observers can use these cues when the task demands it (for review, see Warren, 1998). However, many of these experiments were done under fairly unnatural (i.e., gaze-fixed) conditions. Under normal circumstances, however, gaze provides another useful cue. If the visual system identifies the target of intended movements and directs gaze toward it, steering can then follow in a kind of servo mode. Considerable evidence exists for this mechanism. Under normal circumstances, subjects direct gaze toward anticipated targets with an appropriate lead time (Pelz et al., 2001; Barnes and Marsden, 2002; Hollands et al., 2002). In steering on roads and simulated roads, this means that we often direct our gaze toward the inside of the turn through which we are currently moving (Land and Lee, 1994; Land and Horwood, 1995; Land and Tatler, 2001). Indeed,
motorcycle instruction courses usually advise riders that looking ahead well into a turn will promote
good cornering lines (Hough, 2000). When looking ahead in a turn, the angle of gaze is controlled by
the curvature of the turn, and thus can directly control the amount of steering needed to follow the
turn accurately. In this formulation, optic flow is not used at all.

The two cues (flow and gaze) can but put into conflict in a variety of ways, to test the relative
importance of each, and the results of these experiments are not yet conclusive. In prism
experiments, subjects followed the shifted position of the target and thus walked in a curved path,
despite the presence of optic flow cues signaling the curvature of their trajectory (Rushton et al.,
1998; Harris and Carre, 2001). On the other hand, in a virtual-reality environment, if the optic flow
field is perturbed, subjects adjust their locomotion to compensate (Warren et al., 2001). Therefore, it
remains uncertain to what extent each of these cues is being used. Inevitably, of course, these
psychophysical experiments do not reveal where or how the cues are represented, weighted, and
integrated in the brain. Such mechanistic questions will require the development of a suitable animal
model, in which we can directly explore the underlying brain mechanisms. This is what we are
proposing to do in Aim 3.

b4. Broader significance

Systems neuroscience has been tremendously successful, over the last four decades, at
working out the basic building blocks of perception. This success has been in large part due to a
highly reductionist approach: single cells, simple stimuli. However, this reductionist approach, though
useful, will inescapably fail in the analysis of more complex tasks, such as those that characterize
most of real-life visually guided behavior. Both technical and conceptual advances make the time ripe
for a relaxation of the limits of the approach. However, it clearly is necessary to preserve the spirit of
the reductionist approach by picking particularly tractable problems. The analysis of optic flow is a
perfect example of such a tractable yet complex problem. The sensory elements of optic flow analysis
are reasonably well understood, the behavioral context is quite well specified, and many of the
intervening computations are well posed, theoretically. Additionally, with modern computers and
instrumentation, we can relax some of the restrictions of the reductionist approach, without losing
control of the sensory stimuli. Thus, we feel that the kind of work embodied in this proposal is a
natural advance that will produce substantial rewards, both near- and far-term.

For near-term goals, we will uncover how information in complex tasks is shared across
multiple cortical areas, and also be able to start working out the sensorimotor transforms in a very
realistic task. In the long term, this knowledge might help in the fields of robotics and artificial
intelligence. In these fields, truly autonomous, self-navigating robots are an important aim, but one
that has proven surprisingly difficult. Perhaps even more importantly, these results might aid in the
development of new generations of aids for the disabled, for whom lack of autonomy is a deep
problem. It is also possible that the information from these experiments will help in the development
of visual prosthetics for the blind, which might be geared directly toward the coordination of natural
movements such as locomotion.

c. Progress Report

This grant was originally funded in January, 1994, and was last reviewed in June, 1999. In this last
period, we have had considerable success on many projects. Work funded by this grant has resulted
in 8 peer-reviewed papers and 7 abstracts over the last 5 years (section c7).
c1. Progress on the psychophysics of heading in monkeys

We have been studying the neural substrates of heading perception for some time now, using a simple, psychophysically motivated approach. We have treated this as any other perceptual problem, and have designed a simple paradigm to explore the limits of performance and the properties of the relevant neuronal circuits: the two-alternative, forced-choice (2AFC) task illustrated in Figure 1. In this task, a monkey views a simulated trajectory through a three-dimensional (3D) cloud of points, and must judge on each trial whether the trajectory passed to the left or right of "dead ahead" (head-centered or egocentric zero). Heading angle (the difference between the trajectory and dead ahead) is varied horizontally, and the task can be made arbitrarily difficult as the heading angle is made smaller. Following presentation of the stimulus, the monkey indicates its choice by making a saccadic eye movement to one of two targets, presented to the left and the right of dead ahead. This "just-noticeable-difference" task is well suited to measuring the sensitivity of the animal to small changes of heading. It is a relatively natural task in that animals commonly wish to detect small changes in ongoing trajectories (to compensate), and also in that the scene contains a range of depths and thus a range of speeds. Psychophysical data from such an experiment is shown in Figure 2, which plots the distributions of choices in each direction as a function of heading angle. This allows us to describe compactly both the sensitivity to heading (the steepness of the function) and any biases that exist (which change the horizontal position of the function). Using this task, we have also investigated the interaction of heading perception with ongoing eye movements, and typically include in our experiments trials in which the monkey is required to track a pursuit target (data not shown).

Using this task, we have studied the relationship between performance and neuronal signals in candidate areas along the dorsal stream that leads toward the parietal cortex. In particular, we have focused on the well-studied extrastriate area, MST, and the posterior parietal area, VIP. As we show below, we have good evidence linking both these structures to the recovery of self-motion information from optic flow, and to the compensation for ongoing eye movements. We can make a very strong, but circumstantial, case that both MST and VIP are important in the perception of heading. The proposed experiments will both solidify our current understanding of how each area contributes to performance on this task, and determine how they work together in supporting heading.

c2. Progress relating MST to optic flow perception

The main aims of the grant were quantitative analyses of the mechanisms of optic flow processing in areas MT and MST, and tests of the participation of these areas in the perception of complex motion stimuli. I will focus on three main findings from this series of experiments. First, we have demonstrated that area MST is directly and causally involved in the perception of heading. Secondly, our measurements of MST and VIP heading responses have documented that both areas contain signals sufficient to support heading perception. Lastly, we have investigated the role of MST in the discrimination of near-threshold optic flow stimuli (not heading, but "spiral space").
concluded that such discrimination is likely to be based on signals in other cortical areas as well as MST, because the signals in MST, while globally suitable for perception, do not correlate well with performance, either across animals or across trials.

We have documented that MST is directly involved in heading perception using the method of intracortical microstimulation (Appendix A, Britten and Van Wezel, 2002). This method, which has been recently been used in several sensory contexts, allows the demonstration of a causal link between activity in a particular area and perception (Salzman et al., 1992; DeAngelis et al., 1998; Moore and Fallah, 2004). It relies on the presence of nearby neurons tuned similarly for the dimension of interest, since activation will spread some distance. We had previously established this pre-requisite condition for MST (Britten, 1998), so we used microstimulation in the context of the 2AFC heading task described above. Figure 3 shows a single-case example, where activation at 200 Hz with 20 μA, biphasic current pulses caused a significant shift of the perceived heading. In this case, the shift was of about 2 degrees horizontally, and biased decisions in favor of the preferred direction of the multi-unit activity at the recording site. Similar results were found in most cases, but in a noticeable minority of cases, the effect was in the opposite direction, as indicated by the summary histogram in Figure 4. In this histogram, effects that align with the preferred direction are shown as positive values, and opposite effects are shown as negative values. Significant effects are shown as black bars. In about one-third of significant cases, the effect was opposite to the preferred direction. While such a result is puzzling at face value, it can come from several sensible causes. One of the most likely causes is that activity in MST is not alone in leading to perception, and interaction between signals in multiple areas might lead to such complexity in the results from microstimulation.

One piece of evidence supporting the involvement of multiple areas in heading perception comes from recording the tuning of both MST and VIP to heading stimuli. (VIP is described below, in section c3.) In MST, previous evidence had shown good tuning for related optic flow stimuli (Bradley et al., 1996; Page and Duffy, 1999), but the stimuli were sufficiently different from ours as to make quantitative comparison difficult. In particular, previous experiments have used stimuli in which there was no simulated depth. This simplification has important consequences for perception (van den Berg, 1992), which led us to abandon it for the psychophysical experiments just described. Since there was no previous evidence on the tuning of MST cells to more realistic, three-dimensional heading stimuli, we obtained such measurements. In these experiments, such as the one illustrated in Figure 5, we present a single cell with a range of headings, under three pursuit conditions. The data allow us to estimate both the nature and quality of heading signals in MST, as well as their sensitivity to the presence of smooth pursuit eye movements. In the example case shown, we see that the neuron showed quite sensitive sigmoidal tuning to heading, and the tuning was relatively invariant in the presence of smooth pursuit eye movements. As we shall see below, these properties are all also associated with the heading signals in VIP. Summary data comparing the two areas will be shown in the next section.
The last set of observations, (Appendix C, Heuer and Britten, 2004) were guided by the successful series of studies relating activity in area MT to the perception of weak, local motion patterns (Britten et al., 1992; Britten et al., 1996; Shadlen et al., 1996). In our recent experiments, we asked whether a similar relationship existed between MST activity and the perception of complex optic flow. In this experiment, we used "spiral space" stimuli, which are combinations of radial and rotary flow (Graziano et al., 1994). These stimuli are well suited to the properties of MST cells, just as the stimuli in the previous studies were well suited to the properties of MT neurons. Monkeys were trained to discriminate opposite-direction patterns of this sort (e.g., CW from CCW rotation, or expansion from contraction), and performed this task while neurons were simultaneously recorded in area MST. As in the previous experiments, the stimuli were made weak by being diluted with uncorrelated motion noise. From these data, we were able to estimate the sensitivity of single neurons in MST, as well as the choice probability, a metric that captures correlation between neuronal activity and decisions on a trial-by-trial basis. Correlations of both sorts have been used to argue in favor of a role for specific areas in specific perceptual functions (Britten et al., 1996; Dodd et al., 2001; Krug et al., 2004).

In the MST experiments, neither correlation was particularly impressive. Neurons were somewhat less sensitive to such patterns than was the monkey, although this varied between animals. Also, in neither animal was there a significant choice probability, indicating that neuronal variability was uncorrelated with decision variability. These results were a little surprising, but supports the interpretation that performance on this task depends on activity in multiple areas. Pooling of signal across multiple areas would allow better psychophysical performance (relative to the single neurons), and would dilute the trial-by-trial correlation captured in the choice probability.

All of these observations on MST, collectively, paint a picture of an area involved—albeit not too tightly—in multiple complex-motion tasks. It seems as though the tight correlation found between neurons in MT and simple, linear translation judgments might be the exception rather than the rule, especially in higher areas of cortex. More complex (and more realistic) tasks are nearly certain to depend on more widespread patterns of activity spread across multiple cortical areas.

c3. Progress on VIP and heading perception.

VIP is a good candidate for supporting heading perception because it has MST-like optic flow responses (Schaafsma and Duysens, 1996), and because it has been reported to have spatial receptive fields in head-centered coordinates (Duhamel et al., 1997). Therefore, we were interested in its responses to our heading stimuli, as well as whether these might compensate well for ongoing eye movements.

c3.1. Heading signals in VIP. We found that VIP has high-quality heading signals, and that these are extremely stable in the face of smooth pursuit (Appendix C, Zhang et al., 2004). Figure 6 shows a single example neuron under 3 pursuit conditions, illustrating both these features. The tuning, which is sigmoidal in this case, is quite tight. We quantified the tuning of these cells by fitting appropriate tuning functions to the data. For cells like the one shown, we used probit functions (smooth curves in Figure 6). Other cells (approximately one-third; not shown) were bandpass-tuned, and better fit with Gaussian functions.
For both types of cells, the amplitude and tuning width of the best-fit function gives an estimate of the quality of the heading signal carried by the cells. Histograms of these fit parameters are shown in Figure 7.

Overall, good heading signals are common in VIP, as in MST. As further evidence that these signals might be useful substrates for perception, they are also remarkably stable against pursuit eye movements. To quantify this, we compared the values of the best-fit parameters for each cell, with and without pursuit. For the means (tuning centers), we simply measured the difference; for bandwidth and amplitude, we calculated ratios. We present these results below in Table 1.

c3.2. MST and VIP compared. From the independent measurements we have just summarized, we can conclude that there is substantial information about heading in both MST and VIP. The data, however, allow a more quantitative comparison, which is provided in Table 1. This summarizes the primary statistics of tuning in both areas (amplitude, bandwidth), as well as how these are affected by pursuit. Standard errors are shown in parentheses. This table reveals considerable similarity in the tuning of neurons in both structures to such stimuli. This is consistent with their many common inputs, and is evidence for shared function across the two areas. We propose to investigate this directly in the context of a heading task in the experiments in Aim 2 of this proposal.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>MST</th>
<th>VIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>amplitude</td>
<td>29.5 (3.95)</td>
<td>27.0 (2.16)</td>
</tr>
<tr>
<td>bandwidth</td>
<td>3.08 (0.44)</td>
<td>4.22 (0.34)</td>
</tr>
<tr>
<td>amp. ratio w/ pursuit</td>
<td>0.72 (0.13)</td>
<td>1.18 (0.10)</td>
</tr>
<tr>
<td>bw. ratio w/ pursuit</td>
<td>0.40 (0.13)</td>
<td>0.27 (0.05)</td>
</tr>
</tbody>
</table>

c3.3. Clustering of heading tuning in VIP. We also verified that heading signals are clustered in VIP, since such clustering is necessary for the success of the microstimulation experiments in Aim 1. We made many long penetrations through the area. We measured either single- or multi-unit heading tuning frequently, and could estimate how fast tuning changed along electrode penetrations. Two aspects of the data convinced us (and the referees of the paper, now in press) that tuning was clustered in VIP. First, nearby multi-unit activity was typically well correlated. To show this, we calculated the correlation coefficients between all pairs of recording sites measured on single penetrations, and plotted this as a function of inter-site distance. Figure 8 shows the results; filled circles are significant correlations, and the red dashed line shows the average correlation. This figure reveals the relationship expected from a clustered organization, in that sites within about 0.5 mm are much more likely to be positively correlated than those at longer distances. Note, particularly, the dense cloud of highly correlated sites in the upper left corner of the figure, and the paucity of anti-correlated sites in the lower left corner. This would not be expected if the organization were random with respect to heading preference.

We also analyzed single-unit tuning and compared it to simultaneously recorded multi-unit activity. In making these measurements, we were fastidious in keeping the isolation criteria for the single-unit and the multi-unit activity non-overlapping. (The Bak discriminator we use has both upper and lower windows.) As always, we used strict criteria for single-unit isolation, so that spikes were well separated from the noise. In this way, we could be certain that the single
cell we were recording did not enter the unresolved multi-unit activity. Nonetheless, single units correlated well with nearby multi-unit activity, as shown in the histogram in Figure 9. This shows the distribution of the correlation coefficient between single- and multi-unit activity for 19 pairs of recordings in two monkeys. In 17 of 19 cases, there was a significant positive correlation between the single- and multi-unit activity, a clear signature of local clustering of response selectivity.

These data show that there are good signals for heading in area VIP, that these signals are well compensated for eye movements, and that these signals are locally clustered, or even possibly columnar. This bodes well for the success of microstimulation experiments in Aim 1.

c4. Progress on the “steering” task

We have designed a simple active-vision task in which monkeys control their heading using a single-axis joystick (for details, see Research Design, section d3). The layout of the virtual scene is shown in Figure 10. A target (red spot) is shown on the screen, and the monkey is translating across a ground plane at a fixed speed. The monkey is rewarded for keeping its trajectory (dashed line) within a specified angular distance of the target. At unexpected times, the experimenter changes the position of the target, and the monkey must make the appropriate steering response to redirect its heading to the new target location.

So far, we have trained one monkey on the task, which it learned easily. After only two weeks of training, the monkey maintains a trajectory within a few degrees of the target, and rapidly adjusts her trajectory to displacements of the target. Typical behavioral results are shown in Figure 11A: the simulated trajectory of a monkey in our task setting. The red trace shows the direction from the simulated observer location to the target, and the blue trace shows the monkey’s virtual trajectory. Both are expressed in degrees according to an arbitrary scene (“exocentric”) coordinate system, where 0 is the direction from the starting camera position to the starting target location. Figure 11B shows a more detailed view of the monkey’s behavior, from a different block of trials where she was repeatedly switching between two headings (+10, -10 degrees) every three seconds. The green trace is the average joystick position for 68 right turns, and the blue trace is the resulting trajectory. Her latency to first response was approximately 300 ms, and she stabilized close to the desired heading about a second later. In both of these blocks of trials, 15-20 second epochs of active steering were obtained, interspersed with short breaks. It should be emphasized that this level of performance is not asymptotic, and the monkey is still improving in both speed and accuracy.

These preliminary behavioral results, which show reliable, rapid, and accurate responses in our task, are very encouraging for the experiments in Aim 3. Many behavioral and neurobiological experiments can be performed using this basic task.
c5. Progress on multiple electrode recording

The experiments in Aim 2 depend on using multiple electrodes to record simultaneously from multiple cortical areas. We have begun related experiments using this technology, and here we show, briefly, some preliminary results to indicate the kind of data that result. For these experiments, we have used two guide tubes placed in a single recording cylinder, approaching the superior temporal sulcus from a caudal and dorsal direction. We have extensively mapped the sulcus in this animal, and know the locations of both MT (on the posterior bank) and MSTd (on the anterior bank). We placed one electrode in each area, and advanced them until brisk, discriminable activity was evident on both electrodes. The two receptive fields were mapped and preferred directions established, as indicated in Figure 12. The MST cell RF was large and bilateral, and completely encompassed the MT cell RF. While the MST cell preferred expansion, it also showed some preference for leftward horizontal motion. Thus, both cells shared a common preferred direction.

Activity from the two electrodes were analyzed using the Plexon recording system, which can isolate single units from the multi-neuron activity using either template matching or principal components analysis. A large dot field was placed over the RF of the MST cell, completely filling the MT cell RF as well, and a series of different stimuli was presented. Figure 13 shows the cross-correlation function of their activity following presentation of a large expanding stimulus, which placed preferred direction motion over the MT cell’s RF. The bold curve is the correlation following subtraction of the shift predictor (trial-shuffled cross-correlogram, Gerstein and Perkel, 1969), which eliminates correlation due to common rate fluctuations driven by the temporal envelope of the stimulus (in our case, a 750-ms presentation of a random-dot stimulus). The thin line above and below the CCF is the 99% confidence interval. This pair of neurons shows a significant, albeit weak, peak in the correlation at positive time lags, denoting activity in MST following spikes in MT. This is consistent with a feed-forward connection between these two areas, such that activity in the MT cell leads to excitation in the MST cell. This setup produces data very reliably: nearly every day’s session yields useful multi-electrode data. The success of this approach augurs well for the success of the experiments in Aim 2.

c6. Progress on other projects.

While much of the work in the last period focuses on the perceptual roles of MT, MST, and VIP, another branch of work, supported in part by NIH funding, has focused on RF mechanisms in upper areas of the motion system. This branch of work has also been quite successful, producing two papers on mechanisms of response summation in area MT (Britten and Heuer, 1999; Heuer and Britten, 2002). This work has also produced another body of data on the more complex RFs of MST neurons, comparing them with the simpler RFs in MT. These data are complete, and a substantial paper is in preparation on this subject. In addition, this work forms the substrate for future collaborative work with a former postdoc, Richard van Wezel, who now holds a position at Utrecht University in the Netherlands. This branch of work will continue, but will be supported by other funding.
c7. **Peer-reviewed papers published or in press since the last review:**


**Peer-reviewed book chapters, reviews, and commentary:**


**Abstracts published since the last review:**


d. Research Design and Methods

d1. Aim 1: Is VIP either necessary or used for heading perception?

We have established that heading signals sufficient to support perceptual performance exist in VIP. This aim will test the hypothesis that these signals are necessary for the discrimination of heading. We will use standard microstimulation methods to activate columns of heading-selective neurons in VIP during a two-alternative, forced-choice heading discrimination task. This experiment resembles the MST experiment we have already performed (to facilitate comparison between the two areas); details beyond the scope of this proposal may be found in Appendix A. To complement this method, we will also inactivate VIP in the context of the same task.

d1.1. Task. We have two monkeys already trained on a two-alternative horizontal heading discrimination (illustrated in Figure 1, section b2), and probably only one more trained animal will be required. A range of headings are possible on a block of trials, symmetrically placed relative to the midsagittal plane (head-centered zero, or subjective “dead ahead”). A cloud of dots appears, simulating a cube of dots viewed in natural perspective (although all blur, size, and stereoscopic depth cues have been removed). This cloud is in motion for one second, simulating a linear trajectory into the near surface of the dot cloud. The stimulus corresponds to a trajectory of 10 meters, starting 55 meters from the center of a cloud 100 meters across. (There exists a family of equivalent situations, differing only in scale.) The stimulus then disappears along with the fixation point, and the targets appear. The monkeys report whether the simulated trajectory on each trial passed to the left or right of the zero point by making a saccadic eye movement to a target placed on that side of the screen. On some trials, the fixation point will be in horizontal motion across the screen, and the monkey must make a smooth pursuit eye movement during the trial. Animals are fairly easy to train on this task, and show asymptotic performance that is similar to that of humans. Both humans and monkeys compensate well for the presence of smooth pursuit, showing little or no bias and only a minor elevation of threshold during pursuit (Britten and Van Wezel, 2002).

d1.2. Microstimulation. We will introduce platinum-iridium recording electrodes into VIP and locate sites with consistent heading responses across at least 250 μm of electrode travel. Once such a site is identified, its RF will be mapped, and its optic flow preferences will be characterized. The fixation point will initially be placed so that the center of the range of headings is roughly superimposed on the RF of the cell, and we will adjust the fixation location to maximize the response difference between far-left and far-right headings. The electrode will then be switched to the stimulus isolation unit (FHC), and blocks of trials will commence in which half the trials contain microstimulation. The microstimulation will be biphasic, with each phase being 0.2 msec in duration and of controllable amplitude. Amplitude will be adjusted “to effect” in preliminary experiments, but will probably be set to 10–20 μA for the main series of experiments, as the dimensions of cell clusters appear similar in MST and VIP. The pulse frequency will be 200 Hz, and the train of pulses will be 1 sec in duration, simultaneous to the visual stimulus motion. These parameters are very similar to those used in other, similar studies in visual cortex (e.g., Salzman et al., 1992; DeAngelis et al., 1998).

d1.3. Analysis of microstimulation data. A complete experiment will consist of six psychometric functions resulting from the full cross of three pursuit conditions (left pursuit, right pursuit, no pursuit)
and the two microstimulation conditions. Such functions are sigmoid, and are well fit with probit functions. Effects on bias reveal themselves with horizontal shifts of these functions, and effects on sensitivity appear as changes in slope. We will test the significance of the main effects of microstimulation, as well as interactions with pursuit, using likelihood ratio testing. All significant effects will be taken as evidence for the involvement of VIP in heading discrimination, but bias effects are the most interpretable. The tuning of the majority of VIP neurons (and sites) is sigmoidal, such that large responses are evoked for all headings to one side. Under most decision rules, artificially elevating such a signal should cause a bias in favor of the preferred direction. This was the most common effect in MST (Britten and Van Wezel, 2002). Another possible outcome is an effect on sensitivity, most likely a reduction. This effect, while indicating that VIP plays a role in heading judgment, would do little to constrain the nature of that role. Getting only sensitivity effects in VIP (which we consider unlikely) would be interesting because it would imply a clear difference between the roles of VIP and MST in heading.

Some cells in VIP (and MST) exhibit bandpass tuning for heading, with maximal responses to near-straight-ahead headings. In our previous experiments in MST, we never found a cluster of such cells sufficiently large to support a microstimulation experiment, but we are hoping this will be possible in VIP. If we identify such a site, we will set the experiment up so that the tested range of headings is on one flank of the tuning function, if at all possible. Then, if time allows, we can perform a very interesting variant by moving the discrimination to the other side of the tuning function. One might expect in such a case to get opposite effects of microstimulation on either side of the site's tuning function. This outcome would be consistent with a vector sum or vector average from VIP informing perception.

Lastly, we will be looking at the interaction with smooth pursuit eye movements. Neurons in VIP compensate well for eye movements (as do monkeys). If one injects signal into a representation of heading that has already been compensated for eye movements, then one might expect similar biases for all pursuit conditions. This would stand in contrast to the observations in MST, where microstimulation effects contingent on pursuit condition were frequent.

**d1.4. Reversible inactivation.** Electrical activation will be complemented with reversible inactivation experiments asking whether the area is necessary for perception. Inactivation experiments have their own technical concerns, of course, but these are different from those of microstimulation. We deemed any lesion experiment testing the role of MST in heading perception to be unfeasible, owing to the large size of MST and to its proximity to MT, which provides input to MST and many other structures. It would be nearly impossible to guarantee a complete lesion of MST while sparing MT. However, VIP is a much more tractable target for this approach. It is compact (approximately 2 by 2 by 10 mm), and its nearest neighbors have quite different properties. We therefore plan to reversibly inactivate VIP while the animal performs the heading discrimination task just described. The agent of choice for this experiment is muscimol, a long-lasting GABA agonist. We will place physiologically guided injections (1-2 μg/μl, 1 μl volume, as used in related studies: Hikosaka et al., 1985; Riquimaroux et al., 1992; Martin and Ghez, 1993) along the full extent of VIP at 1-2 mm intervals, and immediately test the animal's performance on the task. We will test both unilateral and bilateral inactivations; comparing the results will allow us to see if each hemisphere might be specialized for the perception of either ipsilaterally or contralaterally directed headings.

Control experiments will verify the effectiveness and selectivity of our inactivations. In particular, we will test our animals on a standard delayed-saccade task to detect any effect of the inactivation on our operant behavior, a saccadic eye movement. This is a concern because area LIP, which lies immediately adjacent to VIP, is strongly implicated in the guidance of eye movements (Gnadt and Andersen, 1988; Andersen et al., 1990; Barash et al., 1991). While LIP lesions do not produce much effect on visually guided saccades (Li et al., 1999) in other experiments, we would
wish to confirm this in our experimental context. Additionally, in separate experiments, we will record activity at varying distances from muscimol injections, to document the extent of muscimol effectiveness. Lastly, it will be useful to also train the animals on a simple, linear direction-discrimination task to confirm that the inactivation of VIP does not interfere with low-level motion perception.

We are also somewhat concerned about the accumulation of toxicity from repeated muscimol injections, and would if possible use GABA injection instead. Because the short duration of GABA effects prevents multiple injections, complete inactivation of VIP will not be possible. However, if selective effects can be obtained in pilot experiments using GABA, we would use this agent instead.

d1.5. Overall interpretation of experiments in Aim 1. Two complementary interventions are planned: microstimulation and reversible inactivation. Obviously, the most interpretable set of results would be deleterious effects of inactivation, and systematic positive effects of activation. From this pattern of results, we could conclude that VIP was both necessary and causal in the perception of heading. Other possible outcomes exist. We believe it to be fairly likely that microstimulation will be effective, yet inactivation might produce only modest effects or none at all. This would be taken as evidence that VIP helps to support heading perception, but is not necessary. In turn, this would imply that other areas can supply sufficient information to support heading perception in the absence of VIP. If, on the other hand, the lesion experiments prove successful and the microstimulation experiments do not, this will most likely be because the preconditions for microstimulation (adequate clustering of signals) were not met. Based on our preliminary data, we consider this outcome unlikely. Lastly, if neither experiment should produce an effect, it will provide some evidence (though not conclusive) for segregation of function between MST and VIP, despite their similar physiological profiles with respect to heading (see Progress Report, section c3.2). This unexpected outcome would nonetheless be interesting for this series of experiments.

d2. Aim 2: How do multiple areas interact to produce the perception of heading?

Systems neuroscience has made great strides in the last decade linking single areas in cortex to particular functional roles. Yet, it is clear that many perceptual functions are distributed widely in cortex. This has become particularly obvious with the advent of fMRI imaging techniques. Single-cell recording methods have lagged this development. However, it is now possible to record from multiple areas, either simultaneously or in separate sessions, and address questions of how the multiple signals interact to support a particular function. The case of heading perception is a particularly suitable target for such an approach, since we know many of the participating areas, and there is also a strong theoretical framework into which to place the results.

The specific questions we are addressing in this aim are threefold. First, are the signals in the three areas (MT, MST, and VIP) correlated with performance? Second, do these areas interact during the performance of a heading task? Third, what kind of model would best account jointly for the perceptual sensitivity to heading and the physiologically observed signals in multiple areas? The main method used to address these questions will be simultaneous recording from multiple neuronal structures (either pairs of structures or all three simultaneously) while monkeys perform a two-alternative heading discrimination.

Four principal analyses will be used. First, we will measure sensitivity of single neurons to small heading angle differences, with or without pursuit eye movements. Second, we will measure choice probability (relating activity with perceptual decisions) in each area. Third, we will measure correlation between simultaneously recorded neurons, both within and across structures. Fourth, we will use computational modeling to determine how activity in all three structures can best account for behavior on this task.
d2.1. Task. The task is identical to that described in the previous aim and in the Progress Report, so it will not be described in detail. It will be a two-alternative, forced-choice discrimination of horizontally varying headings, with and without horizontal smooth pursuit eye movements.

d2.2. Recording. The lab has been recording from all three structures (individually) for several years using standard techniques. These will need to be modified somewhat to allow simultaneous access to all three structures. Both MT and MST are available through a posterior approach, with a single recording cylinder, oriented 30° above horizontal in a parasagittal plane. This placement will be used in the proposed experiments as well. VIP lies about 8–10 mm medial and about 10 mm anterior, in the fundus of the intraparietal sulcus. We will position an additional recording cylinder to allow a more rostral approach to VIP, ipsilateral to the MT/MST cylinder.

The lab is well-equipped with recording hardware for these experiments. For one of the two cylinders, we will use a Thomas Recording multi-electrode system (3-electrode capability), which places all the electrodes close to each other, independently adjustable. For the other cylinder, we can use either a single- or double-microdrive holder, which advances FHC microelectrodes via a National Aperture stepping motor microdrive. Thus, in total, we have the capability to use 5 electrodes on the two cylinders. The signals will be fed to a Plexon Instruments acquisition system ("Harvey box"), which can acquire data from up to 8 channels. This instrument has been integrated with our Rex "master" computer (see Progress Report, section c5), and the NeuroExplorer software provides an extensive suite of analysis tools, also highly compatible with Matlab, which we use for most of our analysis. Overall, little hardware or software development will be needed for this experiment.

One important aspect of the experimental design is that little or no optimization of the stimuli for individual neurons will be necessary, making it ideal for multi-neuron recording. The stimuli will always cover the screen completely, and the fixation location will be chosen to get as much as possible of all the RFs of the neurons on the screen at once. Where time allows, multiple blocks with different eye positions will be used.

d2.3. Analysis. Many of the analyses we will use are by now fairly standard, and these will be described only briefly. Our analysis of neuronal sensitivity will use total spike counts measured over the 1-second duration of the simulated trajectory (although variants will explore dynamic changes in sensitivity, e.g., Appendix C, Heuer and Britten, 2002). To directly compare neuronal and perceptual sensitivity, we will use ROC analysis, which incorporates both the signal (rate changes as a function of heading) and the noise (discharge variance). Thresholds for the animal are measured in degrees of heading angle, and to get a comparable measure, ROC area will be plotted as a function of heading angle. In a task such as ours, this requires the selection of a "reference" heading—the point against which other responses will be compared (Bradley et al., 1987). We will use two approaches to this. The first, to estimate the maximum sensitivity of each neuron, will be to pick the steepest part of the tuning function (based on a smooth curve-fit, not the individual data points), and choose the closest heading angle to this point. This approach, which will estimate the maximum sensitivity of an neuron, makes assumptions that might not be valid for the particular task the animal is doing. Since the animal is always engaged in discrimination with respect to zero (straight ahead), we will include measurements of neuronal response to zero headings, and use these as a reference as well. In either approach, we will derive a neurometric function, relating ROC area to heading angle difference, from which a neuronal threshold can be estimated. This will allow us to compare the sensitivity to heading in each of the three areas under study.

We will also determine the correlation of activity in each area with performance by calculating choice probability (Britten et al., 1996). This metric estimates the association between activity in a
particular neuron and the variable decisions an animal makes at the same time. Significant choice probabilities have been found in a variety of structures in a variety of task contexts, and interpreted as a signature that the structure is involved in the particular task. In our case, our monkey will be deciding left vs. right headings, so we will assign to each neuron a preference based on the slope of its tuning function as it crosses zero headings. From there, the calculation of choice probability is straightforward (see Appendix C or Britten et al., 1996 for details).

One of the most important analyses we will do involves the multiple signals from multiple areas in the context of the task. In particular, we are interested in evidence of synchrony or active gating of information during performance of this task. It has been frequently suggested that perception depends on neuronal ensembles comprising large numbers of neurons in many areas, and we have considerable evidence in favor of heading perception as a function that depends on multiple areas. One method we will use to examine this idea is the analysis of neuronal cross-correlation (see Progress Report, section c5) during the task. Cross-correlation between neuronal responses in these areas is expected, on the basis of their dense connectivity and shared physiological properties. Simply documenting the properties of any such cross-correlation (time-scale, amplitude, etc.) will be interesting in and of itself. However, we will be in a particularly powerful position because we will be recording the activity during performance of a perceptual task. This allows much more potent analyses of correlation to be performed. We can look at whether correlation is influenced by the stimulus, since we will also record responses to the same stimuli during passive viewing. However, it will be particularly interesting to look at whether anything about the correlation structure of neuronal activity in multiple areas predicts trial-by-trial behavior. If we were to find greater correlation on successful trials than on error trials, this would indeed suggest that cooperative activity in multiple areas might support perception.

An alternate perspective views correlation of multiple signals as a problem, not a solution (Britten et al., 1992; Shadlen et al., 1996). In this view, perceptual performance is improved by pooling of signals, and correlation of signals leads to a reduction in performance because such common noise cannot be averaged out by pooling. Under this view, we might expect to see the exact opposite result—stronger correlation on error trials. Either outcome, however, would be very interesting and revealing.

Another potentially rich avenue for analysis lies in the temporal structure of correlation within the period of a trial. Simple "box diagrams" of perceptual performance often have a series of steps, leading from sensory filtering, through integration at higher levels, and decision-making, to response preparation. The demands on communication between areas might therefore develop over time as a trial proceeds, and our analysis will be able to detect this. For this, joint peristimulus time histograms (Gerstein and Perkel, 1969) might be particularly revealing.

To make sense of the complex data emerging from this experiment, we will need to use a computational approach. The modeling tools we will use will be loosely guided around the "pooling" models developed by Mike Shadlen in the Newsome lab (Shadlen et al., 1996). However, since such models (and their derivatives, e.g., Mazurek et al., 2003) are typically designed to relate the activity in one structure with performance, additional complexity might need to be introduced. The first step will always be to start with the simplest model, and to add free parameters and additional complexity only if needed. It is reassuring that a very simple across-area pooling rule seems to account for modulation by attention in a direction-change detection task (Cook and Maunsell, 2002), and such a simple approach will guide our thinking. In our modeling, we will be assisted by...
and noise estimates in each of three areas, and how these depend on the primary variable, horizontal heading. Additionally, we will have as another constraint how these rates are influenced by pursuit (2 distinct conditions). We will also have the choice probability measurements, which any model must accommodate. Lastly, we will have estimates for the correlation structure of the rates in the population of neurons, which the model cannot violate. On the output side, we have the thresholds for the monkeys, the slopes of their psychometric functions, biases, and how these all are affected by pursuit (see Progress Report). Thus, modeling will be highly constrained by empirical measurement, raising the likelihood of useful insights emerging. While it is unlikely that we will come up with a unique solution as to how the signals in the multiple areas are combined, we hope to be able to rule out a large number of models that simply cannot work in the face of the data.

It should be stressed that such across-area measurements have almost never been made for a visual task, and it is nearly certain that any set of data that results will be interesting and revealing. In some ways, it might be most interesting if the results of this experiment force us outside of the simple hypotheses we start with. No matter what, the results will provide the first characterization of the functional relationships within and between cortical areas during the performance of a well-defined perceptual task.

d3. Aim 3. The role of cortex in an active heading task.

The central goal of this aim is to develop and characterize an animal model of active steering, suitable for use in physiological experiments. The design of the task will be guided by a variety of monkey joystick-control tasks and by the human literature on steering. We will characterize the dependence of steering on visual input (target position, optic flow information) and on eye position and velocity. We will test the animals both in gaze-free situations where we can measure their patterns of eye movements as a dependent variable, and under gaze-fixed conditions, more suitable for physiological experiments to follow.

Once we have a good understanding of the behavior, we can test the involvement of sensory and “association” areas in the task. We start with the broad hypothesis that parietal cortex, and VIP in particular, will be more involved in motor aspects of the task, and that motion areas such as MT and MST will be more dominated by sensory signals. We will test this hypothesis by recording from both motion-related and parietal cortical areas during performance of the task.

d3.1. Task. The monkey will be in a video-game-like situation, controlling its simulated trajectory in the horizontal plane in a 3D virtual environment by moving a joystick attached to the front of the monkey chair (see Figure 10, section c4). The joystick is arranged to give an angular velocity control signal; neutral position implies no angular velocity and thus a continuation of the present trajectory. Increasing deflections will produce proportionately increasing angular velocity, just as with the steering wheel of a car. Screen updating occurs on each video frame (75 or 80 Hz; details in section d3.5). For the main purposes of this experiment, we will use a “ground plane” stimulus, although in variants we plan to use the cloud-of-dots stimulus from our perceptual experiments. The perspective will be as from a camera attached to a vehicle, moving just above the ground plane at a constant speed. While the ground plane we currently use (for training) consists of a grid of intersecting lines, we will use random dots or random textures for most experiments. In the distance, there will be a target in view, toward which the monkey is trained to direct its trajectory. As long as the trajectory is within a criterion angular separation from the target, rewards will be delivered to the animal. In order to direct the monkey’s steering behavior, the target will be moved, and the monkey will have to readjust its trajectory to the new target location in order to continue receiving reward. Thus, the monkey will be attempting to minimize its trajectory error. Trajectory error results from a mismatch between the target location and the current trajectory, which can be estimated from the optic flow information on the screen.
Because the virtual camera is yoked to the trajectory, one can also view this task as one where the monkey is trained to bring the target to the center of the screen using a joystick. In this formulation, as in the Rushton et al. (1999; section b3) perspective on steering, optic flow information would be irrelevant. Therefore, one of the key design goals of the task will be to characterize the dependence of performance on target position information and on optic flow information. While these are normally highly correlated, they can be dissociated in several ways. Additionally, we will seek to establish the effects of eye position and velocity on performance. However, before we discuss these variants, we need to understand the basic measurements that will result from the task.

**d3.2 Behavioral data.** The main behavioral data from this paradigm will be the steering outputs of the monkey in response to trajectory errors. Example data are shown in the Progress Report (c4), above. The trajectory at any point in time is a time integral of the steering behavior of the animal. The behavior will be characterized in terms of gain (how much response do we get to a particular input) and dynamics (latency, filter properties to time-varying input), and precision. We will also be able to characterize the limits of performance of the animal, both for very small inputs as well as for very large target angular velocities. In analyzing the behavioral data, we will rely on the extensive literature on monkey reaching motions, which can provide estimates of the limits associated with the “plant” (the mechanics of the arm and its musculature, e.g., Cheng and Scott, 2000). However, while arm dynamics will enter our calculations, we will try to minimize their impact by setting the joystick sensitivity high, and thus arm and wrist excursion low. Force will always be very low, since the joystick does not provide force feedback, and the return spring on the joystick is quite soft.

In the most natural version of the task, the eyes will be free. We will measure gaze direction and relate it to the target-position and optic flow cues. Since these will often be in different locations, we will be able to assess by an independent behavioral measurement the amount of attention that the monkey is paying to each cue by the gaze direction, and whether the direction of gaze reveals dynamic changes in the importance of different cues as the task proceeds.

**d3.3 Target/flow manipulations.** In a naturally designed task such as this, there is normal correlation between multiple cues in the stimulus. We will first start by analyzing the behavior of the animal in the most natural situation—eyes free and the target moving. The movements of the target will be of two basic varieties: predictable and unpredictable. Unpredictable movements will include steps of position and random-walk trajectories. Predictable movements will include both ramps and sinusoidal target position changes. In this simplest version of the experiment, we will be able to verify that the patterns of steering behavior and eye movements match those of human subjects in related experiments. In particular, we will be interested in the anticipation of future target location (and thus trajectory) by leading eye movements, when the target location is predictable. We will also be able to ask whether the predictable trajectories are more accurately or precisely followed; this will allow us to later explore predictive signals in physiology (Eskandar and Assad, 1999).

However, to address the importance of target and flow cues, we will need to decorrelate them more systematically and measure their impact on performance. We plan the following approach for this. First, we will compare performance with and without optic flow information present. If texture is removed from the ground plane, then the motion of the target is the only cue available to guide the response. Sensitivity and gain will be compared under full (optic flow present) and reduced (optic flow absent) conditions, allowing us to estimate quantitatively the importance of optic flow cues. For this comparison to be accurate, we will need to be certain that the animal is equivalently trained and performance is fully asymptotic for both conditions.

We will also use transient cue-conflict manipulations to test the role of changing each cue without changing the other. Two related versions of this will be used. One is implicit in the design of the task: steps of target position cause a transient difference between the flow cue (signaling
heading) and the target position. In the other, we will induce modest, controlled perturbations to the optic flow field ("flow impulses"), not caused by the monkey's steering behavior. For instance, while the monkey is steering straight ahead, we could induce a fixed displacement of the flow field to the left or right for a small period of time. Just after this impulse, the monkey would not be punished for steering away from the target. If the monkey is using the optic flow field for feedback, then compensatory steering should result. A range of impulse amplitudes and durations can be applied to characterize the monkey's response to optic flow input, and perhaps its dependence on ongoing behavioral state (straight steering, aligned with current steering, or aligned against). These perturbation experiments are guided in principle by similar manipulations used to study the smooth pursuit system (Churchland and Lisberger, 2002), and by the studies of Warren and colleagues on human postural control (Warren et al., 1996; Bardy et al., 1999). From these measurements, we should be able to answer conclusively the question of whether flow is used in steering, and well characterize the behavior of the animal and its dependence on the main cues in the task. These behavioral data will be interesting in and of themselves, as well as setting the stage for physiological experiments that follow.

d3.4. Gaze manipulations. The field of heading has stressed the importance of gaze velocity (Bradley et al., 1996; Andersen et al., 1999), while the field of steering tends to emphasize the importance of gaze direction. We will investigate both these variables directly in our task. While in the basic task, the animals will be allowed to change gaze direction freely, we plan to also measure task performance under gaze-restricted conditions. We will require the monkeys to fixate a spot at various eccentricities, or to pursue a spot that is moving at different velocities. In this way, we will be able to ask whether eye position or velocity induces either biases or gain changes in performance.

d3.5. Physiological measurements. Once we have a good handle on the behavior of monkeys on this task, we will record activity in different cortical areas while the animal performs the task. We will start with two fundamental questions. First, we will ask whether different cortical areas (with MST and VIP being the first targets) show more sensory-related or more motor-related activity. Because the motor output lags the sensory input with a variable latency, we will be able to see if variations in spike rate in any area are more tightly time-locked to the sensory input or to the motor output. We expect that VIP will show substantially more motor-related activity. VIP is propitiously located in the fundus of the intraparietal sulcus, between area LIP and MIP, which have explicit eye-movement and hand-movement responses, respectively (Andersen et al., 1998). In the "free" version of our task, we will be able to relate the activity of a cell to each motor component of our task. By way of comparison, we will need to record while the animal is performing simpler tasks isolating each motor component. However, we will expect to do much of our recording in a reduced version of the task where gaze is fixed. This will allow us to control the retinal location of the visual stimuli, reduce the dimensionality of the motor responses, and make interpretation of the data more straightforward.

We will also be able to ask whether the representation of optic flow is influenced by the task context. We have extensive background information on the precision and gain of heading signals in MST and VIP, and will be able to quantitatively compare them in an active-vision context. We will be able to globally ask if the signals look the same or different in terms of amplitude or bandwidth in the active-vision context. This analysis will be complicated somewhat by the different temporal structure of the signals being compared. In the work we have done to date, heading is set to a particular (usually eccentric) value and held there for a full second. In the active task, the eccentricity of heading will jump transiently to a new value, then be gradually reduced as the animal acquires the new trajectory. We take considerable comfort in this regard from the observations that MST cells appear quite linear in their temporal characteristics, and do not in general show a "turning" signal (Paolini et al., 2000). We do not know whether the same is true of VIP neurons, but we will be able to ask this question directly.
Several control measurements will be needed to make these data fully interpretable. For each neuron, we will also record in a "replay" mode, where the animal is not engaged in the task, but will be stimulated with the same series of headings that it had previously been exposed to while engaged in the task. This will provide additional leverage on the sensory/motor distinction, and also allow more direct comparison with the tuning data we already have. We will also, of course, obtain tuning measurements from each recording session, directly comparable to the ones we have been making. Both these measurements will require relatively little additional time in a recording session, but will provide considerable additional interpretive strength.

**d3.6. Additional experiments.** While the initial round of experiments that we have described is a reasonably extensive endeavor, and will produce important results on its own, we are performing this series to enable a large number of experiments that will build on this foundation. I will list and describe these only briefly, in approximate order of priority. It is very likely that progress on one or more of these additional goals will be substantial during the requested funding period.

- Ground plane vs. 3D cloud. We have been using a 3D stimulus, and will need to characterize the behavioral dependence on both types of scene to relate the results to the psychophysics already completed. Also, the 3D cloud is more appropriate for many physiological experiments.
- Recording from upstream and downstream areas. While responses in MST and VIP are likely to be very interesting, being near to what Lisberger refers to as the "sensorimotor corner", we are quite interested in taking the measurements back to pure sensory areas such as MT, as well as out to premotor structures such as the SMA or motor cortex.
- Obstacle avoidance and landmarks. In real life, trajectories are informed, positively or negatively, by specific visual features in the scene. Behaviorally and physiologically, we can measure the impact of introducing object features into the virtual environment.
- Two-dimensional control. While our current task allows the monkey to control only angular velocity, a generalized (and more realistic) version would allow it to control speed as well.
- Motor constraints. We can vary the motor demands on the task, either in sign (reverse joystick control) or magnitude, to dissociate sensory signals from motor signals.
- Plasticity. With any change in the task (e.g., joystick sign or sensitivity), the animal must adapt its sensorimotor mapping. While simple reflexes like the VOR can adjust their gain using cerebellar and brainstem modifications, it is likely that learning on a more goal-directed task as ours will be cortical. We will be able to study the mechanisms of plasticity directly.

**d3.7. Hardware and software details.** This task has been developed using a new generation of display hardware and software, which we have integrated with our control system (Rex). The display computer contains a high-performance, 3D-accelerated video card, and we use OpenGL to do the 3D rendering. Using this system, we can achieve 75 Hz camera updating, which should be adequate for the present experiments. The joystick is connected to an A/D input on the control computer, which can sample and store the input at rates up to 1 KHz. The two computers are connected via a GPIB instrumentation bus, which is an 8-bit parallel interface. This allows rapid and deterministic communication between the two computers, essential for video updating. In each frame, only 32 bytes are sent to update the virtual camera perspective, and a feedback signal from the rendering computer will allow video frame synch signals to be time-stamped and stored with the other data.

**d4. General methods common to all experiments.**
The PI has been performing related experiments for many years, so these will be described only briefly. More details may also be found in the methods sections of the papers included as Appendices.
d4.1. Subjects, care, and surgery. Monkeys (Rhesus macaques, *M. mulatta*) will be procured from the California National Primate Research Center (CNPRC) located near the Davis campus, and all veterinary care and animal husbandry will be coordinated by the Campus Veterinarian's office and the CNPRC staff. The animals will be housed in the research facility, which has fully equipped primate housing and procedure rooms. Each animal will undergo surgery for the implantation of eye coils, head-restraint posts, and recording cylinders before experiments. All surgeries will be performed at the primate surgical suite at the CNPRC, with consultation and guidance from their veterinary staff. Animal training is performed using operant techniques with fluid rewards. Fluid restriction protocols and all other animal care procedures have been approved by the Institutional Animal Care and Use Committee. The lab has been successfully using UCD's standard operating procedures for several years. In general, these institutionally mandated procedures exceed the stringency of the USDA Guidelines for the care and use of laboratory animals.

d4.2. Physiological recording. The animals will be equipped with recording cylinders (Crist Instruments) to which one attaches, on experiment days, a plastic grid for the guide tubes through which recording is performed (Crist et al., 1988). A 23-gauge guide tube penetrates the dura, allowing the passage of microelectrodes. For recording, Parylene-coated tungsten electrodes of 0.5–1.5 MΩ (FHC, Micro-probe) are used, and for microstimulation we use glass-coated platinum-iridium electrodes (FHC) of 0.3–0.75 MΩ impedance. Electrode signals are processed using standard methods, and discriminated spikes are sent as TTL pulses to the experimental control computer (Pentium running REX, Hays et al., 1982). Data are stored on this computer, and are analyzed using both custom and commercial software ("Unixstat" by Gary Perl, Matlab, SAS). The lab has two fully equipped recording rigs, a third setup used for training, and a Linux cluster for data storage and analysis. In addition, a supplemental shared-equipment grant from NEI to [insert institution] has allowed the purchase of high-capacity, high-throughput data server as a local resource. This will be used to store the large volumes of data from multi-electrode recording experiments.

d4.3. Visual stimuli. For most experiments, visual stimuli are generated on a second, "slave" computer, by custom software ("render"; http://deimos.lbl.gov/~arthur/html/render.html). We use 21" graphics monitors (Mitsubishi DiamondPro), running at 80 Hz, at a resolution of 1280 x 1024 pixels. The 8-bit display mode we use is regularly calibrated for linearity, and is adjusted to a maximum luminance of 60 cd/M². The newer generation of rendering software to be used in Aim 3 is described therein.

d4.4. Histological verification. Monkeys will be initially scanned in a 1.5T research scanner at the CNPRC, before the implantation of head hardware. Following the conclusion of experiments, recording areas are verified histologically by placing small electrolytic lesions at known locations in the recording grid. Necropsy is performed at the CNPRC necropsy facility, and the tissue is processed for myelin- and Nissl-staining in the fully equipped histology labs of [insert institution]. The locations of the lesions are noted with respect to myeloarchitectural, cytoarchitectural, and sulcal landmarks to verify that the recordings were in the intended structures.
d5. Time line for proposed experiments

<table>
<thead>
<tr>
<th></th>
<th>year 1</th>
<th>year 2</th>
<th>year 3</th>
<th>year 4</th>
<th>year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim 1</td>
<td>inact. monkey 1</td>
<td>train monkey 2</td>
<td>microstim/inact. m. 2</td>
<td>data analysis &amp; writing</td>
<td></td>
</tr>
<tr>
<td>Aim 2</td>
<td>write code</td>
<td>record monkey 1</td>
<td>record monkey 2</td>
<td>data analysis &amp; writing</td>
<td>follow-up exps.</td>
</tr>
<tr>
<td>Aim 3</td>
<td>monkey 1 &amp; 2 behavior</td>
<td>monkey 1 recording</td>
<td>monkey 2 recording</td>
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</table>

This shows the anticipated sequence of experiments. The experiments in Aim 1 use developed software and are partially complete; one monkey has been used in microstimulation experiments. Inactivation experiments can begin as soon as funding allows a postdoc or student to join the project. Aim 2 needs modest new software development (integration of Plexon code into heading software), but is ready to begin soon. However, it is anticipated that the data rate on this experiment will be modest, because we expect that multiple neural signals will require somewhat longer recording times for each monkey. Aim 3 animal training and behavioral analysis are underway, and will continue. Because of the novelty of the behavioral task, we plan to get a solid set of behavioral data on two animals before commencing recording on either one.

e. Human Subjects

None.

f. Vertebrate Animals

All experiments outlined in this proposal will be performed using adult rhesus monkeys (Macaca mulatta), male and female, weighing between 4 and 15 kg. We use rhesus monkeys for several reasons. First, rhesus monkeys adapt easily to the behavioral training situations used in our laboratory. They train well, are calm while sitting in a primate chair, and will perform steadily for several hours during daily experimental sessions. Secondly, the extensive body of background data, both from my laboratory and from many others, would be less relevant for another species. It therefore seems prudent to continue with this species since the success of the research depends both on the monkeys' cooperation in the endeavor, and on the scientific compatibility of multiple datasets. Finally, many behavioral experiments have shown that the macaque visual system is an excellent model for human vision. Thus our findings are likely to be directly applicable to understanding analogous perceptual processes in humans.

In terms of the numbers of animals, we use as few as possible. At present the lab has 4 monkeys, and we anticipate that 5 additional monkeys will be needed to complete the experiments. Each monkey will, if possible, be trained on more than one task, to maximize the amount of data obtained from each animal. However, publication of the data requires histological verification of electrode or injection locations, and new animals will be needed for all of the aims.

For the most part, the way that we use the animals is clear from the preceding descriptions of the projects. Here I add general procedural information that is not found above. When an animal is in experimental use, it works in the context of an experiment or training session five days per week. At the beginning of the day, the monkey is led from its home cage using a pole and collar handling procedure. The monkey is seated in a primate chair, weighed, and then worked on a fixation task or a visual discrimination task for 2–6 hours depending upon the demands of the experiment or training regime. The primate chair is adjustable along several critical dimensions so that a comfortable fit can be achieved for each animal. At the end of the experiment, the monkey is returned to its home cage. After several days of training, these procedures become routine for the animals and for the
investigator. Gentle handling and a modicum of common sense go a long way toward establishing a good working relationship with each animal. A calm, non-threatening working environment is in the best interest of the animal and of the investigator who wishes to maximize the quality of the data produced.

Training is accomplished by operant conditioning techniques using positive rewards for desired behavior. No aversive conditioning is used in this laboratory. Our animals work for liquid reward (water or juice), and we therefore control water intake carefully. A minimum daily level of fluid intake for adequate hydration is established individually for each animal (judged during training), and supplemental fluid is given if the animal does not obtain its minimum during the experimental session. Extra fluid is provided on weekends. Hydration levels are monitored daily for each animal by measurement of body weight, assessment of skin turgor, and visual inspection of feces. These indicators are occasionally augmented by measurements of urine specific gravity. This water restriction protocol was designed by the veterinary staff at the California National Primate Research Center, the Campus Veterinarian’s Office, and the researchers at the Center for Neuroscience, and is described in a local standard operating procedure (CNPRC S.O.P. PP-1).

The only painful procedures performed in the lab are surgical implantation of search coils and recording cylinders. These are accomplished with standard surgical techniques and are absolutely necessary since none of the proposed experiments can be performed without them. All surgical procedures are performed under surgical anesthesia (isofluorane) and aseptic conditions in an animal surgical facility administered by the CNPRC. The animals reside in the acute care facility at the CNPRC for several days post-surgically, where they receive analgesia (valium, narcotics) and antibiotics, before returning to the research facility.

All animals are euthanized following termination of experiments. This is necessary so that we may reconstruct electrode tracks and confirm the locations of recording and stimulation sites within the cortex. Euthanasia is accomplished with an overdose of barbiturates administered intravenously, and conforms to guidelines established by the Panel on Euthanasia of the American Veterinary Medical Association.

The veterinary care of our animals is excellent. The CNPRC has a staff of 3 full-time clinical veterinarians, one of whom is always on call. Over the last few years, the primate researchers at the have established an excellent working relationship with these veterinarians; they are familiar with the procedures to be used in this grant, and any complications arising from our procedures are dealt with humanely and promptly.

g. Literature cited


Schaafsma SJ, Duysens J, Gielen CC (1997) Responses in ventral intraparietal area of awake macaque monkey to optic flow patterns corresponding to rotation of planes in depth can be explained by translation and expansion effects. Vis Neurosci 14:633-646.


June 16, 2004

Kenneth H. Britten
Center for Neuroscience, UC Davis
1544 Newton Ct.
Davis, CA 95616

Dear Ken,

As we discussed on the phone, I would be delighted to help you in any way I can in the development of an active vision (a.k.a, “steering”) task in your laboratory. My own laboratory is working on related problems in sensori-motor control, though in a different specific experimental context. However, our expertise (and perhaps even software) should be very applicable to your experiments. I think that the project is interesting and likely to produce valuable results. Stay in touch as your development proceeds.

Sincerely yours,
June 24, 2004

Dear Ken,

It would be with great pleasure that I offer to help you with the modeling associated with Aim 2 of your NIH R01 being submitted ("Hierarchical processing in the motion system"). I have done a lot of modeling like what you are considering, and have both the experience and some of the tools that would help you get this very worthwhile project off the ground quickly. I think the collaboration will be both fun and productive.

Sincerely yours,
CHECKLIST

TYPE OF APPLICATION (Check all that apply.)

☐ NEW application. (This application is being submitted to the PHS for the first time.)

☐ SBIR Phase I  ☐ SBIR Phase II: SBIR Phase I Grant No. ________

☐ STTR Phase I  ☐ STTR Phase II: STTR Phase I Grant No. ________

☐ SBIR Fast Track  ☐ STTR Fast Track

☐ REVISION of application number:

(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

☒ COMPETING CONTINUATION of grant number: EY10562

(INVENTIONS AND PATENTS

(Competing continuation appl. and Phase II only)

☒ Yes. If “Yes,” ☐ No. If “No.”

☐ Previously reported

☐ Not previously reported

☐ SUPPLEMENT to grant number: ____________________________

(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of principal investigator/program director.

Name of former principal investigator/program director: ____________________________

☐ FOREIGN application or significant foreign component.

1. PROGRAM INCOME (See instructions.)

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

<table>
<thead>
<tr>
<th>Budget Period</th>
<th>Anticipated Amount</th>
<th>Source(s)</th>
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</table>

2. ASSURANCES/CERTIFICATIONS (See instructions.)

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications are provided in Section III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

☒ Human Subjects; ☐ Research Using Human Embryonic Stem Cells;

☒ Research on Transplantation of Human Fetal Tissue; ☒ Women and Minority Inclusion Policy; ☒ Inclusion of Children Policy; ☒ Vertebrate Animals;

☒ Debarment and Suspension; ☒ Drug-Free Workplace (applicable to new [Type 1] or revised [Type 1] applications only); ☒ Lobbying; ☒ Non-Delinquency on Federal Debt; ☒ Research Misconduct; ☒ Civil Rights (Form HHS 441 or HHS 690); ☒ Handicapped Individuals (Form HHS 641 or HHS 690); ☒ Sex Discrimination (Form HHS 639-A or HHS 690); ☒ Age Discrimination (Form HHS 680 or HHS 690); ☒ Recombinant DNA and Human Gene Transfer Research; ☒ Financial Conflict of Interest (except Phase I SBIR/STTR); ☒ STTR ONLY: Certification of Research Institution Participation.

3. FACILITIES AND ADMINISTRATIVE COSTS (F&A)/INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 2/25/99 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with ____________________________ Regional Office.

☐ No DHHS Agreement, but rate established with ____________________________ Date

CALCULATION* (The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)

<table>
<thead>
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<th>a. Initial budget period:</th>
<th>Amount of base $191,594 x Rate applied 49.50% = F&amp;A costs $94,839</th>
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<td>c. 03 year</td>
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<td>e. 05 year</td>
<td>Amount of base $191,594 x Rate applied 52.50% = F&amp;A costs $100,587</td>
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TOTAL F&A Costs $491,439

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base

☐ Off-site, other special rate, or more than one rate involved (Explain)

Explanation (Attach separate sheet, if necessary):

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