Form Approved Through 05/2004 OMB No. 0925-0001

Department of Health and Human Services

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Do not exceed character length restrictions indicated.

PI: GALLANT, JACK L

2 R01 EY012241-05

Dual:

IRG: CVP

Council: 01/2005

IPF:577502

Received: 07/01/2004

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces a...)*

Shape representation and attention

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☒ NO ☐ YES *(If "Yes," state number and title)*

Number: Title:

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR | **New Investigator** ☒ **No** ☐ **Yes**

3a. NAME *(Last, first, middle)*: Gallant, Jack L.

3b. DEGREE(S): A.B. Ph.D.

3c. POSITION TITLE: Associate Professor of Psychology and Neuroscience

3d. MAILING ADDRESS *(Street, city, state, zip code)*:
University of California
Helen Wills Neuroscience Institute
132 Barker Hall #3190
Berkeley, CA 94720-3190

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT: Helen Wills Neuroscience Institute

3f. MAJOR SUBDIVISION: Vice Provost Academic Affairs and Faculty Welfare

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 510-642-2606 FAX: 510-643-4966

E-MAIL ADDRESS: gallant@socrates.berkeley.edu

4. HUMAN SUBJECTS RESEARCH ☒ No ☐ Yes

4a. Research Exempt ☐ No ☐ Yes
If "Yes," Exemption No.

4b. Human Subjects Assurance No.

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

5. VERTEBRATE ANIMALS ☐ No ☒ Yes

5a. If "Yes," IACUC approval Date: pending

5b. Animal welfare assurance no.: A3084-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
05/01/05	04/30/10	$ 250,000	$ 348,996	$ 1,250,000	$ 1,843,448

9. APPLICANT ORGANIZATION

Name: Regents of the University of California

Address: c/o Sponsored Projects Office
336 Sproul Hall
University of California
Berkeley, CA 94720-5940

Institutional Profile File Number (if known)

10. TYPE OF ORGANIZATION

Public: → ☐ Federal ☒ State ☐ Local

Private: → ☐ Private Nonprofit

For-profit: → ☐ General ☐ Small Business

☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER

DUNS NO. 12-472-6725

Congressional District 9th

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE

Name: Patricia A. Gates

Title: Acting Associate Director, Federal Projects

Address: Sponsored Projects Office
336 Sproul Hall #5940
University of California
Berkeley, CA 94720-5940

Tel: 510-642-8109 FAX: 510-642-8236

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13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION

Name: Patricia A. Gates

Title: Acting Associate Director, Federal Projects

Address: Sponsored Projects Office
336 Sproul Hall #5940
University of California
Berkeley, CA 94720-5940

Tel: 510-642-8109 FAX: 510-642-8236

E-Mail: pgates@berkeley.edu

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

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*

DATE: 06/22/04

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

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*

Patricia A. Gates
Asst. Director, Federal Projects
Acting for

DATE: 6-30-04

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This proposal addresses the way the visual system processes complex shape. We focus on two intermediate visual areas, V2 and V4, located in the ventral processing stream immediately beyond primary visual cortex (area V1). These areas serve as the major input stages for higher-order shape processing areas in the temporal cortex. We propose neurophysiological experiments to investigate the way that shape is represented in these areas and the way that attention modulates these representations. Shape is difficult to describe and parameterize, so previous neurophysiological studies of shape processing have utilized simple, regular shapes that are experimentally convenient. However, intermediate shape processing is highly nonlinear, so results obtained with reduced stimulus sets may not generalize to other stimuli. We therefore propose to use both complex, natural stimuli and simpler stimuli such as gratings. To facilitate this, we are developing novel nonlinear regression algorithms to estimate the stimulus-response mapping functions of neurons in V2 and V4. The underlying shape dimensions represented therein can then be determined by applying visualization algorithms (developed in our laboratory) to the stimulus-response mapping functions estimated for single neurons. In another series of experiments we plan to investigate how extrastriate visual areas integrate information from earlier sensory areas. Finally, we propose to examine how visual attention affects shape representations in V2 and V4. We will accomplish this by quantifying the effects of selective attention to a specific shape (feature attention) and attention directed toward a specific location in space (spatial attention) on neuronal tuning curves. Successful completion of these projects will provide critical information to aid in development of quantitative computational models of shape processing in intermediate vision.

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

University of California at Berkeley
Helen Wills Neuroscience Institute
132 Barker Hall MC 3190
Berkeley, CA 94720-3190

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

Name	Organization	Role on Project
Gallant, Jack L.	University of California at Berkeley	Principal Investigator

Principal Investigator/Program Director (Last, First, Middle): Gallant, Jack L.

The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

RESEARCH GRANT

TABLE OF CONTENTS

(Items A-D: not to exceed 25 pages*)

* *SBIR/STTR Phase I: Items A-D limited to 15 pages.*

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

Check if Appendix is Included

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

Number of publications and manuscripts accepted for publication *(not to exceed 10)* 8

Other items (list):

BUDGET JUSTIFICATION PAGE
MODULAR RESEARCH GRANT APPLICATION

Initial Budget Period	Second Year of Support	Third Year of Support	Fourth Year of Support	Fifth Year of Support
$ 250,000	$ 250,000	$ 250,000	$ 250,000	$ 250,000
Total Direct Costs Requested for Entire Project Period			**$**	1,250,000

This project will require the work of six postdoctoral researchers and/or graduate students to perform the neurophysiological experiments, conduct data analysis and modeling, and develop and evaluate new analysis and modeling algorithms. We also request funds to purchase several pieces of equipment to conduct the proposed multiple-single-unit and long-term recording projects. The proposed experiments will require six animals. Funds are requested for their purchase, for surgery and preparation and for animal care. Finally, funding is requested for expendable recording supplies.

PERSONNEL

Jack L. Gallant, Ph.D., Principal Investigator (summer), will direct all aspects of the project involving neurophysiological recordings and data analysis. He will also train postdoctoral researchers and graduate students as necessary to complete the proposed experiments.

Postdoctoral Research Associate (will be responsible for neurophysiological experiments on representation in area V2 and V4. preliminary data are included in this proposal.

Postdoctoral Research Associate will be responsible for neurophysiological experiments on representation in area V2 and V4. is an experienced neurophysiologist laboratory. will focus on large scale and long-term neurophysiological recordings.

Graduate Student Researcher summer), will be responsible for neurophysiological experiments in all Aims. graduate student with extensive neurophysiological experience. Preliminary data that has already collected are included in this proposal.

EQUIPMENT

Funds are requested for purchase of equipment to complete construction of a third neurophysiological recording rig. We have already acquired most of the equipment for this rig; the only item remaining is a neurophysiological amplifier and spike sorting system. Our two other rigs use the Plexon system, so we would like to use that system here as well.

3 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:

specify that recording rooms be configured so that animals are separated from experimenters during

items: an Intel Linux workstation running customized software for experimental control, stimulus generation and display (all developed in our laboratory); hardware amplifiers, filters and window discriminators for neurophysiological data collection (Plexon, Inc.); and a video eye tracker (EyeLink II). These rooms are also equipped with an extensive array of additional equipment required to support neurophysiological recordings.

Clinical:

Not applicable

Animal:

This space is near my physiology laboratory space in the same building, so that transportation is minimized. also contains complete quarantine, surgical, surgical support, necropsy and histology facilities.

Computer:

Each recording rig includes an Intel Linux workstation which can be used for analysis and development when experiments are not in progress. Each member of the laboratory has a dedicated workstation in his/her office. All of these computers are linked by gigabit Ethernet to RAID storage systems (currently 3 terabytes total) and to our computer cluster (currently consisting of about 20 CPUs).

Office:

Other:

Electronics and Machine shops: The Department of Psychology maintains separate electronics and machine shops. These shops charge no hourly fee, but do charge for materials. Some highly specialized pieces of machinery may have to be fabricated in the machine shop at the School of Optometry. We have access to this shop as long as we maintain funding through NEI.

Administrative Support. Administrative support will be provided by the Helen Wills Neuroscience Institute.

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

Our major equipment consists of (1) two complete rigs for conducting neurophysiological recordings, (2) a third rig for training animals before recording, and (3) extensive facilities for computational analysis (discussed above).

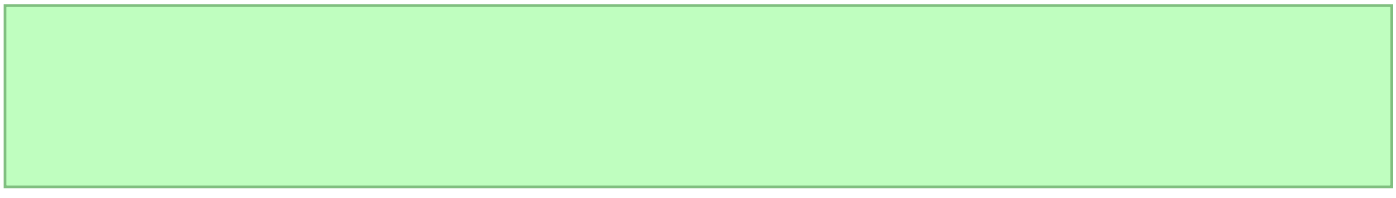
RESEARCH PLAN

A. SPECIFIC AIMS

The goal of this proposal is to understand how intermediate visual areas V2 and V4 represent complex shapes, and how those representations are modulated by attention. Shape processing has traditionally been assessed by characterizing neuronal responses to parameterized, synthetic stimuli (e.g., non-Cartesian gratings, curved contours). Although V2 and V4 neurons have been found to exhibit tuning along many dimensions, researchers have been unable to provide a general model of shape processing in these areas (in contrast to V1). We plan to characterize shape selectivity using a combination of novel experimental and system identification techniques. This information will be critical for development of general models of shape processing that can account for responses of V2 and V4 neurons to arbitrary stimuli.

In Aim 1 we propose to determine how neurons in V2 and V4 integrate information from earlier visual areas. At each stage of visual processing, neurons pool information across many inputs. The specific form of this integration operation determines how shape information is transformed at successive processing stages. If inputs are pooled according to simple linear summation, then successive stages simply rotate the coordinate system but do not provide any more information than is available at the preceding stage; if pooling is nonlinear then each stage can make explicit new information that could not be obtained by a mere rotation of the coordinate system. Previous studies have produced conflicting results regarding the nature of integration in extrastriate cortex.

In Aim 2 we propose to explore shape representation by means of nonlinear system identification. Linear system identification procedures have long been used to characterize quantitatively how single cells map stimuli onto responses. During the previous award period we developed a suite of nonlinear regression procedures (parametric and linearized reverse correlation, neural network analysis and kernel methods) to estimate spatio-temporal receptive fields (STRFs) in V2 and V4. We also developed visualization algorithms that can be applied to STRFs to reveal their underlying shape dimensions.



In Aim 3 we propose to investigate whether and how attention changes the way that shape is represented in V2 and V4.. Previous studies of attention in V4 have produced conflicting reports of changes in response mean or

B. BACKGROUND AND SIGNIFICANCE

Shape representation in the ventral stream

Our perception of the shape of objects is mediated by a hierarchically organized set of visual areas known as the ventral processing stream (Ungerleider and Mishkin, 1982; Van Essen and Gallant, 1994). The earliest cortical stage of shape processing is primary visual cortex (area V1), where cells are tuned for relatively simple aspects of local shape such as retinal position, orientation and spatial frequency (Hubel and Wiesel, 1959; DeValois et al., 1982). V1 neurons also possess specific nonlinearities that influence shape representation, including phase invariance (Movshon et al., 1978), contrast gain control (Heeger, 1992a; Wilson and Humanski 1993), temporal adaptation (David et al., in press) and an output nonlinearity (Heeger, 1992b). This neurophysiological information has been integrated into several computational models (Field, 1987; Heeger, 1991; Carandini et al., 1997; David et al., in press).

The highest stages of shape processing are located in the inferior temporal cortex (IT). IT neurons are selective for complex two- and three-dimensional shapes like faces and hands (Gross et al., 1972; Desimone et al., 1984). Responses in IT are highly nonlinear. For example, IT cells show substantial size and position invariance (Tovee et al., 1994; Ito et al., 1995). In contrast to V1, the general principles underlying shape representation in IT are unknown. It is difficult to determine which dimensions best describe shape tuning, and there is currently little agreement about appropriate models of shape representation in IT.

The transformation from the simple, local shape dimensions represented in V1 to the representation of complex shapes in IT occurs incrementally across several intermediate visual areas including V2, V4 and TEO/PIT (Van Essen and Gallant, 1994). **The long-term goals of our laboratory are to understand how shape is represented in these various visual areas, and how these representations are modulated by attention.** Such information is essential for constructing quantitative models of intermediate visual processing as powerful as those used to describe V1. Developing models will require three critical types of information: [1] the set of dimensions for describing shape representation in each area; [2] the key nonlinear transformations that occur between different areas; [3] the form and extent of attentional modulation of these representations.

Difficulties in assessing shape representation

Our current understanding of shape coding in extrastriate areas V2 and V4 is more like that prevailing in IT than in V1. Previous studies have shown that V2 and V4 neurons are selective for shape-related dimensions such as non-Cartesian energy (Gallant et al., 1993; Kobatake and Tanaka, 1994; Gallant et al., 1996), cross-oriented edges (Kobatake and Tanaka, 1994; Hegde and Van Essen, 2000), local curvature (Pasupathy and Connor, 1999) and stereo cues to shape (Bakin et al., 2000; Hinkle and Connor, 2002). These studies suggest that V2 and V4 can be viewed as banks of nonlinear, multidimensional filters sensitive to moderately complex shape attributes. However, all these experiments have been limited by the choice and size of the stimulus set. It is impossible to know whether observed shape selectivity represents a fundamental coding property or is merely a consequence of tuning along some other, unknown dimension that was not sampled fully in the experiments.

Many of the experimental and theoretical tools used in neurophysiology were derived from linear systems theory. These tools may not be optimal for application to areas V2 and V4, which contain significant nonlinearities not found at earlier stages of processing. For example, some V2 neurons respond to the modulation frequency of amplitude-modulated (AM) gratings (Zhou and Baker, 1994). AM sensitivity can only by implemented using nonlinear mechanisms. Similarly, V4 shows a substantial degree of position invariance (Desimone and Schein, 1987; Gallant et al., 1996), a property that can only be computed by nonlinear circuit elements. These and other nonlinearities (Peterhans and von der Heydt, 1987; von der Heydt and Peterhans, 1987) are likely to be critical for object recognition.

In addition to nonlinear spatial processing, V2 and V4 are also continuously modulated by attentional state (Moran and Desimone, 1985; Maunsell et al., 1991; Mazer and Gallant, 2003). This suggests that if we

investigate only one attentional state (such as passive fixation), our observations may not generalize to other states. Both of these problems decrease experimental efficiency and so make the search for underlying principles of representation more difficult.

Our integrated approach

This proposal is based on an integrated approach to studying visual representation and attention that is designed to overcome the limitations noted above. Instead of focusing on a single, arbitrary stimulus set and model, we use quantitative, nonlinear system identification procedures to estimate the nonlinear stimulus-response mapping function of each neuron, and the effect of attention on that mapping, over as broad a range of activity as is feasible. The resulting models can be used to derive new hypotheses that can then be tested experimentally.

In visual neurophysiology the function that relates stimuli to responses is called the spatio-temporal receptive field (STRF). It describes both the spatial tuning of a cell and the evolution of tuning over time (Theunissen et al., 2001). STRFs are usually estimated by reverse correlation of recorded action potentials against preceding stimuli (Jones and Palmer, 1987; DeAngelis et al., 1995) and several different algorithms have been proposed for performing this computation (Marmarelis and Marmarelis, 1978; Ringach et al., 1997; Theunissen et al., 2001; Touryan et al., 2002; Willmore and Smyth, 2003; David et al., in press; Prenger et al., in press). System identification methods have also been applied successfully to sensory systems other than vision (DeBoer and Kuyper, 1968; deCharmes et al., 1998; DiCarlo et al., 1998; Klein et al., 2000; Theunissen et al., 2001).

Stimulus selection. To estimate the STRF, we must first acquire an appropriate set of stimulus-response data. Classical experiments usually use stimuli that are relatively simple and easily parameterized. However, during nonlinear system identification it is desirable to sample a wide range of stimuli. As a general rule, the greater the number and variety of stimulus-response pairs available for estimation, the more accurate the estimated model will be (Willmore and Smyth, 2003; David et al., in press).

Although white noise is theoretically optimal for system identification (Marmarelis and Marmarelis, 1978), we find empirically that white noise elicits relatively little response from neurons beyond V1. One way to overcome this problem is to characterize cells using natural visual stimuli (Theunissen et al., 2001). Because the visual system evolved to process natural scenes, these stimuli should elicit robust responses from neurons throughout the visual system. An additional motivation for using natural scenes is that estimates of the STRF derived from artificial stimuli are often poor predictors of neuronal behavior under natural conditions (David et al., in press). Although natural scenes introduce difficult technical problems (notably a bias introduced by the $1/f^2$ spatial power spectrum), recent work in our lab has made substantial progress in solving these problems (Theunissen et al., 2001; David et al., in press; Prenger et al., in press).

Nonlinear regression. The analysis methods employed by previous neurophysiologists for STRF estimation have been almost exclusively linear (though see Touryan et al., 2002). Since all cortical visual processing beyond V1 simple cells is overwhelmingly nonlinear, these linear methods are not optimal. To approach this problem, during the previous period of this award we put considerable effort in to developing appropriate nonlinear system identification procedures (see Progress Report).

It is useful to divide these methods into two classes: parametric and nonparametric. Parametric methods use a single, fixed model to constrain regression, and they assume that stimulus and response distributions take a specific form (e.g., reverse correlation: Ringach et al., 1997; Mazer et al., 2002; Willmore and Smyth, 2003; David et al., in press). Nonparametric procedures use unsupervised learning or optimization to find a solution, and the size of the model can grow as more data are acquired (e.g., neural network analysis: Lehky et al., 1992; Lau et al., 2002; Prenger et al., in press; kernel methods: Scholkopf and Smola, 2002 and see Appendix A). These procedures do not necessarily make specific assumptions about stimulus or response distributions. Parametric procedures maximize efficiency and power, and they are easily interpretable. Nonparametric procedures are more general but may be more difficult to interpret.

To understand intermediate vision it is also important to characterize top-down influences such as attention. According to the system identification approach, attention is simply another input that can modulate responses nonlinearly. It is therefore straightforward to integrate the study of attention into the framework described above. It is desirable to sample many states of attention, particularly those occurring during natural vision.

Interpretation and visualization. If a parametric model has been used to estimate the STRF then it can be interpreted directly in terms of the model parameters. For example, parametric reverse correlation against orientation and spatial frequency provides direct estimates of neuronal tuning along these dimensions (Mazer et al., 2002). However, if a nonparametric method such as a neural network has been used, then the STRF cannot be interpreted directly. Instead, a secondary stage of analysis is required to re-express the STRF and reveal the stimulus dimensions that best describe it. We have developed analysis and visualization methods for this purpose (Prenger et al., in press).

The final stage of nonlinear system identification is common to all neurophysiology studies: information must be aggregated across a large sample of neurons in order to identify general principles that describe a specific visual area. If parametric methods are used to estimate STRFs for individual neurons, then all the data exist in the same parameter space and aggregation is straightforward (Mazer et al., 2002; David et al., in press). However, if STRFs are obtained by nonparametric methods then a common parameter space (or multiple spaces) must be found within which to express the data. This can be accomplished with appropriate clustering procedures (Gallant et al., 1996).

Our proposal

During the previous award period we demonstrated the feasibility of our integrated approach by applying it to area V1, where the principles of shape representation are relatively well understood, and V4, where much is known about selective attention (see Progress Report). This renewal focuses on visual areas V2 and V4, the two stages of shape processing subsequent to V1. In Aim 1 we propose to use classical experimental approaches to evaluate specific hypotheses about a key nonlinearity, integration of inputs in V2 and V4. In Aim 2 we propose to use nonlinear system identification to enumerate general principles of complex shape representation. In Aim 3 we propose to combine classical experimental methodology with modern nonlinear regression techniques to systematically characterize the modulatory effects of attention.

If our experiments are successful they will reveal fundamental new principles of shape representation and attention in areas V2 and V4. These could form the foundation of explicit functional models of V2 and V4 analogous to those already developed in V1. Experience there suggests that such models would dramatically increase our understanding of shape processing and would spawn many follow-on experiments. Work in higher areas such as TEO and IT would also benefit from our studies, because it is generally easier to investigate any visual area when its proximal inputs are understood.

C. PROGRESS REPORT

The current award was meant to support three specific Aims. (1) To determine how neurons in area V1 respond during natural vision; (2) To develop and evaluate quantitative models of V1 neurons that can account for their responses during natural vision; (3) To discover how attention modulates neuronal responses during natural vision. **All three of these Aims were completed successfully during the previous award period**, though there were some changes in experiments as a result of new technical developments and experimental results. Here we summarize briefly relevant published work and preliminary results that are not directly pertinent to the renewal.

Previous Aim 1: V1 responses during natural vision. This Aim was addressed by combining a new experimental tool (movies that simulate natural vision) with quantitative analyses (information theory, parametric and linearized reverse correlation). Several issues were resolved. First, in a study published in

Science, we confirmed a longstanding hypothesis that area V1 represents natural scenes by means of a sparse code (Vinje and Gallant, 2000). We also demonstrated that this effect is mediated primarily by the non-classical receptive field, and that the process increases information rates and processing efficiency (Vinje and Gallant, 2002). Second, we published the first report of dynamic changes in spatial frequency tuning in area V1 (Mazer et al., 2002), an observation that has already been confirmed and replicated in other laboratories (Bredfeldt and Ringach, 2002; Frazor et al., 2004). This effect appears to be due to differences in the temporal latencies of magno- and parvo-cellular inputs to V1. Third, we published a very detailed quantitative study of V1 response properties focused on changes in spatial and temporal response properties when measured under natural viewing conditions, as compared to conventional methods (David et al., in press). We found that natural stimuli engage nonlinear temporal adaption and modulate spatially tuned inhibition in ways that cannot be predicted from responses to the simpler synthetic stimuli.

Previous Aim 2: Quantitative models of V1 neuronal properties during natural vision. The intent of this Aim was to test a wide variety of quantitative V1 processing models to see which could best account for neuronal responses during natural vision. We found that the most efficient and general way to approach this problem was to develop a new modeling framework, linearized reverse correlation. We used this to develop a more sophisticated model of both spatial and temporal responses in area V1 (David et al., in press). The framework was designed to enable us to fit nonlinear models to complex naturalistic data sets using reverse correlation, and to provide goodness of fit and predictive power statistics. It allowed reverse correlation methods to be applied, for the first time, to complex cells in V1 and to extrastriate neurons in V2 and V4 (see David et al., in press, and Preliminary Results sections 4 and 5).

We also improved nonlinear neural network regression procedures that have been used rarely in neurophysiology (Lehky et al., 1992; Lau et al., 2002). We used these methods to recover nonlinear STRF estimates for direction-selective complex cells in V1 (Prenger et al., in press). We have found that nonlinear regression methods such as linearized reverse correlation (David et al., in press), parametric reverse correlation (Mazer et al., 2002) and neural network analysis (Prenger et al., in press) are extremely powerful tools for investigating both representation and attention throughout the visual system. The current proposal therefore places strong emphasis on further development and use of these methods.

Previous Aim 3: Attentional modulation of neuronal responses during natural vision. This Aim was addressed in two series of experiments. First, we designed a novel free viewing visual search (FVVS) task that allowed us to investigate both bottom-up (stimulus-related) and top-down (feature attention) mechanisms in a natural visual search task (Mazer and Gallant, 2003). This experiment allowed us to confirm, for the first time, the longstanding hypothesis that intermediate sensory areas function as a salience map that guides eye movements during natural visual behavior. Those data also demonstrate that salience computations are modulated by feature attention. In this renewal we propose to combine the FVVS task with our nonlinear system identification algorithms to determine how tuning is modulated during the different attentional states of natural vision. A second, more recent study investigated spatial and feature attention using a delayed match to sample task. These experiments are still in progress (see Preliminary Results section 5).

Publications related to this award

Vinje, W. E., & **Gallant, J. L.** (2000). Sparse coding and decorrelation in primary visual cortex during natural vision. *Science*, 287, 1273-1276.

Gallant, J. L. (2000). The neural representation of shape. In K. K. DeValois (Ed.), *Seeing*. San Diego, CA: Academic Press.

Gallant, J. L., Shoup, R. E., Mazer, J. A. (2000). A human extrastriate cortical area that is functionally homologous to Macaque area V4. *Neuron*, 27, 227-235.

Mazer, J. A., & **Gallant, J. L.** (2000). Object recognition: Seeing us seeing shapes. *Current Biology*, 10, 668-670.

Gallant, J. L., & Vinje, W. E. (2001). Reverse Spikeology: Predicting Single Spikes. *Neuron*, 30, 646-647.

Theunissen, F. E., David, S. V., Singh, N. C., Hsu, A., Vinje, W. E., **Gallant, J. L.** (2001). Estimating spatial temporal receptive fields of auditory and visual neurons from their responses to natural stimuli. *Network: Computation in Neural Systems*, 12, 289-316.

Mazer, J. A., Vinje, W. E., McDermott, J., Schiller, P. H., & **Gallant, J. L.** (2002). Efficient characterization of spatial frequency and orientation tuning dynamics in area V1 of awake behaving animals. *Proceedings of the National Academy of Sciences USA*, 99, 1645-1650.

Vinje, W. E., & **Gallant, J. L.** (2002). Natural stimulation of the non-classical receptive field increases information transmission efficiency in V1. *Journal of Neuroscience*, 22, 2904-2915.

Gustavsen, K., & **Gallant, J. L.** (*2003*). Shape perception: complex contour representation in area V4. *Current Biology, 13*, R234-R235.

Gallant, J. L. (2003). Neural mechanisms of natural scene perception. In L. M. Chalupa and J. S. Werner (Eds.), *The Visual Neurosciences*. MIT Press, Boston, MA.

Mazer, J. A., & **Gallant, J. L.** (2003). Goal-related activity in area V4 during free viewing visual search: Evidence for a ventral stream salience map. *Neuron*, 40, 1241-1250.

Abstracts published in this period

Mazer, J. A., David, S. V., & Gallant, J. L. (2000). Spatiotemporal receptive field estimation during free viewing visual search in macaque striate and extrastriate cortex. *Soc. Neurosci. Abs.*

Mazer, J. A., David, S. V., & **Gallant, J. L.** (2001). Attentional modulation of Macaque V4 neurons during free viewing visual search. *Soc. Neurosci. Abs.*

Vinje, W. E., & **Gallant, J. L.** (2001). Stimulation of the non-classical receptive field helps V1 neurons separate the wheat from the chaff. *Soc. Neurosci. Abs.*

Mazer, J. A., & **Gallant, J. L.** (2002). Evidence for perceptual saliency maps in area V4 during freeviewing visual search. *Vision Sciences Society*, 2, 250.

David, S. V., Vinje, W. E., & **Gallant, J. L.** (2002).Spatio-temporal response properties in V1 of awake primate during natural stimulation. *Gordon Research Conference on Natural Scene Statistics*.

Mazer, J. A., & **Gallant, J. L.** (2002). Evidence for perceptual saliency maps in area V4 during freeviewing visual search. *Gordon Research Conference on Natural Scene Statistics*.

David, S. V., Mazer, J. A., & **Gallant, J. L.** (2002). Pattern-specific attentional modulation of V4 spatiotemporal receptive fields during free-viewing visual search. *Soc. Neurosci. Abs.*

Wu, M. C-K., David, S. V., & **Gallant, J. L.** (2002). How can a neuron interpret a spike train? *Soc. Neurosci. Abs.*

Gallant, J. L., Theunissen, F. E. & Zhang, J. (2003). STRFPak: The linear and nonlinear sensory system identification toolbox. *Human Brain Project Conf.*

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Gustavsen, K., David, S. V., Mazer, J. A., & Gallant, J. L. (2004). Stimulus interactions in V4: A comparison of linear, quadratic and MAX models. *Soc. Neurosci. Abs.*

Preliminary results related to this renewal

4 pages redacted--preliminary results

D. EXPERIMENTAL DESIGN AND METHODS

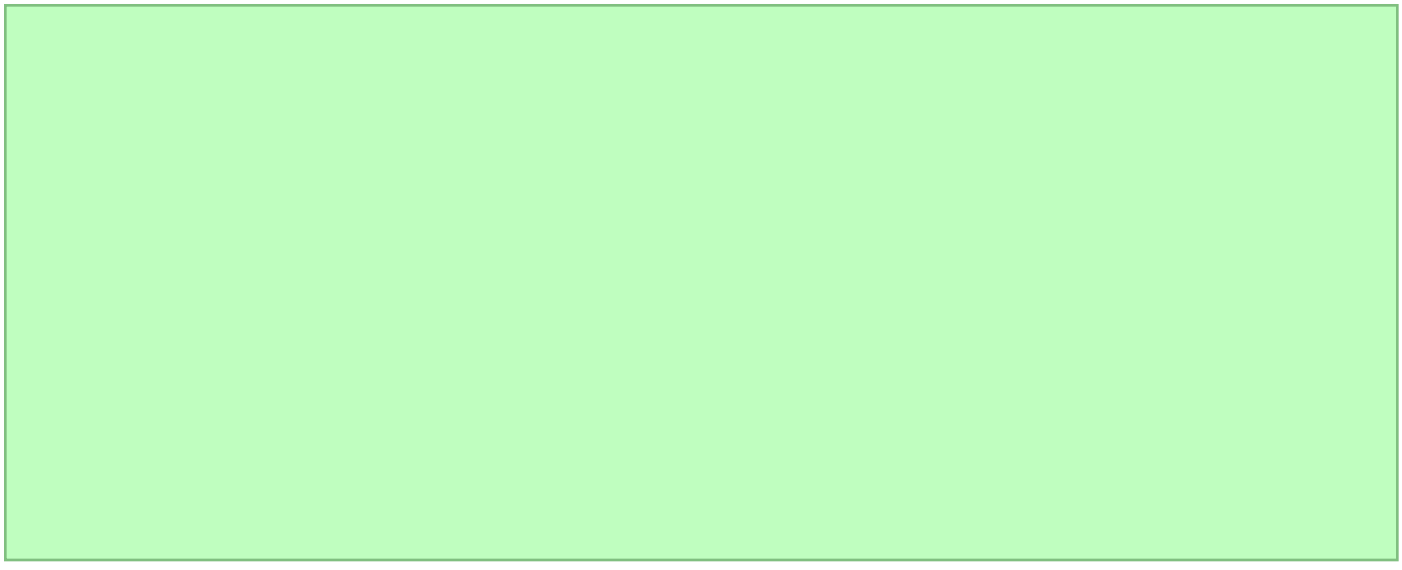
The long term goals of this program are to understand how extrastriate visual areas represent information about stimulus shape, and how these representations are modulated by selective attention. Extrastriate areas are known to be highly nonlinear, which presents a challenge: Even if we can characterize how these areas respond to one restricted stimulus set, those results may not generalize across stimulus conditions. We therefore place strong emphasis on coding and representation of natural stimuli, under natural viewing conditions. Vision is also an active process; a neuron may encode the same stimulus differently, depending on its behavioral relevance. Experiments that explore only passive fixation would miss such effects. Thus, we must also determine how attention modulates stimulus representations. We also focus on development and validation of nonlinear regression (i.e., system identification) algorithms that can reveal the potentially nonlinear dimensions underlying shape representation, often without need for an explicit model.

The proposed experiments are divided into three Aims. In Aim 1 we propose to determine how V2 and V4 neurons pool their inputs from earlier visual areas. In Aim 2 we propose using two inductive methods to discover the nonlinear dimensions that best describe the way extrastriate neurons represent shape. In Aim 3 we propose to study the way that the top-down control mechanisms of feature and spatial attention can alter shape representation dynamically.

Aim 1: Summation and pooling of information in V2 and V4

One critical factor determining how shape is represented in any visual area is the way that single neurons pool their inputs from earlier, upstream areas. In primates virtually all input to areas V2 and V4 passes first through primary visual cortex, area V1. Previous studies suggest V2 neurons pool their V1 inputs nonlinearly (Zhou and Baker, 1994; Hegde and Van Essen, 2000). The same is likely true in V4 (Desimone and Schein, 1987; Gallant et al., 1996), though the rules governing integration may be different than in V2.

A standard method for investigating nonlinear pooling is to compare neuronal responses to single stimulus elements (e.g., bars or gratings) and to their combinations. One study has examined integration within extrastriate receptive fields when attention is directed toward or away from the recorded receptive field (Reynolds et al., 1999). That study reported pooling by weighted averaging in the absence of spatial attention. A different experiment used fixating animals that had not been trained on an attention task (Gawne and Martin, 2002). Pooling appeared to follow a MAX operation. The response to paired stimuli was equivalent to the response to the better stimulus alone. The other stimulus has no influence on responses.



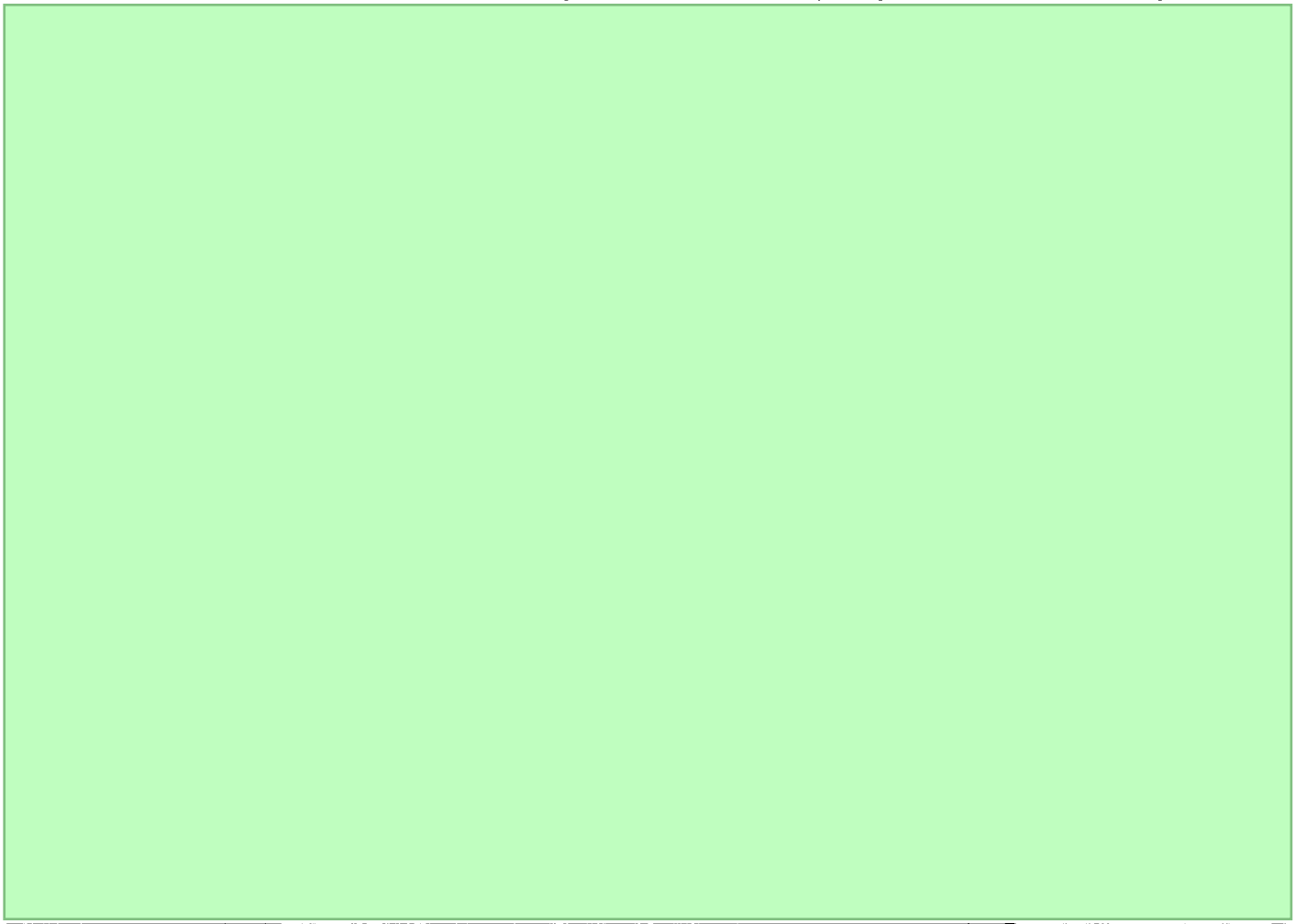
3 pages redacted--aim 1 experimental method

Aim 2: Direct estimation of shape representation

As discussed in the Background and Significance, we currently know little about which stimulus dimensions best describe shape representation in ventral stream areas beyond V1. Many studies have investigated small sets of synthetic shapes, but it is not known whether tuning in these experiments represents fundamental dimensions of shape coding or merely correlation with some other shape dimension. In Aim 2 we propose to use nonlinear system identification to estimate the nonlinear spatio-temporal receptive field (STRF) of neurons in areas V2 and V4. Estimated STRFs can then be interpreted by applying appropriate visualization algorithms (see Background and Significance and Prenger et al., in press) in order to discover the general set of dimensions for describing shape selectivity in these areas.

Successful STRF estimation depends primarily on two factors: appropriate nonlinear regression algorithms and optimized experimental designs. Our laboratory has expended considerable effort in developing a suite of nonlinear regression procedures appropriate for analysis of neurophysiological data. These are described elsewhere in this proposal. (See Background and Significance, Progress Report, and Appendix A.)

Two major experimental factors determine the quality of estimated STRFs: the number of stimulus-response pairs and the number of spikes available for analysis (Theunissen et al., 2001; David et al., in press). Additionally, for the STRF to function as a general model of a cell's behavior, the stimuli should thoroughly sample the parts of stimulus space that are relevant for the cell. These considerations suggest that we should collect neuronal responses to a set of natural image stimuli that is as large as possible. Because our experiments



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Aim 3: Attentional modulation of form representation

Previous experiments in area V4 have shown that that spatial attention can increase neuronal response rate (Moran and Desimone, 1985; Motter, 1993), the gain of orientation tuning curves (McAdams and Maunsell, 1999), and contrast gain (Reynolds et al., 2000). These effects are likely to increase the influence of single neurons relative to the population as a whole, while leaving the essential tuning characteristics of the cell intact.

In theory, attention might also alter more basic tuning properties (e.g., the width or shape of the tuning curve). This would effectively change the representation of shape across the entire population of cells within a single visual area. The only published evidence that this occurs is a demonstration that spatial attention can bias the spatial receptive field profile in V4 (Connor et al., 1997). Our Preliminary Results (see section 6) also suggest that attention can simultaneously modulate response baseline, response gain and the structure of tuning curves of individual V4 neurons. However, our preliminary study examined attention to a specific feature rather than attention to a retinotopic location as examined in earlier studies.

1 page redacted--aim 3 experimental method

Proposed timetable

We ask for five years of support. We have carefully planned our procedures so that the proposed research can be completed within the requested funding period.

training is one of the most time-consuming stages in working with awake behaving animals. It takes from three to nine months to train a naive animal to perform an experimental task (three months: simple fixation/dimming; nine months: covert attention). Neurophysiological recordings take an additional year per animal. A published neurophysiology study requires two animals (one hemisphere each). Training requires the work of one person, recording requires one to two. Some savings occur because animals can be used in multiple experiments involving the same basic task.

General Methods

1. Fixation (dot-dimming) task. Several of the proposed experiments require animals to perform a fixation task for 3-5 seconds while stimuli are presented in and around the classical receptive field. Animals must maintain fixation on a small dot within a small (0.25-1.0 deg) window and simultaneously monitor the luminance of the dot. When the dot dims they must immediately release a bar to obtain liquid reward. This is a standard task that is used in many physiology laboratories.

2. Delayed match-to-sample task. Animals will initiate each trial by taking hold of a touch bar and fixating on a central spot. A natural image patch sample will appear briefly at fixation, indicating the target patch (feature attention cue). At the same time, a small black bar will appear at the outer edge of the feature cue, located either on the side nearest the receptive field, or 180 degrees opposite to it. This spatial cue will indicate the relevant stimulus location. After a brief delay two stimulus sequences will appear simultaneously, in the receptive field and in the opposite hemifield. The sequences appearing at the two locations will be different. Stimulus characteristics and rate will depend on the experiment. To perform the task correctly and receive a reward the animal must attend to the cued spatial location (ignoring the uncued location) and release the touch bar when he detects a stimulus matching the feature cue. Catch trials, in which the correct target appears at the uncued location or patches which have previously been used as targets appear at the cued location, occur on a certain proportion of trials (depending on experiment). These ensure that the animal maintains the correct attentional state. Both spatial and feature attention conditions will be run in blocks of 10 trials, and the feature and spatial cues will appear only on the first trial of the block of 10. Blocking will facilitate behavioral performance, and the absence of the cues on most trials will ensure that the data are not contaminated by unknown interactions between the cues and the subsequent stimulus sequences.

3. Receptive field mapping. Two convergent procedures will be used to map the spatial receptive field of each recorded cell. First, receptive fields will be mapped by hand while the animal performs the fixation task. Hand plotting uses bar and grating stimuli whose position, length, width, color and orientation are under the experimenter's manual control. For single units the CRF of a cell will be delineated as an elliptical region that evokes a reliable response. Second, receptive fields will be mapped with a dynamic sparse noise sequence. This will consist of an array of spots or bars whose color and orientation are chosen to match the manually mapped preferences of the neuron. The stimuli will be flashed in 3-5 second sequences while the animal performs the fixation task. The boundaries of the CRF will be estimated by reverse correlation with respect to spot position and polarity. We have extensive experience with these procedures and find that they produce excellent and reliable receptive field estimates.

4. Relationship to functional subdivisions of V2 and V4. It is well known that area V2 is composed of compartments (stripes) that are both anatomically and functionally distinct (Van Essen et al., 1994; Roe and Ts'o, 1995; Ts'o et al., 2001; Sincich and Horton, 2002). This may also be true in V4 (Felleman et al., 1997). For V2, by performing functional characterization using drifting sinusoidal gratings, we will be able to estimate which compartment each neuron is in. We will first obtain tuning curves for achromatic gratings, at spatial frequencies covering the SF tuning of the cell, and drifting at temporal frequencies between 1 and 20 Hz. This will distinguish between neurons in thick (disparity/motion) stripes and pale (orientation) stripes. We will then measure the color tuning of cells, using colored versions of the optimal grating. These will sample DKL color space at 45° intervals (Levitt, Kiper & Movshon 1994). Strong tuning in this space suggests that a cell is located in a thin (color) stripe.

5. Electrophysiological procedures. Recording methods will be similar to those described in published work from our laboratory (Vinje and Gallant, 2002; Mazer and Gallant, 2003; David et al., in press). Recording will be made with epoxy-coated tungsten microelectrodes positioned over a 5 mm well and advanced by a lightweight microdrive. Our recording system provides exceptional stability and enables recording from single cells in awake, behaving animals for up to 4-5 hours. Experiments will be controlled by software developed in

our laboratory. Spikes will be amplified and isolated using the Plexon system. Stimulus display events are correlated with spikes using the frame refresh signal of the monitor.

6. Eye movement monitoring. During the current award period we adapted a high resolution infrared video eye tracker for use in our experimental setup, as a replacement for invasive scleral search coils. Our extensive calibrations show that the EyeLinkII (SR Research, Toronto, Canada) system that we have adapted has an effective resolution of 0.125 deg, very close to the effective resolution of traditional search coils (0.1 deg). The tracking system is calibrated on each recording day. For fixation-based experiments this is a simple matter of zeroing the tracker while the animal maintains central fixation. For experiments that require accurate tracking of eye movements across the entire video display, we employ the following calibration procedure (Mazer et al., 2003). The experimenter defines an array of 50-100 points, covering the entire viewing area. Points are selected in random order as fixation spot locations. The animal is required to acquire and fixate each spot for 3-5 seconds, and the entire array is repeated 2-3 times. Differences between the recorded eye position for each point and its actual screen location are computed. A spline fit to this difference map provides an interpolated calibration surface, which is used to map recorded eye position data into screen coordinates.

E. HUMAN SUBJECTS

Not applicable.

F. VERTEBRATE ANIMALS

1. The proposed experiments require neurophysiological recording from awake behaving primates. In brief, macaques will have a post and recording chamber affixed to the calvarium using standard surgical procedures conducted in accordance with NIH and U.C.B. ACUC guidelines. Animals will be trained to perform a visual fixation task for a liquid reward. Some animals will also be taught to perform a covert attention task. When training is complete, daily neurophysiological recording will begin. During recording a sterile microelectrode will be passed through a sterile sealed chamber, across the dura and into the cortical area of interest. Animals will be maintained on a water schedule during training and recording, and fluid intake will be monitored closely to ensure sufficient hydration. The proposed experiments here will require 4 animals of either sex, weighing 3-10 kg. To minimize the number of animals used in the lab, animals may also be in additional experiments not discussed here.

2. There are no alternatives to the use of animals in these studies. Neurophysiological experiments provide crucial data that cannot be obtained by any other means. The proposed experiments are designed to address the neural mechanisms of vision in humans, so it is necessary to use a preparation whose visual system is similar to the human. The macaque is a good model system for human vision and there is a large body of existing research on this preparation. Because macaques are a precious and valuable resource the data gathered in these experiments will be analyzed thoroughly and will also be used in the construction and evaluation of computer models of cortical processing.

3. All research proposed here will be supervised by the U.C. Berkeley office of laboratory animal care (OLAC). The experiments will be conducted in campus animal facilities that conform to all current NIH, USDA and AALAC standards. OLAC employs a full veterinary staff that is available 24 hours a day.

4. Every step will be taken to minimize pain and discomfort during the proposed experiments and to ensure the physical and mental health of the animals. During training and recording animals will be seated comfortably in a primate chair that allows freedom of movement and postural adjustment. All training tasks will be performed via operant conditioning so animals will be free to perform according to their own schedule. Animals on water schedule will be monitored closely to ensure that they receive sufficient hydration and will be given liquid

supplement as necessary. Surgical procedures will be conducted using approved analgesics and anesthetics (e.g., Ketamine, Xylazine, Isoflurane, etc.). During surgery animals will be monitored closely to ensure sufficient levels of anesthesia. Post-operative pain will be minimized with approved analgesics (e.g., Buprenex, Tylenol), along with antibiotics given to prevent infection.

5. Euthanasia, if required, will be conducted according to the recommendations of the American Veterinary Association, and in compliance with NIH and U.C.B. IACUC regulations. Animals will be euthanized with a large overdose of Nembutal (90 mg/kg IV), verified by checking for absence of heartbeat and flat EEG. Euthanized animals will then be perfused and their brains prepared for later analysis. Tissue not needed for experimental analysis will be distributed to other laboratories.

G. CONSULTANTS/COLLABORATORS

None.

H. CONSORTIUM/CONTRACTUAL ARRANGEMENTS

None.

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Principal Investigator/Program Director (last, First, Middle): Gallant, Jack L.

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. _____ ☐ SBIR Fast Track

☐ STTR Phase I ☐ STTR Phase II: STTR Phase I Grant No. _____ ☐ 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: R01 EY12241-04

(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl. and Phase II only)*

☒ No ☐ Previously reported

☐ Yes. If "Yes," ☐ 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 request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

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 ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: March 13, 2002 ☐ 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.)*

a. Initial budget period:	Amount of base $	190,377	x Rate applied	52.00	% = F&A costs	$	98,996
b. 02 year	Amount of base $	239,414	x Rate applied	52.00	% = F&A costs	$	124,495
c. 03 year	Amount of base $	238,356	x Rate applied	52.00	% = F&A costs	$	123,945
d. 04 year	Amount of base $	237,190	x Rate applied	52.00	% = F&A costs	$	123,339
e. 05 year	Amount of base $	235,910	x Rate applied	52.00	% = F&A costs	$	122,673
					TOTAL F&A Costs	$	593,448

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

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

Explanation *(Attach separate sheet, if necessary.)*:

Equipment and student registration fees are not included in the Modified Total Direct Cost base.

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