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Grant Number

5R01EY12389-9

Total Project Period

From: 02/01/1999 To: 06/30/2009

EIN: -------------------- **Review Group:** CVP

Requested Budget Period:

From: 07/01/2008 To: 06/30/2009

Title of Project:

Diencephalic Mechanisms of Visuomotor Integration

Due Date: 05/16/2008
Submitted Date: 05/14/2008

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Human Subjects: [X] **No** [ ] **Yes**

Research Exempt: [X] **No** [ ] **Yes**

Exemption No: **FWA Number:** FWA00001435

Full IRB: [X] **No** [ ] **Yes**

Phase III Clinical Trial: [X] **No** [ ] **Yes**

Program Income: [X] **No** [ ] **Yes**

Vertebrate Animals: [ ] **No** [X] **Yes**
Animal Assurance Number: A3391-01

Inventions and Patents: [X] **No** [ ] **Yes**

[ ] **Previously Reported**

[X] **Not Previously Reported**

Budget Period	**Anticipated Amount**	**Source**
F&A Changes:		
Performance Sites:		
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Principal Investigator: TERRENCE R STANFORD	**Grant Number** 5R01EY12389-9
Applicant Organization: WAKE FOREST UNIVERSITY HEALTH SCIENCES	**Period Covered by this Report:** 07/01/2007 - 06/30/2008
Title of Project: Diencephalic Mechanisms of Visuomotor Integration	

SNAP Questions:

Has there been a change in the other support of key personnel since the last reporting period?

☒ **No** ☐ **Yes**

Justification:

Will there be, in the next budget period, a significant change in the level of effort for the PI or other personnel designated on the Notice of Grant Award from what was approved for this project?

☒ **No** ☐ **Yes**

Justification:

Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total budget?

☒ **No** ☐ **Yes**

Justification:

Changes in Select Agent Research? ☒ **No** ☐ **Yes**

Changes in Multiple PI Leadership plan? ☒ **No** ☐ **Yes**

Human Subject Education Requirement:

Has the Involvement of Human Subjects changed since previous submission? ☒ **No** ☐ **Yes**

Has the Involvement of Animal Subjects changed since previous submission? ☒ **No** ☐ **Yes**

Publications:

Citation ID:	Citation Text:
	May, P.J., Zhou, L., Perkins, E., Lin, RC-S, Redgrave, P., Stanford, T.R., and McHaffie, J.G. (2007) Looped circuitry modulating tectally directed gaze behavior. Looped circuitry modulating tectally directed gaze behavior. 17th Neuronal Control of Movement Society Satellite Symposium Abstr.
	Coizet, V., McHaffie, J.G., May, P.J., Stanford, T.R., Jiang, H., Costello*, M.G., Graham, J.H., Overton, P.G., and Redgrave, P. (2007) The tecto-subthalamic projection: A source of short-latency visual input to the subthalamic nucleus. 9th Triennial International Basal Ganglia Society Abstracts, 9: 47.
	Shankar, S., Costello*, M.G., Stanford, T.R., and Salinas, E. (2007) A diffusion model of the perceptual decision-making process in a Compelled-Saccade task. Soc. Neurosci. Abst. 33, Program No. 617.14.

Research Accomplishments: File is not uploaded
Other Document File: File is not uploaded
Other Support File: File is not uploaded

Personnel Report	
Principal Investigator:	**Grant Number**
TERRENCE R STANFORD	5R01EY12389-9

Name:	Degree(s) Name:	SSN:	Role on Project:	Months Devoted to Project		
				Cal	Acad	Sum
TERRENCE R STANFORD	PHD	------	PI	6.0		

Studies and Results

This report considers progress made during the Year 4 of the current grant period. During this time we have continued to concentrate on our principle objective of evaluating the hypothesis that cortico-subcortical interactions are an essential part of the neural substrate for visuomotor cognition. During this year our emphasis has shifted from exploration of the cortical targets of visuomotor thalamus, to thalamus itself. The ongoing experiments are designed to examine the degree to which thalamic signals related to high-order aspects of visuomotor behavior (e.g., decision-making, target selection, working memory) are the precursors to those present in frontal cortical target regions and as such, provide a test of the hypothesis that such signals are the product of cortico-subcortical interactions. During this year we have 1) recorded from three monkeys prepared for dual thalamic/frontal cortex recordings, shifting our emphasis from frontal cortex to central thalamus and begun to characterize thalamic neurons for the ability to contribute to forming perceptual decisions, selecting motor responses, and signaling reward contingency; 2) we have continued computational modeling efforts to incorporate both our behavioral and neurophysiological findings related to perceptual decision-making and, more recently, reward bias 3) we have completed analysis and submitted for publication (see below) results from a series anatomical tracer experiments designed to define the inputs to oculomotor thalamic nuclei and associated subcortical structures; 4) to better understand our findings relating to reward contingency, in one monkey we have begun to explore relationship between DA signaling and visuomotor stimulus coding. Some of this work has been published in abstract form (see below).

Neurophysiological recordings

Compelled-response paradigm reveals neural correlate of evolving perceptual decision in frontal cortex and thalamus Since the last progress report, we have shifted the majority of our efforts from the recording neurons in frontal cortex and have focused on exploration of thalamus in monkeys performing the compelled-saccade paradigm. The cortical findings have been published in abstract form (Costello MG, Massoglia DP and Stanford TR. (2006) Temporal correlates of saccadic choice accuracy in macaque frontal cortex. *Soc. Neurosci. Abstr.* **32**, Program No. 138.110) and we are in the process of preparing a manuscript detailing these results. Briefly, the compelled-saccade paradigm probes the time course of perceptuomotor decision-making by decoupling the perceptual decision from movement preparation. To do so, we compel the monkey to prepare and execute a saccade at various times during the evolving perceptual decision process in which a visual target must be differentiated from a distracter. As such, the probability of making a correct choice becomes a "read-out" of the state of the decision process. As reported previously, the behavioral findings are consistent with this hypothesis as we find that choice performance varies smoothly from chance to optimal over a period of approximately 100 ms; for perceptual processing times of less and 100 ms, monkeys perform at chance (i.e., in a 2 alternative task, they guess) while for processing times greater than 140 ms, performance approaches 100% correct. Between these extremes, performance improves gradually, indicative of an evolving decision signal. This paradigm has proven to be exceptionally revealing, both unmasking the covert process of the forming perceptual decision and differentiating between neurons that are involved in response selection versus those involved in perceptual discrimination. Our early findings suggest that visuomotor thalamus contains neurons with similar discrimination capabilities and provides preliminary support to the hypothesis that cortico-subcortical loops participate in the perceptual decision-making process. We anticipate presenting these findings at the 2008 meeting for the Society for Neuroscience.

Modeling the perceptual decision process As describe in the last progress report, the compelled saccade paradigm yields a behavioral dataset that is unique in revealing the covert process of perceptual decision-making. During the past year we have developed a model that accounts for the primary features of the behavioral data and, in addition, provided some predictions that we have begun to examine. The compelled saccade task is unique in that it exposes the fact that perceptual and motor processes are not strictly serial. As such, the model is novel in that it approximates the decision process with two separate races-to-threshold, one each for the perceptual and motor processes. The model successfully reproduces the main features of the behavioral data; reaction times remain stable and the probability that the monkey makes a correct choice depends on processing time and serves as a read-out of the current state of the decision process. Along with providing constraints for understanding the neural implementation of the decision process, the model makes qualitative and quantitative predictions about how behavior on the compelled task will be affected by the imposition of either a sensory or a motor bias – precisely the type of biases that that we are exploring in our neurophysiological studies of reward contingency (described below). We have adapted our reward bias paradigm to the compelled saccade task such that when the target appears in one location, a correct response is more highly rewarded than when it appears in the alternative location. Via its impact on the motor diffusion process, the model predicts that the motor bias induced by this reward-direction asymmetry will result in an increase in saccades to the more highly-rewarded direction even though this results in a lower percentage of correct (and thus rewarded) saccades. The model also predicts shorter RTs to the highly-rewarded direction and longer RTs to the low-rewarded one, across all processing times. We have trained a monkey on the biased task to validate these predictions and found good agreement between the monkey's performance and the model's predictions. In the future, we plan examine and behaviorally validate the model's performance under more complicated stimulus conditions (complex stimuli and more distracters) and ultimately begin to explore their neural correlates in thalamus and cortex. The initial version of the model has been published in abstract form (Shankar, S., Costello, M. G., Stanford, T. R. & Salinas, E. A diffusion model of the perceptual decision-making process in a Compelled-Saccade task. *Soc Neurosci Abstr.* **33**, Program No. 617.14 (2007)) and a manuscript of these findings is in preparation. Results from the more recent modeling efforts are currently being presented at the Twelfth International Conference on Cognitive and Neural Systems (ICCNS) at Boston University on May 14-17. An abstract of these findings has also been submitted for the 2008 meeting for the Society for Neuroscience.

Modulation of sensorimotor signals and behavior by reward probability We have observed profound effects of reward probability on the both behavior and on the activity of visuomotor neurons in cortical targets of visuomotor thalamus. We have completed a study of frontal cortex and are currently preparing a manuscript of these findings. In the meantime, we have switched our emphasis to a complementary study of neurons in visuomotor thalamus and data collection is proceeding steadily. Briefly, our analysis of cortical data has revealed what we believe to be more than one, seemingly independent, neural correlate of a biased behavioral decision process. Using a paradigm that manipulates the magnitude of reward associated with saccades to a particular stimulus, the principle behavioral effect is a decrease in reaction time to heavily reward goals and an increase in reaction time to lightly rewarded goals. As we previously reported, we find that sensory and motor-related responses of visuomotor neurons are generally increased for movement to the highly reward target and decreased for those the less rewarded goal. More specifically, however, we find that a neural correlate of the behavioral bias is present both within activity that *precedes* stimulus presentation and that which precedes the movement. Thus, there is reward-related anticipatory activity that is neither stimulus nor motor-linked. Thus, this cognitively derived anticipatory activity promotes actions to the “wrong” location on half of the trials (i.e., when the target is presented at the less rewarded location) and must be overcome to produce the correct movement. Using signal detection theory methods to evaluate the time course of target discrimination, we have shown that such anticipatory activity could indeed contribute to more rapid reaction times for saccades to highly rewarded locations and longer reactions times for saccades to less rewarded locations. Whether or not this putative substrate for mediating the influence of expected reward on perception and action has its origins in the cortico-subcortical loops is the focus of our ongoing complementary studies of neurons in visuomotor thalamus.

Perceptual decisions and dopamine (DA) signaling There is little doubt that reward contingencies have a powerful impact on the activity of visuomotor neurons. We have observed reward signaling and reward-related modulation of visuomotor activity at both the thalamic and cortical levels and recent studies from other laboratories indicate that along with striatum, motor thalamus receives a strong dopaminergic input. The prevailing theory of DA signaling, the reward prediction error hypothesis, posits that a short latency, phasic dopamine response found among neurons in the substantia nigra pars compacta (SNpc) predicts the reward value of visual stimuli and is therefore a key element in learning associations between stimulus, response, and reward outcome. While the reward prediction error hypothesis is compelling and widely accepted, our studies using the compelled saccade task suggest that this hypothesis is incompatible with the protracted time course over which perceptual decisions are formed within the brain. In short, we believe that the so-called short latency DA response occurs too soon to be informed by the outcome of the perceptual discrimination and thus cannot possibly predict the reward value of the visual stimulus. Noting several potential confounds in prior studies, we have trained one monkey on a simple visual discrimination task and using the same recording well as for our thalamic recordings, we intend to record from DA neurons. This study is designed to disambiguate the nature of the sensory evoked DA response and provides a critical test of the very influential reward prediction error hypothesis.

Anatomical studies

As noted in the prior progress report, we completed a series of anatomical experiments to provide information about the input/output circuitry of these thalamic regions and associated subcortical regions as an adjunct to our physiological studies. These studies are designed to show how the sensorimotor signals that we record in oculomotor thalamus relate topographically to the thalamic regions receiving input from the SC and to the thalamic regions providing output to the striatum. The first of these manuscripts detailing the anterograde projections of the SC to midbrain dopamine neurons has been submitted for publication (May, P. J. et al. (2008) Tectonigral Projections in the Primate: A Pathway for Pre-Attentive Sensory Input to Midbrain Dopaminergic Neurons. *J. Neuroscience* (submitted) and analysis of data relating to projections to the subthalamic nucleus and visuomotor thalamus are ongoing.

Significance

These ongoing studies remain at the forefront of those exploring the relationship between cortical and subcortical structures and the role of their interaction in guiding visuomotor behavior. These studies will be crucial to our understanding of the essential circuitry that links sensory information to motor actions via cognition. In the long term, we feel that these studies will provide critical insights into the mechanisms underlying sensorimotor disturbances ranging from hemi-neglect to Parkinson's Disease.

Plans

During Year 5 we will continue to record in single-unit activity in both the thalamus and cortex, but with major emphasis in thalamus. A primary objective is to complete several manuscripts that are currently in preparation and to complete data collection and analysis for complementary studies of the thalamus. These manuscripts will detail how decision, reward, and mnemonic signals in thalamus compare to those observed in cortex and provide essential insights into how cortical and subcortical structures interact.