## Progress Report Scanning Cover Sheet

# 5R01EY015271-04

PI Name: ANGELAKI, DORA
Org: WASHINGTON UNIVERSITY
Start Date: 08/01/2007
Snap: Y
Appl ID: 7270400
Rec'd Date: 05/07/2007

Form Approved Through 09/30/2007 — OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

# Grant Progress Report

| Review Group | Type | Activity | Grant Number |
|---|---|---|---|
| SMI | 5 | R01 | EY015271-04 |

Total Project Period
From: 08/01/2004 Through: 07/31/2008

Requested Budget Period
From: 08/01/2007 Through: 07/31/2008

1. TITLE OF PROJECT
Studies of Three-Dimensional Ocular Kinematics

MAY 0 7 2007

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR
(Name and address, street, city, state, zip code)
Angelaki, Dora E.
Department of Anatomy and Neurobiology
Washington University School of Medicine
660 South Euclid, Campus Box 8108
St. Louis, MO 63110

3. APPLICANT ORGANIZATION
(Name and address, street, city, state, zip code)
Washington University
660 South Euclid, Campus Box 8018
St. Louis, MO 63110

2b. E-MAIL ADDRESS
angelaki@pcg.wustl.edu

4. ENTITY IDENTIFICATION NUMBER

2c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Anatomy and Neurobiology

2d. MAJOR SUBDIVISION
01 School of Medicine

5. TITLE AND ADDRESS OF ADMINISTRATIVE OFFICIAL
Director, Grants and Contracts
Washington University
660 South Euclid, Campus Box 8018
St. Louis, MO 63110

E-MAIL: G&C@msnotes.wustl.edu

6. HUMAN SUBJECTS
☒ No ☐ Yes

6a. Research Exempt ☐ No ☐ Yes

6b. Human Subjects Assurance No.
FWA00002284

If Exempt ("Yes" in 6a):
Exemption No.

6c. NIH-Defined Phase III Clinical Trial ☐ No ☐ Yes

If Not Exempt ("No" in 6a):
IRB approval date — ☐ Full IRB or ☐ Expedited Review

7. VERTEBRATE ANIMALS
☐ No ☒ Yes

7a. If "Yes," IACUC approval Date
01/03/05

7b. Animal Welfare Assurance No.
A3381-01

8. COSTS REQUESTED FOR NEXT BUDGET PERIOD
8a. DIRECT $
8b. TOTAL $

9. INVENTIONS AND PATENTS
☒ No ☐ Yes If "Yes," ☐ Previously Reported ☐ Not Previously Reported

10. PERFORMANCE SITE(S) *(Organizations and addresses)*
Washington University School of Medicine
660 South Euclid, Campus Box 8108
St. Louis, MO 63110

11a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)*
Angelaki, Dora E.
TEL 314-747-5528
FAX 314-362-3446

11b. ADMINISTRATIVE OFFICIAL NAME *(Item 5)*
Michnowicz, John
TEL 314-747-4134
FAX 314-362-0315

11c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 14)*
NAME John Michnowicz
TITLE Director, Grants and Contracts
TEL 314-747-4134 FAX 314-362-0315
E-MAIL G&C@msnotes.wustl.edu

12. Corrections to Page 1 Face Page

13. 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 11c. *(In ink. "Per" signature not acceptable.)*
Acting for John Michnowicz

DATE 4/25/07

Principal Investigator/Program Director (Last, First, Middle): Angelaki, Dora E.

| **PROGRESS REPORT SUMMARY** | GRANT NUMBER<br>5 R01 EY015271-04 | |
|---|---|---|
| | PERIOD COVERED BY THIS REPORT | |
| PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR<br>Angelaki, Dora E. | FROM<br>08/01/06 | THROUGH<br>07/31/07 |
| APPLICANT ORGANIZATION<br>Washington University | | |
| TITLE OF PROJECT (Repeat title shown in Item 1 on first page)<br>Studies of Three-Dimensional Ocular Kinematics | | |

A. Human Subjects (Complete Item 6 on the Face Page)

Involvement of Human Subjects ☒ No Change Since Previous Submission ☐ Change

B. Vertebrate Animals (Complete Item 7 on the Face Page)

Use of Vertebrate Animals ☒ No Change Since Previous Submission ☐ Change

C. Select Agent Research ☒ No Change Since Previous Submission ☐ Change

D. Multiple PI Leadership Plan ☒ No Change Since Previous Submission ☐ Change

SEE PHS 2590 INSTRUCTIONS.

**WOMEN AND MINORITY INCLUSION: See PHS 398 Instructions. Use Inclusion Enrollment Report Format Page and, if necessary, Targeted/Planned Enrollment Format Page.**

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

**Two Grants Completed:**

NASA: NNA04CC77G "Multisensory interactions to discriminate gravity from translational accelerations" completed as of 06/30/07.

NIH: 1 S10 RR21169 "Human Motion System" completed as of 03/31/07.

**Two New Grants:**

NIH: 1 R01 DC007620 "Vestibular influences on spatial constancy and movement planning" 07/01/06 - 06/30/11.

NIH: 1 R01 EY017866 "Neural basis of self-motion perception" 02/01/07 - 01/31/12. See "current other support" page.

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.**

Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25 percent of the current year's total budget? **No.**

## OTHER SUPPORT

**ANGELAKI, Dora E.**

**ACTIVE**

5 R01 EY12814-08 (Angelaki) — 07/01/03 – 06/30/08 — 2.4 Cal Months
NIH/NEI — $272,319
**Neural Organization and Plasticity of the VOR**
This project characterizes the functional properties of the translational vestibuloocular reflex (VOR) and examines the properties of eye movement-sensitive neurons in the vestibular nuclei during lateral and fore-aft translation.

5 R01 DC04260-08 (Angelaki) — 09/01/04 - 08/31/09 — 1.2 Cal Months
NIH/NIDCD — $222,154
**Neural Mechanisms of Vestibular Function**
This project uses electrophysiological, neuroanatomical and behavioral approaches to study vestibular projections to the thalamus.

5 R01 EY015272-03 (Angelaki) — 08/01/04 – 07/31/08 — 2.4 Cal Months
NIH/NEI — $244,125
**Studies of three-dimensional ocular kinematics**
The proposed studies the role of premotor neurons, motoneurons and muscle mechanics in the three-dimensional properties and Listing's law for eye movements

1 R01 DC007620-01A1 (Angelaki) — 07/01/06-06/30/11 — 1.2 Cal Months
NIH/NIDCD — $321,011
**Vestibular Influences on Spatial Constancy and Movement Planning**
The major goal of this project is to characterize the functional properties and neural basis for subcortical extra-retinal signals on spatial constancy, with a particular focus on vestibulary-driven mechanisms.

1 R01 EY017866-01 (Angelaki) — 02/01/07-01/31/12 — 1.2 Cal Months
NIH — $250,000
**Neural Basis of Self-Motion Perception**
The major goal of this project is to understand the neural basis for multisensory cue integration pertinent to self-motion perception and spatial orientation.

**PENDING**
None

**OVERLAP**
None

***R01-EY15271, "Studies of three-dimensional ocular kinematics"***

### *A. SPECIFIC AIMS*

Our understanding of how the brain controls eye movements has benefited enormously from the comparison of neuronal activity with eye movements and the quantification of these relationships with mathematical models. Whereas this task has been very successful when considering eye movements in a single direction, much uncertainty and controversy have dominated oculomotor control in three-dimensions over the past decade. The debate has primarily been based on behavioral, imaging or modeling data, with very little effort being devoted to understanding the properties of single neurons in motor and premotor pathways. Furthermore, efforts were primarily focused on saccadic eye movements, with a paucity of neurophysiological studies on pursuit and the vestibuloocular reflex (VOR). The long-term goals of these studies are to provide a comprehensive characterization of oculomotor neural activities in 3D and to understand how different eye movements share common premotor circuitry but exhibit distinct kinematic properties. The current application proposes a series of systematic investigations of the responses from both motoneurons and premotor cells during both fast and slow eye movements, including saccades, pursuit, as well as the rotational and translational VOR (RVOR and TVOR). The motoneuron experiments (aim 1) are motivated by the 'active pulley hypothesis' (APH) which proposes that extraocular muscle pulleys are responsible for implementing the 'half-angle rule' of 3D eye rotations. According to APH, rectus pulleys provide for an eye position-dependent muscle pulling direction, thus accounting for the eye position-dependent torsional eye velocity necessary to keep the eyes in Listing's plane. The premotor neurophysiological experiments (aim 2) are motivated by recent preliminary results providing first-time evidence of torsional eye movement sensitivity in vestibular nuclei (VN) neurons during horizontal/vertical smooth pursuit at eccentric eye positions, suggesting the existence of a 3D neural controller for pursuit eye movements. Specifically, we propose the following aims:

Specific aim 1: We will characterize and compare neural activities of motoneurons as a function of gaze during small-amplitude, high-frequency VOR, smooth pursuit and saccades. We hypothesize that during eye movements that follow Listing's law (i.e., pursuit, saccades and the TVOR), there will be no neural correlate in the firing rates of superior/inferior oblique and superior/inferior rectus (collectively referred to as 'vertical/torsional') motoneurons of the eye position-dependent torsional eye velocity (half angle rule). This is so because, according to APH, the eye position-dependent torsional component is not due to a dynamic activation of motoneurons, but rather due to the eye position-dependent change in the pulling direction of the rectus muscles brought about by extraocular muscle pulleys. In contrast, these motoneurons are expected to exhibit sensitivity to torsional eye velocity during eye movements that do not follow Listing's law (e.g., the RVOR), because a neurally-generated dynamic torsion signal must offset the eye position-dependent change in the pulling direction of the rectus muscles.

Specific aim 2: We will characterize and compare the firing rates of different classes of eye movement sensitive neurons in the rostral vestibular nuclei (VN) during both pursuit and the VOR at different initial eye positions. The VOR will be studied during high frequency yaw/pitch rotations and lateral translations in complete darkness while trained animals maintain fixation on extinguished targets at different eccentricities. For pursuit eye movements, the eye position-dependence of neural activities will be studied during vertical and horizontal pursuit at different initial eye positions. We hypothesize that neural responses to pursuit exhibit significant eye position dependencies and that the axis of eye rotation that maximally excites the neurons during steady-state pursuit is 3D (rather than being restricted in the horizontal/vertical plane). We further hypothesize that complementary observations will also hold during head movements suggesting that pursuit and the VOR use a common coordinate system.

### *B. STUDIES AND RESULTS*

We are in the process of completing all stated aims of the original grant. In a first study *(Ghasia and Angelaki, Neuron 2005)* we have recorded motoneuron activities during pursuit and the VOR (aim 1). We found that vertical/torsional motoneuron activities do not carry the necessary torsional signal for the non-commutative driven torsion during pursuit eye movements. These results argue against a neural implementation of 3D kinematics. These conclusions have further been supported during electrical stimulation of the abducens nerve, where we found that the evoked eye movement follows the half-angle rule *(Klier et al., J. Neuroscience 2006)*. Both of these studies have provide robust neurophysiological evidence that the half-angle rule is implemented by the eye plant (aim 1). During the past year, we have been recording from different premotor areas (vestibular nuclei, prepositus hypoglossi, interstitial nucleus of Cajal, cerebellar flocculus/ventral paraflocculus), in order to directly compare the eye position-dependence during smooth pursuit with those of extraocular motoneurons. This work has been presented in abstract form *(Dickman et al. SFN 2006)* and we are currently in the process of preparing a manuscript for publication.

Funds from this grant have also been partially used to complete the 3D characterization of ocular following responses *(Adeyemo and Angelaki, J. Neurophysiology 2005)* and the dependence on the TVOR on spatial attention *(Wei and Angelaki, J. Neuroscience 2006)*. Finally, funds have also been used to partially support studies of the role of vestibular signals in memory saccades and spatial updating *(Klier et al., J. Neurophysiology 2005; 2006; Li et al., J. Neurophysiology 2005)*. Finally, we have also recently investigated whether the visuospatial updating mechanism takes into account the non-commutativity of rotations, as previously shown for the VOR. We used a visuospatial updating task to investigate whether saccades to remembered visual targets are accurate after intervening, whole-body rotational sequences. The sequences were reversed, either yaw-then-roll or roll-then-yaw, such that the final required eye movements to reach the same space-fixed target were different in each case. While each subject performed consistently irrespective of target location and rotational combination, we found great inter-subject variability in their updating ability. Nevertheless, subjects made eye movements to distinct final endpoint locations. However, the distance between these endpoints was, on average, less than half that predicted by perfect non-commutativity, suggesting that the brain maybe approximating the correct non-commutative endpoints. This work has been submitted to the Journal of Neurophysiology *(Klier et al., J. Neurophysiology 2007)*.

### *C. Significance*

Results from these experiments will provide fundamental information needed to understand the mechanical and neural aspects of eye movement control in three dimensions. The first aim seeks for the first time to provide a direct neurophysiological test of the hypothesized action of the extraocular muscle pulleys that has so far been based solely on imaging and theoretical studies. The second aim will provide a thorough quantitative test for the existence of a 3D (as opposed to 2D) neural controller during pursuit and the VOR. These two hypotheses (i.e., the APH and the existence of a 3D neural controller) are not contradictory, contrary to popular beliefs for the opposite. We believe that, by providing a thorough quantitative and systematic neurophysiological investigation of these issues, the proposed studies will help resolve the controversies of the past decade by providing the missing link between behavioral studies, imaging and modeling. Furthermore, by quantitatively comparing neural data with existing or appropriately-modified and expanded mathematical models of 3D eye movement control, we hope to achieve as good an understanding of the relationships between neuronal activities and 3D eye movements as those currently existing for one-dimensional oculomotor control.

### *D. Plans*

There are no modifications to the original plans or specific aims. We expect to complete all aims during the coming year.

### *E. Publications*

Recent abstracts of unpublished work:

Dickman, J.D., Ghasia F.F., Meng H., Watanabe S. and Angelaki D.E. (2006) Do premotor neurons carry 2D or 3D signals during pursuit eye movements?, *Soc. Neurosci. Abstr.* 32, Atlanta GA.

### *F. Project Related Resources*

None.

Principal Investigator/Program Director (Last, First, Middle): Angelaki, Dora E.

# KEY PERSONNEL REPORT

Place this form at the end of the signed original copy of the application. Do not duplicate.

**GRANT NUMBER**
5 R01 EY015271-04

**All Key Personnel for the Current Budget Period (do not include Other Significant Contributors)**

| Name | Degree(s) | SSN (last 4 digits) | Role on Project (e.g. PI, Res. Assoc.) | Date of Birth (MM/DD/YY) | Months Devoted to Project | | |
|---|---|---|---|---|---|---|---|
| | | | | | Cal | Acad | Sum |
| Angelaki, Dora E. | Ph.D. | | P.I. | | 2.4 | | |

Please Note: There was a typographical error made in reporting T&E for Angelaki in prior years.
T&E expended on this grant has been as per original application.