PI: **Mysore, Shreesh P**	Title: Multisensory competition and spatial selection: Neural circuit and computational mechanisms	
Received: 02/03/2016	FOA: PA13-302	Council: 10/2016
Competition ID: FORMS-C	FOA Title: RESEARCH PROJECT GRANT (PARENT R01)	
1 R01 EY027718-01	Dual: DC	Accession Number: 3898667
IPF: 4134401	Organization: JOHNS HOPKINS UNIVERSITY	
Former Number: 1R01MH111728-01	Department: PSYCHOLOGICAL AND BRAIN SCIENC	
IRG/SRG: SPC	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 270,123 Year 2: 294,811 Year 3: 298,646 Year 4: 308,685 Year 5: 318,936	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: Y Early Stage Investigator: Y
Senior/Key Personnel:	*Organization:*	*Role Category:*
Shreesh Mysore	Johns Hopkins University	PD/PI

OMB Number 4040-0001
Expiration Date 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier** MD: Maryland

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED 2016-02-03

Application Identifier 00081683

5. APPLICANT INFORMATION **Organizational DUNS*:** 001910777

Legal Name*: Johns Hopkins University
Department: PSYCHOLOGICAL AND BRAIN SCIENC
Division: KRIEGER SCHOOL OF ARTS & SCIEN
Street1*: 3400 N. Charles Street, N600 Wyman Park Building
Street2: Business and Research Administration
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 21218-2685

Person to be contacted on matters involving this application
Prefix: First Name*: Nancy Middle Name: R Last Name*: Kerner Suffix:
Position/Title: Sponsored Project Administrator
Street1*: 3400 N Charles St
Street2: Wyman Park Bldg N600
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 21218-2686
Phone Number*: 4105167111 Fax Number: Email: nkerner1@johnshopkins.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1520595110A5

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY* NATL INST OF HEALTH

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE: Research Project Grant (Parent R01)

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Multisensory competition and spatial selection: Neural circuit and computational mechanisms

12. PROPOSED PROJECT
Start Date* 09/01/2016
Ending Date* 08/31/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
MD-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Shreesh Middle Name: Pranesh Last Name*: Mysore Suffix:
Position/Title: Assistant Professor
Organization Name*: Johns Hopkins University
Department: PSYCHOLOGICAL AND BRAIN SCIENC
Division: KRIEGER SCHOOL OF ARTS & SCIEN
Street1*: 3400 N Charles St
Street2: Ames Hall Rm 232
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 21218-2685
Phone Number*: 4105166706 Fax Number: Email*: smysore1@johnshopkins.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$2,340,291.28
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$2,340,291.28
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Nancy Middle Name: R Last Name*: Kerner Suffix:
Position/Title*: Sponsored Project Administrator
Organization Name*: Johns Hopkins University
Department: ARTS & SCIENCES DEAN'S OFFICE
Division:
Street1*: 3400 N Charles St
Street2: Wyman Park Bldg N600
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 21218-2686
Phone Number*: 4105167111 Fax Number: Email*: nkerner1@johnshopkins.edu

Signature of Authorized Representative*
Kerner, Nancy R

Date Signed*
02/03/2016

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:M-13_RRSF424_Cover_Letter.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Johns Hopkins University
Duns Number:	001910777
Street1*:	[redacted]
Street2:	Business and Research Administration
City*:	Baltimore
County:	
State*:	MD: Maryland
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	21218-2685
Project/Performance Site Congressional District*:	MD-007

File Name

Additional Location(s)

Funding Opportunity Number: PA-13-302. Received Date: 2016-02-03T11:02:07.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ❍ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ❍ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ● No

IACUC Approval Date: 09-09-2014

Animal Welfare Assurance Number A3272-01

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	M-7_Project_Summary.pdf
8. Project Narrative*	M-3_Narrative.pdf
9. Bibliography & References Cited	M-6_Bibliography_and_References_C ted.pdf
10.Facilities & Other Resources	M-4_Facilities.pdf
11.Equipment	M-5_Equipment.pdf

Funding Opportunity Number: PA-13-302. Received Date: 2016-02-03T11:02:07.000-05:00

Project Summary

Animals are constantly exposed to a barrage of multisensory input from their stimulus-rich environments. They handle this informational complexity by having their behavior guided by the most physically salient (or more generally, the most important) stimulus source in the environment. The identification of the most physically salient stimulus occurs through neural mechanisms of stimulus competition, which must necessarily operate across sensory modalities and across spatial locations. Although the mechanisms of multisensory integration have been studied extensively, the circuit and computational principles underlying competition within and across sensory modalities are largely unknown. Recent evidence from behaving monkeys has revealed the midbrain superior colliculus (SC) as being critical for normal competitive stimulus selection. In parallel, our recent work in the barn owl optic tectum (OT, the avian homolog of the SC) has revealed special neural response properties, namely categorical signaling of the strongest stimulus, that can account for the SC's critical role in selection behavior. Inhibition from a GABAergic midbrain nucleus, the isthmi pars magnocellularis (Imc), is necessary to mediate these response properties. Nonetheless, the computational and mechanistic logic of Imc function in service of competitive stimulus selection remain unknown. Here, we propose to systematically unravel fundamental computations orchestrated by the Imc-OT network for multisensory competition, and to map their implementation explicitly onto circuit elements. Specifically, we first aim to elucidate how the reliable signaling of the strongest stimulus in the presence of noise, i.e, "robust" signaling, is implemented. Our hypothesis is that special donut-like patterns of spatial inhibition from the Imc to the OT play a central role. Second, we aim to understand if the Imc is an active computational locus for stimulus competition in the OT. Our hypothesis is that competitive interactions within the Imc control the accuracy and strength of categorization by the OT. Third, we ask how the OT resolves competition in cluttered sensory scenes that contain several stimuli. Our hypothesis is that a dynamic inhibitory balance among the multiple competing locations protects OTid responses from being driven to zero and permits network wide decoding of the strongest stimulus. We will test the hypotheses using *in vivo* electrophysiology and drug iontophoresis in awake, head-fixed barn owls together with computational modeling. In all cases, we will explicitly test whether the hypothesized mechanisms of competition generalize across sensory modalities. Preliminary data from the three aims support our hypotheses. They indicate that results from the proposed experiments have the power to reveal strategic principles of circuit organization for executing the sophisticated computations that subserve multisensory competition and stimulus selection.

Project Narrative

Selecting the most important information in a stimulus-rich world is a fundamental function that the brain must perform. It is an essential part of cognitive abilities such as attention, decision-making, and perception, and is disrupted in several psychiatric disorders including ADHD and schizophrenia. This proposal will uncover fundamental principles by which the brain processes competing stimuli and reliably selects the strongest one, both within and across sensory modalities. Results from this work will contribute to an improved understanding of psychiatric conditions that are associated with abnormal processing of complex sensory scenes.

FACILITIES

The Johns Hopkins University and the Department of Psychological and Brain Sciences have made a major commitment to the establishment of my lab, including PI-designed lab space and a total startup-funding package of over $1.1M (not including lab renovation costs, summer salary support, confocal time, and backstop funding for a postdoctoral scholar for 3 years). Our lab suite is approximately 1500 square feet and is located in [redacted]). Renovations of the lab space were completed about a year ago and we have since been using the space. We have five testing rooms for our experiments, a surgery room with two surgery suites, one BSL-2 rated room with a biosafety cabinet for viral injections, a room for electronics, electrodes and equipment testing, and separate area for bench work (two rows). Our vivarium is conveniently located [redacted]

The lab has separate office space large enough to seat 8 members, a small lounge area, and a shared conference and kitchen area. The department has a full-time grant manager, accounting staff and a secretary, and computer support is provided by a full-time IT professional.

A state-of-the art Integrative Imaging Center (a shared microscopy facility) is available in [redacted] for visualization of IHC samples, confocal imaging, and anatomical tracing. Our department also administers a central neurogenetics and behavior core that is available for use by all neuroscience researchers on campus. We have an excellent in-house machine shop that provides us truly exceptional manufacturing support.

SCIENTIFIC ENVIRONMENT

The Hopkins neuroscience community is world-class. Our lab is located amidst several neuroscience labs that share our interest in behavioral and systems neuroscience. Some labs are located adjacent to us in [redacted]) while others are located in nearby buildings within a few minutes walking distance [redacted] etc). The Mind-Brain Institute and the Department of Biology both contain research labs doing cutting-edge neuroscience and they are located next door to us. In addition, the Department of Neuroscience and the Brain Science Institute are located in the medical school campus a shuttle ride away. This environment allows us to be steeped in neuroscience research and is absolutely wonderful.

The academic environment at Hopkins is highly collegial, collaborative and nurturing. [redacted], both senior faculty in the department, are my official faculty mentors. Not only have I been benefiting from their mentorship, but other senior faculty in the department have also been extremely generous with their time and expertise. Their advice has been invaluable as I have been setting-up my lab, starting an independent research program, hiring lab personnel and beginning to write grant applications.

The department offers multiple regular forums for the presentation and discussion of data. There are also numerous seminar series in our department and across campus (such as the Bodian seminars) in areas related to the proposed research: behavioral neuroscience, neurophysiology, sensory neuroscience, cognitive neuroscience, and cellular neuroscience.

The intellectual atmosphere on the Hopkins campus is wonderfully stimulating and will provide a highly supportive environment for building the research program described here.

EQUIPMENT

Electrophysiology rig
We have set-up one head-fixed electrophysiology rig for owl experiments, which includes a sound proof recording booth (IAC), a 65” monitor for presenting visual stimuli, an din ear headphones. In addition, we have a 3-axis microdrive controller (Newport) that allows for the remote and independent positioning of three electrodes.

32-ch neural recording system (TDT)
We have a 32-channel high performance neural recording system (TDT) along with a system for the delivery of high fidelity auditory stimuli (TDT). We have been successfully using this rig, and have obtained preliminary data for the proposed aims.

Iontophoresis system
We currently use a 1-channel iontophoresis box (DAGAN) to eject (retain) drug in one barrel of a glass electrode.

Computers
Each member of the lab has their own high-end computer for data analysis, as well as word processing and other software.

Surgery suite
We have a fully operational surgical suite.

Imaging facility
As part of my start-up package, I have been provided with 1500 hours of free confocal microscope time in this facility that can be used during the first three years of my position (this consideration ends 9/1/2016).

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix:	First Name*: Shreesh	Middle Name Pranesh	Last Name*: Mysore	Suffix:

Position/Title*:	Assistant Professor
Organization Name*:	Johns Hopkins University
Department:	PSYCHOLOGICAL & BRAIN SCIENCES
Division:	KRIEGER SCHOOL OF ARTS & SCIE
Street1*:	3400 N Charles St
Street2:	Ames Hall Rm 232
City*:	Baltimore
County:	
State*:	MD: Maryland
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	21218-2685

Phone Number*: 4105166706 Fax Number: E-Mail*: smysore1@johnshopkins.edu

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	ID-00168603_BN-1_BIOSKETCH pdf
Attach Current & Pending Support:	

Tracking Number: GRANT12078532
Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Mysore, Shreesh Pranesh

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor of Psychological and Brain Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Indian Institute of Technology, Madras	B. Tech.	06/97	Mechanical Engineering
Pennsylvania State University	M.S.	06/99	Industrial Engineering
Pennsylvania State University	M.A.	06/00	Mathematics
California Institute of Technology	Ph.D.	06/07	Control & Dynamical Systems (Minor: Neurobio)
Stanford University	Postdoctoral scholar	08/11	Neurobiology
Stanford University	Basic Life Science Research Associate	08/13	Neurobiology

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

My research interests are to discover the circuit and cellular mechanisms underlying complex cognitive behaviors such as scene processing, attention and decision-making, both in normal and in disease states. I have had a highly interdisciplinary educational training cutting across engineering, mathematics, and neurobiology. In addition, my research training has been both diverse and intensive, including: (1) *in vivo* electrophysiological recordings and neural inactivation (iontophoretic and optogenetic) in midbrain and forebrain structures for the study of the neural basis of selection, (2) design of advanced signal processing tools for the analysis of complex datasets, and (3) computational neural modeling. The current application builds logically on these strengths. Importantly, it builds on my recent postdoctoral work, which laid a solid foundation for examining midbrain mechanisms of competition in owls, and opened up several exciting questions (three of which are the focus here). My background, skills, and direct expertise with the proposed research system and techniques make me ideally suited to carry out the work successfully.

a. **Mysore SP**, and Knudsen EI (2011). Flexible categorization of relative stimulus strength by the optic tectum. *J Neurosci. 31:7745-52*. PMID: 21613487.
b. **Mysore SP**, Knudsen EI (2012). Reciprocal inhibition of inhibition: A circuit motif for flexible categorization in stimulus selection. *Neuron 73: 193-205.* PMID: 22243757. *[Previewed in Neuron] [Faculty of 1000 pick]*
c. **Mysore SP**, Knudsen EI (2013). A shared inhibitory circuit for both exogenous and endogenous control of stimulus selection. *Nat Neurosci 6(4):473-8.* PMID: 23475112. *[Previewed in Nat. Rev. Neurosci]*
d. **Mysore SP**, Knudsen EI (2014). Descending control of neural bias and selectivity in a spatial attention network: Rules and mechanisms. *Neuron 84(1):214-26*. PMID: 25220813. [*Covered in ScienceDaily*]

B. Positions and Honors

Positions and Employment

11/2006-8/2011 Postdoctoral Scholar, Neurobiology, Stanford University (Dr. Eric Knudsen)

9/2011-8/2013	Basic Life Science Res. Assoc., Neurobiology, Stanford University (Dr. Eric Knudsen)
9/2013-present	Assistant Professor, Psychological and Brain Sciences, Johns Hopkins University

Other Professional Experience and Memberships

2003	FSL/Freesurfer course for fMRI data analysis, Los Angeles.
2003	NEURON Simulation Course, UCSD.
2003	Mathematical Modeling in Neuroscience Workshop, Santa Fe Institute.
2004-	Member, Society for Neuroscience
2007-	Review Editor, Frontiers in Neural Circuits
2011	Short course in optogenetics, Stanford University.

Honors and Awards

2000-2001	Engineering and Applied Sciences Fellowship, California Institute of Technology.
2003	Travel award, Workshop on Theoretical Neuroscience, Cold Spring Harbor Lab.
2003	Travel award, Mathematical Modeling Workshop, Santa Fe Institute.
2005	1st place poster (shared), 12th Joint Symposium on Neural Computation.
2005	Travel grant for Intl Joint Conf. on Neural Networks, IEEE Computational Intelligence Soc.
2005	Finalist, Harvard Society of Fellows Junior Fellowship (2006-2009).
2006	Science and Technology Council Postdoctoral Fellowship, Princeton University (decl.)
2008	Postdoctoral fellow travel award, Society for Neuroscience (administered by C-WIN).
2008,2009	Dean's Postdoctoral Fellowship, Stanford University School of Medicine.
2009	1st place poster, Stanford Neuroscience Institute (SINTN).
2012	Finalist, Sammy Kuo award for postdoctoral research excellence, Stanford (SINTN)
2013	Finalist, MQ Fellows Programme (UK)

C. Contribution to Science

1. My early work as a doctoral candidate investigated the mechanisms of structural plasticity in the brain. With experiments, I studied the dynamics of dendritic spines in dissociated rat hippocampal neurons, and their regulation by a cell-adhesion molecule, N-cadherin. Using viral GFP expression, time-lapse confocal microscopy, voltage clamp recordings and a probabilistic approach for spine analysis, I showed that brief disruption of N-cadherin results in a massive loss of functional spines, and that metrics of spine motility early after disruption predict the later fate of individual spines. I also designed software for the automated 3D analysis of the distributions of proteins in immunostained samples, a tool that is currently being used in several laboratories.

   In parallel, with computational modeling of spiking neurons, I analyzed the computational steps leading to rewiring in the barn owl brain following prism exposure. My results identified a novel potential trigger for the onset of structural plasticity. They also revealed that from the perspective of computational complexity, structural plasticity is a qualitatively different algorithm than synaptic plasticity.

   a. **Mysore SP** and Quartz SR (2005). Modeling structural plasticity in the barn owl auditory localization system with a spike-time dependent Hebbian learning rule, *Proc. IJCNN, Montreal, 5: 2766-2771.*
   b. Tai C-Y, **Mysore SP**, Chiu C and Schuman EM, 2007. Activity-regulated N-cadherin endocytosis, *Neuron, 54(5):771-785.* PMID: 17553425.
   c. **Mysore SP**, Tai C-Y and Schuman EM, 2007. Effects of N-cadherin disruption on spine morphological dynamics, *Front Cell Neurosci, 1: 1-14*. PMID: 18946519.
   d. **Mysore SP**, Tai C-Y, Schuman EM (2008). N-cadherin, spine dynamics, and synaptic function, *Frontiers in Neuroscience, 2: 168-175.* PMID: 19225589

2. Subsequently, as a postdoctoral scholar, I transitioned to examining how neural circuits handle multiple, competing streams of information in real-time. I investigated the neural representations of competing stimuli in the owl optic tectum (**OT**, analog of the mammalian superior colliculus), a midbrain structure important for controlling spatial attention. **(A)** Using extracellular recordings, I discovered that the OT flexibly categorizes two competing stimuli based on their relative strength into "stronger" vs. "other" (independently of sensory modality). This categorization is expressed in neural responses by means of powerful all-or-nothing competitive suppression whose magnitude is controlled with exquisite sensitivity by

relative stimulus strength. **(B)** In addition, I showed that an animal's internal goals can substantially improve the quality of categorization in the OT. Thus the OT categorizes stimuli based not just on their physical strength, but rather, on a combination of stimulus strength ("bottom-up" property) and internal goals associated with the stimulus ("top-down" property). These results provided the first synthetic explanation of striking behavioral deficits that have been reported following SC inactivation in monkeys performing selection tasks.

a. **Mysore SP***, Asadollahi A*, and Knudsen EI (2010). Global inhibition and stimulus competition in the owl optic tectum. *J Neurosci. 30: 1727-1738*. PMID: 20130182.
b. Asadollahi A, **Mysore SP** and Knudsen EI (2010) Stimulus-driven competition in a cholinergic midbrain nucleus. *Nat Neurosci. 13: 889-895*. PMID: 20526331.
c. **Mysore SP**, Asadollahi A, Knudsen EI (2011) Signaling of the strongest stimulus in the owl optic tectum. *J Neurosci 31: 5186-5196.* PMID: 21471353. *[Cover article][Covered in Nature News].*
d. **Mysore SP**, Knudsen EI (2014). Descending control of neural bias and selectivity in a spatial attention network: Rules and mechanisms. *Neuron 84(1):214-26*. PMID: 25220813. [*Covered in ScienceDaily*]

3. With additional experiments, I began investigating circuit mechanisms underlying categorization in the OT. **(A)** Using the technique of reversible neural inactivation, I demonstrated that a specialized GABAergic nucleus in the midbrain, the Imc, is entirely responsible for both bottom-up and top-down global competitive suppression of neural responses in the OT. These experiments led to a particularly exciting finding in answer to a long-standing open question: do bottom-up and top-down control of sensory processing *share* neural circuits? **(B)** In parallel, with computational modeling, I identified a novel, anatomically grounded circuit motif for implementing flexible categorization, namely, reciprocal inhibition of lateral inhibition. This motif implements categorization faster and more reliably than all previously proposed circuits for selection. I further demonstrated (collaboratively) that in accordance with model predictions, such a circuit motif indeed exists within the **Imc**.
   a. **Mysore SP**, Knudsen EI (2012). Reciprocal inhibition of inhibition: A circuit motif for flexible categorization in stimulus selection. *Neuron 73: 193-205.* PMID: 22243757. *[Previewed in Neuron] [Faculty of 1000 pick]*
   b. **Mysore SP**, Knudsen EI (2013). A shared inhibitory circuit for both exogenous and endogenous control of stimulus selection. *Nat Neurosci 6(4):473-8.* PMID: 23475112. *[Previewed in Nat. Rev. Neurosci]*
   c. Goddard CA, **Mysore SP**, Bryant AS, Huguenard JR, Knudsen EI (2014). Spatially reciprocal inhibition of inhibition within a stimulus selection network in the avian midbrain, *PLoS One 9(1):e85865.* PMID: 24465755

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1r5T2XgGqk6kw/bibliograpahy/48057725/public/?sort=date&direction=ascending

D. Research Support

List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). Begin with the projects that are most relevant to the research proposed in the application. *Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.*

Ongoing Research Support

09/2013 – open
Departmental Start-up Grant, Johns Hopkins University
Role: PI
Research goals: The purpose of this grant is to set up my laboratory and to support preliminary research investigating neural circuits and computations that underlie complex cognitive behavior.

07/2014 –
Science of Learning Institute, Johns Hopkins University,
Role: Co-PI (with 3 other Johns Hopkins PIs)

06/2016 *Research goals:* The overall goal of the project is to study perceptual learning in the sensory (barrel) cortex of mice. My role is to develop novel tools for the analysis of population neural dynamics in mice (observed optically using genetically encoded Ca^{++} sensors).

Completed Research Support

None.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Johns Hopkins University

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Shreesh	Pranesh	Mysore		PD/PI	[redacted]	[redacted]	0	0	29,004.90	9,861.67	38,866.57

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **38,866.57**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12	0	0	48,240.00	9,310.32	57,550.32
1	Graduate Students	12	0	0	30,150.00	2,306.48	32,456.48
0	Undergraduate Students	0	0	0	0.00	0.00	0.00
0	Secretarial/Clerical	0	0	0	0.00	0.00	0.00
1	Other	12	0	0	28,140.00	9,567.60	37,707.60
0	Other Professionals	0	0	0	0.00	0.00	0.00
0	Allocated Admin Support	0	0	0	0.00	0.00	0.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**127,714.40**

Total Salary, Wages and Fringe Benefits (A+B) **166,580.97**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	Funds Requested ($)*
1 . Minolta Luminance Spectrometer	5,000.00
2 . Zeiss Operating Microscope	8,000.00
3 . DAGAN 6400 MultiChannel Iontophoresis box	10,000.00
4 . B&K Sound Level Meter	5,000.00
Total funds requested for all equipment listed in the attached file	
Total Equipment	**28,000.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other: Other		0.00
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	44,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Other Direct Costs	23,542.00
9 . All Other Costs	0.00
Total Other Direct Costs	**67,542.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**270,122.97**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	62	232,380.97	144,076.20
		Total Indirect Costs	**144,076.20**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	US Department of Health and Human Services, Steven Zuraf (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**414,199.17**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: M-12_S2S_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Johns Hopkins University

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Shreesh	Pranesh	Mysore		PD/PI	[redacted]	[redacted]	0	0	29,875.05	10,157.52	40,032.57

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **40,032.57**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12	0	0	49,687.20	9,589.63	59,276.83
2	Graduate Students	24	0	0	61,204.50	4,682.15	65,886.65
0	Undergraduate Students	0	0	0	0.00	0.00	0.00
0	Secretarial/Clerical	0	0	0	0.00	0.00	0.00
1	Other	12	0	0	28,984.20	9,854.63	38,838.83
0	Other Professionals	0	0	0	0.00	0.00	0.00
0	Allocated Admin Support	0	0	0	0.00	0.00	0.00
4	**Total Number Other Personnel**					**Total Other Personnel**	**164,002.31**

Total Salary, Wages and Fringe Benefits (A+B) **204,034.88**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other: Other		0.00
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12078532 Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	44,000.00
2. Publication Costs	3,000.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Other Direct Costs	35,776.00
9 . All Other Costs	0.00
Total Other Direct Costs	**82,776.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**294,810.88**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	62	274,742.88	170,340.58
		Total Indirect Costs	**170,340.58**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	US Department of Health and Human Services, Steven Zuraf (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**465,151.46**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: M-12_S2S_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Johns Hopkins University

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Shreesh	Pranesh	Mysore		PD/PI	[redacted]	[redacted]	0	0	30,771.30	10,462.24	41,233.54

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **41,233.54**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12	0	0	51,177.82	9,877.32	61,055.14
2	Graduate Students	24	0	0	63,040.64	4,822.61	67,863.25
0	Undergraduate Students	0	0	0	0.00	0.00	0.00
0	Secretarial/Clerical	0	0	0	0.00	0.00	0.00
1	Other	12	0	0	29,853.73	10,150.27	40,004.00
0	Other Professionals	0	0	0	0.00	0.00	0.00
0	Allocated Admin Support	0	0	0	0.00	0.00	0.00
4	**Total Number Other Personnel**					**Total Other Personnel**	**168,922.39**

Total Salary, Wages and Fringe Benefits (A+B) **210,155.93**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other: Other		0.00
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12078532 Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	44,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Other Direct Costs	36,490.00
9 . All Other Costs	0.00
Total Other Direct Costs	**80,490.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**298,645.93**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	62	277,975.93	172,345.08
		Total Indirect Costs	**172,345.08**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	US Department of Health and Human Services, Steven Zuraf (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**470,991.01**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: M-12_S2S_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Johns Hopkins University

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Shreesh	Pranesh	Mysore		PD/PI	[redacted]	[redacted]	0	0	31,694.44	10,776.11	42,470.55

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **42,470.55**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12	0	0	52,713.15	10,173.64	62,886.79
2	Graduate Students	24	0	0	64,931.86	4,967.29	69,899.15
0	Undergraduate Students	0	0	0	0.00	0.00	0.00
0	Secretarial/Clerical	0	0	0	0.00	0.00	0.00
1	Other	12	0	0	30,749.34	10,454.78	41,204.12
0	Other Professionals	0	0	0	0.00	0.00	0.00
0	Allocated Admin Support	0	0	0	0.00	0.00	0.00
4	**Total Number Other Personnel**					**Total Other Personnel**	**173,990.06**

Total Salary, Wages and Fringe Benefits (A+B) **216,460.61**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other: Other		0.00
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12078532 Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	44,000.00
2. Publication Costs	3,000.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Other Direct Costs	37,224.00
9 . All Other Costs	0.00
Total Other Direct Costs	**84,224.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**308,684.61**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	62	287,394.61	178,184.65
		Total Indirect Costs	**178,184.65**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	US Department of Health and Human Services, Steven Zuraf (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**486,869.26**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: M-12_S2S_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: Johns Hopkins University

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Shreesh	Pranesh	Mysore		PD/PI	[redacted]	[redacted]	0	0	32,645.27	11,099.39	43,744.66

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **43,744.66**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12	0	0	54,294.54	10,478.85	64,773.39
2	Graduate Students	24	0	0	66,879.81	5,116.31	71,996.12
0	Undergraduate Students	0	0	0	0.00	0.00	0.00
0	Secretarial/Clerical	0	0	0	0.00	0.00	0.00
1	Other	12	0	0	31,671.82	10,768.42	42,440.24
0	Other Professionals	0	0	0	0.00	0.00	0.00
0	Allocated Admin Support	0	0	0	0.00	0.00	0.00
4	**Total Number Other Personnel**					**Total Other Personnel**	**179,209.75**

Total Salary, Wages and Fringe Benefits (A+B) **222,954.41**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other: Other		0.00
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12078532 Funding Opportunity Number: PA-13-302 . Received Date: 2016-02-03T11:02:07.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Johns Hopkins University

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	44,000.00
2. Publication Costs	6,000.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8 . Other Direct Costs	37,982.00
9 . All Other Costs	0.00
Total Other Direct Costs	**87,982.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**318,936.41**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	62	297,006.41	184,143.97
		Total Indirect Costs	**184,143.97**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	US Department of Health and Human Services, Steven Zuraf (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**503,080.38**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: M-12_S2S_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

DIRECT COSTS
Personnel

Salaries and Wages – Key Personnel

- The Principal Investigator, Shreesh P. Mysore, PhD will devote [redacted]) each year. He will supervise and train personnel in recording, iontophoresis, surgery, data analysis, and computational modeling. The PI will be responsible for overall project direction and coordination, for assuring successful project completion, including submission of progress reports, as required. He will be directly involved in all aspects of these projects, including data collection, analysis, and publication.

Salaries and Wages – Other Personnel

- A postdoctoral researcher (PD) has been budgeted at 12 calendar months of effort per year. This person will be trained by the PI, and will be responsible for Aim 2 (see Table 1).
- One research technician has been budgeted at 12 calendar months of effort per year. This person will be trained by the PI and will assist in all experiments. Their duties will include maintenance of owl breeding colony and owl feeding, histology, assisting in surgery, recording, and general laboratory management.
- One graduate student (GS1) has been budgeted at 12 calendar months of effort per year, 9 months during the academic year and support for 3 summer months. This person will be trained by the PI, and responsible for Aim 1 and 3a (see Table 1).
- A second graduate student (GS2) has been budgeted at 12 calendar months of effort per year, 9 months during the academic year and support for 3 summer months, starting in Year 2. This computationally adept student will be trained in experimental techniques by the PI, and will take the lead on modeling in Aims 1 and 3. They will also perform experiments for Aim 3b (see Table 1).

Fringe Benefits: Fringe Benefits are calculated at The Johns Hopkins University's standard rates of 34% for faculty and staff, 19.3% for postdocs, and at 8% for graduate students during summer only.

Aim	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
1			GS1(e)	GS1(e)	GS1(e)+ GS2(m)
2a	PD(e)	PD(e)			
2b			PD(e)	PD (e+m)	PD
3a	GS1(e)	GS1(e) + GS2 (m)			
3b			GS2(e)	GS2(e+m)	

Table 1. Summary of duties of personnel. *PD: postdoc; GS1: grad student #1; GS2: grad student #2; 'e': experiments; 'm': modeling. The timeline of aims and the assignment of personnel to them has been designed so that mentees start by learning the more readily tractable experimental skills, and then moving on to more difficult experimental questions and modeling. Each color of shading represents a different expected publication (4 total); the papers resulting from Aims 1 and 3 will each be co-authored by GS1 and GS2. The PI will be involved in all aspects of Aims 1-3.*

Materials and Supplies

Drug/Histology supplies ($5,000): Drugs for iontophoresis, general histological supplies, including staining chemicals (Nissl, antibodies), and tracers (dextrans), microscope slides, cover slips, slide boxes, dry ice, glassware, etc.
Surgery supplies ($6,000): General surgical supplies, including anesthetic agents, antibiotics, sterile gloves and pads, syringes, bone wax, sterile blades, dental acrylic, bone screws, illuminator bulbs, etc.
Recording supplies ($12,000): Tungsten and glass electrodes for recording and iontophoresis, respectively. Also, multichannel silicon probes (from Neuronexus); equipment to construct recording chambers; general

electronics supplies, such as cables, connectors, wire, boxes, etc. for maintenance of equipment and construction of other small devices.
Owl housing and food ($21,000): Housing for 20 owls per year (including 4 breeding pairs), and purchase of food (frozen rats from Rodentpro).

Publication Costs
Funds are requested to cover publication and illustration expenses such as page charges, reprint costs, color figure charges, publication materials, slides, posters, and design costs.

Service Center Costs
Funds are requested for in-house machinist to help design and manufacture various custom parts for head-fixed electrophysiology rig.

Computer Services
Funds are requested each year for data management costs, including archiving and sharing data. The following provides a description of the data products that will be collected as part of this proposal. I anticipate that we will generate upwards of 500 GB of data per year, and share about 25 GB – 50 GB.
Electrophysiological data: consisting of raw voltage signals sampled at 25 kHz, spike times, spike waveforms, and LFPs, processed spike counts, spectra, and spectrograms. Data will be in MATLAB's ".mat" format (and if necessary, also in text format). Meta data will include sampling rate, electrode impedances, electrode type and configuration, identity of recording/amplifying electronics equipment, and state of anesthesia of animal.
Protocols: Experimental protocols, instrument manuals, software package descriptions, and details of vendors for materials and supplies. In addition, when applicable, short videos illustrating key tricks or tips (for instance, for pulling glass electrodes for iontophoresis) will also be recorded. This is inspired by the usefulness of the videos in the Journal of Visualized Experiments.
Analysis programs: Custom programs in MATLAB used for data analysis along with standard documentation within the programs.

Travel
Domestic Travel: Funds are requested in Years 1-5 to cover travel cost for PI, postdoctoral researcher and graduate students to present results at the annual Society for Neuroscience meeting. This includes costs to cover airfare, accommodations, per diem, etc.

Graduate Student Tuition and Insurance
JHU graduate research assistantships include funding for 20% of the graduate tuition and 100% of graduate health insurance plan costs, for which funds are requested from NIH according to standard Univeristy rates.

Equipment
Funds are requested for the purchase of:
Multi-channel iontophoresis box (DAGAN 6400): to allow simultaneous loading of more than one drug into multi-barrel iontophoresis electrodes. This will permit efficient testing of multiple drugs to cross-validate effects of iontophoresis.
Spectrophotometer (Minolta) and Sound meter (B&K): Calibrations are currently being done with meters from neighboring labs. Having meters in lab on a permanent basis will be more convenient.
Operating microscope (Zeiss): The PI has performed all the surgeries, thus far, and an operating microscope has not been necessary because of his experience. Going forward, because the students, the postdoc and the technician will be trained to perform their own surgeries as part of the proposed work, the use of an operating microscope will facilitate their learning process and improve surgery quality.

INDIRECT COSTS
The indirect cost rate for Johns Hopkins University is 62 percent of the Modified Total Direct Costs (MTDC) base, excluding tuition, equipment, off-campus facilities, and the portion of subcontracts over $25,000. This charge has been approved by the cognizant government agency, the Department of Health and Human Services, represented by Darryl Mayes, Deputy Director of the Division of Cost Allocation. This rate was approved on June 18, 2015.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		206,347.89
Section B, Other Personnel		813,838.91
Total Number Other Personnel	19	
Total Salary, Wages and Fringe Benefits (A+B)		1,020,186.80
Section C, Equipment		28,000.00
Section D, Travel		40,000.00
1. Domestic	40,000.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		403,014.00
1. Materials and Supplies	220,000.00	
2. Publication Costs	12,000.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	171,014.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,491,200.80
Section H, Indirect Costs		849,090.48
Section I, Total Direct and Indirect Costs (G + H)		2,340,291.28
Section J, Fee		0.00

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*: Shreesh
Middle Name: Pranesh
Last Name*: Mysore
Suffix:

2. Human Subjects

Clinical Trial? ● No ○ Yes
Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

Funding Opportunity Number: PA-13-302. Received Date: 2016-02-03T11:02:07.000-05:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	M-8_PHS_ResearchPlan_SpecificAims.pdf
3. Research Strategy*	M-11_PHS_ResearchPlan_ResearchStrategy.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	
6. Inclusion of Women and Minorities	
7. Inclusion of Children	
Other Research Plan Sections	
8. Vertebrate Animals	M-9_PHS_ResearchPlan_VertebrateAnimals.pdf
9. Select Agent Research	M-14_PHS_ResearchPlan_SelectAgentResearch.pdf
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	
13. Resource Sharing Plan(s)	
Appendix (if applicable)	
14. Appendix	

SPECIFIC AIMS

Despite the critical importance of stimulus competition and sensory selection to most adaptive behaviors, the underlying neural algorithms and their circuit implementations are not well understood. A multisensory-motor hub in the vertebrate midbrain called the optic tectum (OT, or superior colliculus in mammals), and specifically, its intermediate and deep layers (or OTid), play a major role in these processes. Our past work in barn owls has revealed that an evolutionarily conserved collection of GABAergic neurons in the midbrain tegmentum, called the isthmi pars magnocellularis (Imc), is essential for controlling the representations of competing stimuli in the OTid. Here, we will deconstruct the functional logic of the Imc-OT circuit and examine how it implements fundamental computations for multisensory competition and selection. Specifically, we will ask (a) how stimulus competition that is robust to noise is achieved in the OTid, (b) whether competition within the Imc contributes to categorical signaling of the strongest stimulus by the OTid, and (c) how competition in cluttered environments (with numerous competing stimuli) is resolved by the OTid. We will address these questions with neurophysiological experiments in the awake, head-fixed barn owl, and with computational modeling.

AIM 1. Determine whether robust stimulus competition in the OTid is achieved by donut-like spatial patterns of inhibition from the Imc. The OTid signals the stronger stimulus between two competing stimuli robustly, i.e., in a manner resistant to sensory and neural noise. Our theoretical simulations predict that robust OTid signaling can be achieved through a special pattern of inhibition from the Imc to the OTid: one that is “donut-like”, with a “hole” sparing just the portion of the OT that provides input to the Imc. To test for such a pattern of inhibition, we will extracellularly record the responses of OTid neurons to stimuli (visual and auditory) without or with simultaneous iontophoretic inactivation of Imc neurons. We will target OTid neurons with RFs matching that of the Imc neuron, as well as mismatched, to measure, respectively, the strengths of self- vs. competitive inhibition in the OTid. *Hypothesis*: *Self-inhibition driven by Imc neurons will be substantially weaker than competitive inhibition driven by them, for both visual and auditory stimuli.* Next, using a computational model of the circuit that incorporates the observed pattern of inhibition, and ideal observer analysis, we will compare the actual robustness of OTid signaling with the theoretically optimal prediction. Results will unpack the computational strategy used by the Imc-OT circuit for robust sensory selection in the presence of noise.

AIM 2. Determine whether Imc neurons show competitive interactions between spatially separated stimuli, and whether these interactions contribute to the categorical signaling of the stronger stimulus by the OTid. Representations of competing stimuli in the OTid depend critically on inhibitory input from the Imc. However, it is not known if the Imc passively drives inhibition to the OTid that then constructs these representations, or whether the Imc itself constructs them. To test this, we will extracellularly record the responses of Imc neurons to a sensory stimulus (visual or auditory) inside the spatial receptive field (RF), while simultaneously presenting a distant competitor stimulus. *Hypothesis 2a*: *Imc neurons exhibit signatures of stimulus competition (both within and across modalities).* Next, to test the specific contribution of competition within the Imc to signaling of the strongest stimulus by the OTid, we will record competitive responses in the OTid without or with simultaneous inactivation of competition within the Imc using focal drug iontophoresis. Our computational modeling predicts that competition within the Imc shapes categorical signaling by the OTid very specifically. *Hypothesis 2b*: *Competition within the Imc controls the accuracy and strength of the categorical signal of the strongest stimulus in the OTid.*

AIM 3. Determine how the OTid resolves competition among several (more than two) stimuli. The above aims construct a detailed mechanistic picture of competition between two stimuli. However, sensory environments are typically complex, containing *several* (>2) competing stimuli. To test if (and how) the OTid resolves such competition, we will record the responses of neurons across the OTid space map to several sensory stimuli (visual or auditory). The number and the relative strengths of the stimuli will be systematically varied. Through previously developed single site and network-wide analyses, we will examine how the number of stimuli affects the decoding of the strongest stimulus from individual OTid sites versus from network activity patterns. Both firing rates and response latencies will be examined. *Hypothesis 3a: Unlike competition between just two stimuli, the location of the strongest among several competing stimuli cannot be unambiguously decoded from the responses of individual OTid neurons. Instead, network-wide decoding is essential.* Literature suggests that increasing the number of stimuli can progressively drive SCid responses to zero, potentially abolishing its ability to signal the strongest stimulus in cluttered scenes. To examine the limits in SCid/OTid’s ability to resolve competition, we will measure asymptotic values of different properties of competitive responses in the OTid as a function of number of stimuli, and incorporate these results into a computational model. *Hypothesis 3b: Although some OTid neurons exhibit floor effects (consistent with literature), others do not, allowing for reliable signaling of the strongest stimulus in complex scenes.*

SIGNIFICANCE

Essential to most adaptive behaviors is an animal's ability to process sensory scenes containing numerous competing stimuli, and to identify the most important stimulus to guide behavior. Much research has carefully examined the neural encoding of individual sensory stimuli, and great strides have been made in dissecting the neural bases of multisensory integration [4], i.e., the process by which stimuli of different sensory modalities occurring at the same spatial location potently modulate neural responsiveness. However, the circuitry and mechanisms underlying competition (and selection) among multiple stimuli across space are poorly understood.

A common observation across animal species is that stimulus competition manifests in neural activity as response suppression [6-15]. Several brain regions have been implicated in the underlying processes, including several cortical and subcortical areas (such as the lateral intraparietal area, visual cortex, prefrontal cortex, the superior colliculus, pulvinar and thalamus [16-22]). Among these, a midbrain isthmo-tectal network has emerged as a rich neural substrate to study the mechanisms of multisensory competition and selection [23,24]

The midbrain isthmo-tectal network. This network, found in all classes of vertebrate species from fish to mammals, includes the superior colliculus (SC, or optic tectum, OT, in non-mammals), and interconnected nuclei in the midbrain tegmentum *(Fig. 1)* [1,2,25-27]. These nuclei include a group of specialized GABAergic neurons called the periparabigeminal lateral tegmental nucleus (or isthmi pars magnocellularis, Imc, in non-mammals), and a group of specialized cholinergic neurons called the parabigeminal nucleus (or isthmi pars parvocellularis, Ipc, in non-mammals).

The superior colliculus (abbreviated as SC/OT here), is a major sensorimotor hub. It plays a vital role in multisensory processing and in directing an animal's gaze towards a highly salient or behaviorally relevant stimulus in the sensory environment [28-35]. The intermediate and deep layers of the SC (abbreviated as SCid/OTid) contain topographic maps of multisensory (and motor) space [24,36]. Neurons in the SCid/OTid respond with higher firing rates to stimuli of higher salience (such as higher contrast, greater speed of motion, louder sounds, etc) [24,37], while not being systematically tuned for the features of the stimuli (such as orientation, direction of motion, etc) [38,39]. (In addition, these responses are known to be modulated by endogenous signals [40,41].) The isthmic nuclei, also contain topographic maps of space [42-46], but their functional properties and roles in sensory processing are far less well studied; work to date implicates them broadly in stimulus selection [22,47,48].

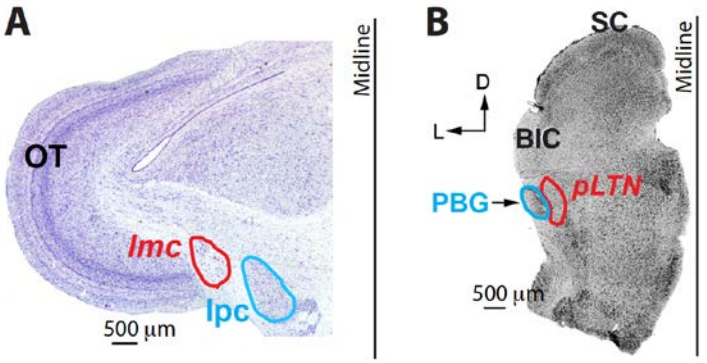

Figure 1. The isthmo tectal network. A) *Coronal section through barn owl midbrain showing the OT, Imc and Ipc. .* ***B)*** *Coronal section[5] through rodent midbrain showing the SC, pLTN[25] and PBG[5] (analogs of the avian OT, Imc, and Ipc, respectively).*

The isthmo-tectal network and stimulus competition. Several lines of evidence demonstrate a causal role for the SCid/OTid in stimulus competition and selection. When monkeys are presented with multiple competing stimuli, focal electrical microstimulation of the SCid biases selection behavior in favor of the stimulus location encoded by the microstimulation site [31,49-51]. Furthermore, recent work has now demonstrated a necessary role for the SC/OT in competitive stimulus selection. Inactivation of the intermediate and deep layers of the SCid in behaving monkeys severely impairs their ability to select a target among relevant distracters [17,52,53]. Thus, intact representations of competing stimuli in the SCid are critical for normal sensory competition and selection. (The resulting selection signal from the midbrain is thought to combine with forebrain signals to drive behavior[16,17,54].)

Categorical signaling of the strongest stimulus in the OTid. Clues about the neurophysiological and circuit bases of these SCid-dependent deficits in stimulus competition have emerged, in parallel, from my recent postdoctoral work in the barn owl OTid[3,9,48,55-57]. The experiments used a "competition protocol" (Fig. 2A) in which two sensory stimuli were presented simultaneously: one inside the receptive field (RF) of an OTid neuron and the other, far outside ("competitor"; presented ~ 30º away). We found that responses of OTid neurons to the RF stimulus are powerfully suppressed by the presence of a distant competitor (Fig 2BC). This response suppression operates globally, occurring independently of the location of the competitor, and it generalizes across sensory modalities, occurring whether the competing stimuli are visual or auditory[9]. Notably, the magnitude of response suppression increases with the strength of the competitor (Fig. 2B). In a

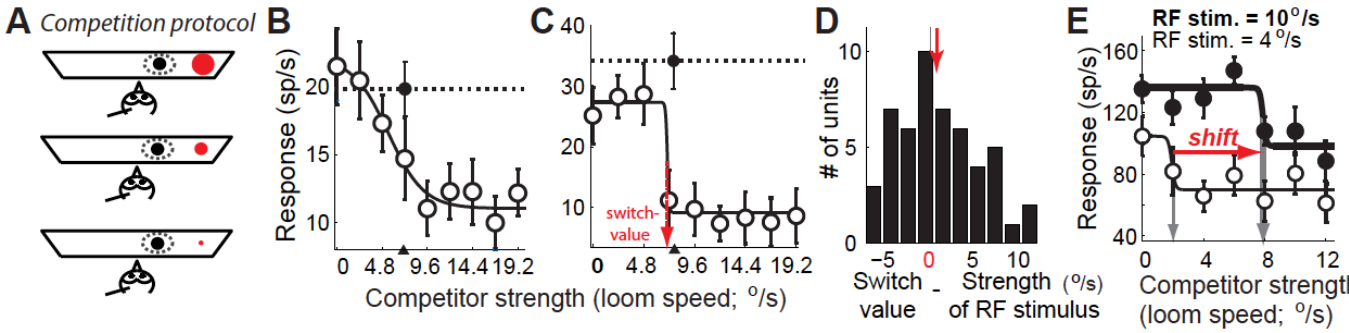

Figure 2. Neural correlates of competitive stimulus selection in the owl OTid[56]. A) *Schematic of "competition protocol" showing a head-fixed (but awake) owl, a tangent visual screen and electrode in the OTid. Dotted oval: receptive field (RF); black dot: RF stimulus of fixed strength (here, speed of visual loom); gray dot: distant competitor of varying strength. Size of dot schematizes strength of stimulus.* ***B-C)*** *Competitor strength response profiles (**CRPs**) of example OTid neurons measured using competition protocol. (B) Gradual competitive suppression. (C) Switch-like competitive suppression; switch-value is indicated. Black triangle: strength of the RF stimulus.* ***D)*** *Across neurons, switch-value ~= RF stimulus strength.* ***E)*** *Switch-value of an example neuron shifts adaptively[56] with strength of RF stimulus.*

sub-population of OTid neurons, this suppression increases in an abrupt (or "switch-like") manner (Fig. 2C). We found that the competitor strength that causes this abrupt change in responses, called "switch-value" (Fig. 2C), equals the strength of the RF stimulus on average (Fig. 2D). Moreover, it shifts adaptively when the strength of the RF stimulus is changed (Fig. 2E). Such switch-like responses occur both within and across sensory modalities. Remarkably, they can account for the pattern of behavioral deficits observed in primates after SC inactivation[58]. Notably, although only 30% of OTid neurons respond in a switch-like manner, the pattern of activity across the OTid network categorizes stimuli based on their relative strength into "stronger" or "other" (Fig. 3). The OTid, thus, categorically signals the stronger of the competing stimuli[3,59], both within and across sensory modalities, thereby facilitating multisensory selection.

Imc generates competitive inhibition. We found that the GABAergic Imc neurons (Fig. 4AB) are the source of long-range competitive suppression underlying categorization in the OTid (Fig. 4C-E): Focal blockade of activity in the Imc abolished all competitive response suppression in the OTid[48]. This role of the Imc is independent of sensory modality. Thus, competitive inhibition provided by the Imc, a nucleus that is conserved across all vertebrates [2,25,27] is necessary for creating the representations of competing stimuli in the OTid. (Separately, the cholinergic Ipc, serves to amplify the representation of the selected stimulus and predictively codes its location [22,45,60].)

These findings have identified the isthmo-tectal circuit as an excellent site in the brain at which to dissect the mechanistic underpinnings of stimulus competition. Here, we propose to uncover precise mechanisms in this circuitry that orchestrate specific, sophisticated neural computations for multisensory competition and sensory selection.

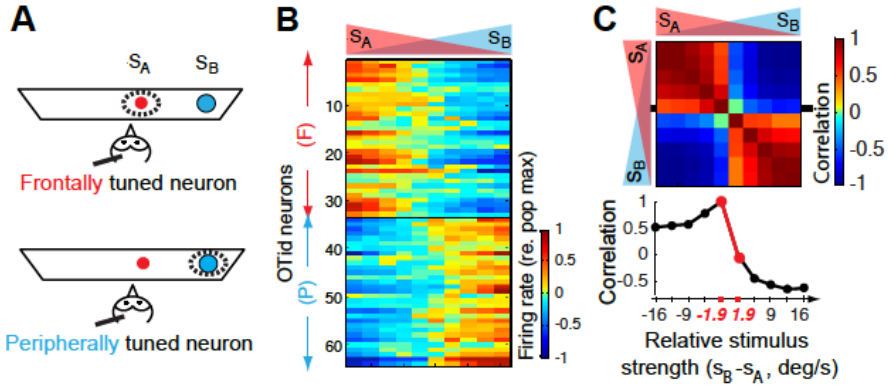

Figure 3. Network-wide categorical signaling of the stronger stimulus by the owl OTid [3]. A) *Schematic of "morphing" stimulus protocol: Strength of s_A is systematically decreased, while that of s_B is increased. Dashed ovals: RFs of frontally tuned (top) or peripherally tuned (bottom) OTid neurons.* ***B)*** *Mean-centered responses from 33 frontally tuned (F) and 31 peripherally tuned (P) neurons organized as a matrix: Each row represents a neuron, each column represents the network response pattern corresponding to a particular relative stimulus strength value.* ***C)*** *Top: Correlation matrix showing pair-wise correlations between OTid network response patterns at different relative strengths (i.e., different columns of B). Bottom: Horizontal transect through correlation matrix at location indicated in top panel, showing abrupt, categorical change in the response pattern around relative strength=0.*

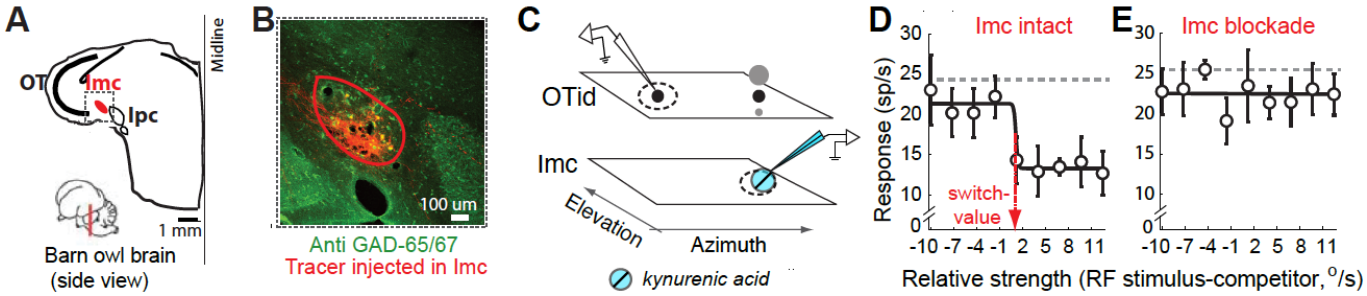

Figure 4. Imc inactivation abolishes competitive inhibition in the OTid[48]. A) *Schematic showing key isthmo-tectal nuclei in owl midbrain.* ***B)*** *Immunofluorescence image showing that Imc neurons are GABAergic. Red: dextran tetramethyl rhodamine tracer injected iontophoretically into the Imc; green: GAD-65/67 staining; yellow: double labeled (red + green) Imc somata.* ***C)*** *Schematic of experimental design showing the standard stimulus competition protocol that measures the CRP (same as in Fig. 2A). In addition, a second iontophoresis electrode is positioned in the Imc.* ***D)*** *Example OTid neuron showing switch-like responses to competition protocol (Fig. 2A). Strength: loom-speed; Dashed line: Responses to RF stimulus alone.* ***(E)*** *Focal inactivation of the portion of Imc that encodes the competitor abolishes switch-like competitive suppression in the OTid[48].*

INNOVATION

Our recent discovery of categorical, cross-modal signaling of the strongest stimulus by the OTid[3,56], and of the Imc as the primary source of long-range competitive inhibition in the OTid[48] have opened up several innovative questions at the mechanistic level. In addressing three of them, this proposal reveals neural principles of multisensory selection at a high level of computational and neural resolution:

1) *Investigation of robust neural computations*: Robustness is a core design principle for reliable computations in the presence of noise. Aim 1 will test the novel hypothesis that a specialized circuit strategy is used by the Imc circuit to achieve stimulus competition and neural selection of the strongest stimulus that is resistant to noise: namely, a donut-like spatial pattern of inhibition.
2) *Investigation of neural implementation of categorization*: Categorical responses have been found in brain areas across species [61]. Aim 2 will test an explicit mechanistic principle for neural microcircuits to control the location of the category boundary and its precision (or sharpness). In doing so, it will investigate a clear computational rationale for the considerable biological "cost" involved in creating apparently redundant long-range connections and GABAergic synapses within the Imc.
3) *Investigation of correlates of competition in cluttered scenes*: Aim 3 will examine whether the rules for decoding competition between two stimuli extend automatically to competition among three or more stimuli. It will explore the novel hypothesis that by balancing the increase in the number of sources that drive competitive inhibition to any location, with the decrease in the net effectiveness of each stimulus source via mutual inhibition, the network may continue to signal the strongest stimulus even as the number of stimuli increases.
4) *Avian system:* This proposal is also innovative in its choice of the avian model system to address the above questions. The exquisite organization of the avian isthmo-tectal network, the wealth of neuroanatomical information available, the recent body of novel findings (from owls, pigeons and chickens), and the strong potential link to other vertebrates owing to the evolutionary conservation of the isthmo-tectal circuit, all speak to the possibility of accelerated discovery of key mechanisms and broad, cross-species implications. This is especially germane because the fundamental neural computations underlying multisensory selection, and their specific circuit implementations, are not yet well understood in any model system.

APPROACH

AIM 1. Determine whether robust stimulus competition in the OT is achieved by donut-like spatial patterns of inhibition from the Imc.

Rationale: An essential property that must be implemented by neural circuits engaged in stimulus competition and selection is robustness to sensory and neural noise. Specifically, the circuit must signal the strongest stimulus accurately even when competing stimuli are close in strength (sensory ambiguity), and in spite of trial-to-trial variability in neural responses (neural noise). The OTid indeed signals the stronger of two competing stimuli robustly, and it does so by differentially enhancing its responses to the stronger stimulus over the responses to the other competing stimulus [56]. How is this achieved?

Our theoretical simulations predict that for a circuit (such as the OTid) in which stimulus competition is mediated by competitive inhibition, a simple and efficient way to facilitate differential neural representation is for the strongest stimulus (and, operationally, each stimulus) to suppress others more strongly that it suppresses itself, i.e., for competitive inhibition to be much stronger than self-inhibition. Consider two putative neurons encoding locations distant from one another. Let s_1 and s_2 be the competing stimuli driving them, respectively. The responses of the neurons can be written as:

$$r_1(s_1,s_2) = \mathbf{f}\,(e(s_1) - i_{self}(s_1) - i_{comp}(s_2)) \qquad \textit{(eqn. 1A)}$$
$$r_2(s_1,s_2) = \mathbf{f}\,(e(s_2) - i_{self}(s_2) - i_{comp}(s_1)) \qquad \textit{(eqn. 1B)}$$

Here, r is the firing rate of each neuron, f is its input-output function, $e(s_p)$ is the excitatory drive due to stimulus s_p (p=1 or 2), $i_{self}(s_p)$ is the self-inhibition due to s_p and $i_{comp}(s_p)$ is the competitive inhibition due to s_p. Because the neurons encode two distant locations, each neuron is driven by only one of the two stimuli, with the other being outside its spatial receptive field. The amount of inhibition produced by a stimulus is typically proportional to its strength [9,62], and for our purposes here, can be taken to be proportional to the excitatory drive it produces:

$$i_{comp}(s_p) = k_{comp} * e(s_p),\ \text{and}\ i_{self} = k_{self} * e(s_p);\ p=1 \text{ or } 2 \qquad \textit{(eqn. 2)}$$

Here, k_{comp} and k_{self} are constants representing the strengths of competitive and self-inhibition, respectively. As a result, equations (1) reduce to:

$$r_1(s_1,s_2) = \mathbf{f}\,(e(s_1)*(1-k_{self}) - k_{comp}*e(s_2)) \qquad \textit{(eqn. 3A)}$$
$$r_2(s_1,s_2) = \mathbf{f}\,(e(s_2)*(1-k_{self}) - k_{comp}*e(s_1)) \qquad \textit{(eqn. 3A)}$$

Simulating the responses of the two neurons at different k_{self} values demonstrates that $k_{self}=0$ produces robust signaling of the stronger stimulus (Fig. 5A-D).

From a mechanistic perspective, how might the computational strategy of $k_{self}=0$ (or, more generally, $k_{self} << k_{comp}$) be actually implemented in the Imc-OTid circuitry? Imc neurons are known to receive input from a focal portion of the OT (specifically, a focal portion of layer 10; OT_{10}), but to send their inhibitory output back *broadly across* spatial locations encoded in the OTid (layers 11-15)[2] (Fig. 6 &7A). In parallel, Imc neurons also suppress broadly the collection of cholinergic neurons in the midbrain tegmentum, the Ipc[1] (Fig. 6B; in blue), which are known to potently amplify OTid activity through point-to-point recurrent connectivity[45]. Together, these two pathways of inhibition (direct and indirect, respectively) allow the Imc to effectively suppress the OTid representations of competing stimuli at distant locations.

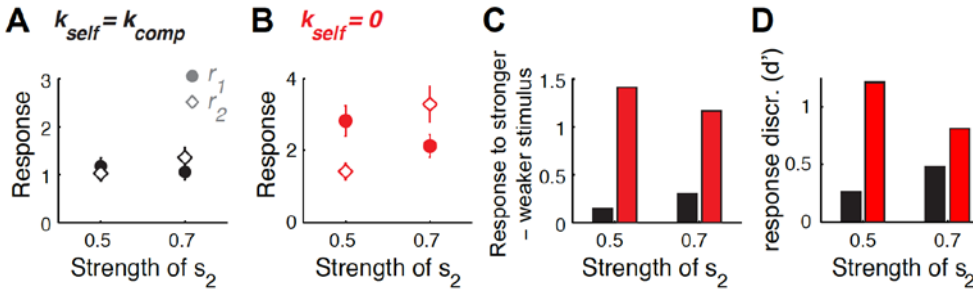

Figure 5. Modeling showing that robust competitive signaling of the stronger of two stimuli can be achieved with self-inhibition being much smaller than competitive inhibition. (A-D) *Simulation of equations (3). The input-output function f is assumed to be a standard sigmoid (based on experimental measurements in the OTid [9]): $f(x) = c + s/(1+e^{(-(x-d)*m)})$ with c=0 (min. response), s=2.5 (max. response), d = 0.4 (x-value that produces half-max response), and m=20 (max. slope parameter). Strength of s_1 = 0.6, k_{comp} = 0.3.* ***(A)*** *Responses of the two neurons when the strength of s_2 is close to that of s_1 (s_2 = 0.5 or 0.7) with $k_{self} = k_{comp}$, or with* ***(B)*** *$k_{self}=0$.* ***(C)*** *Difference between responses to the stronger vs. weaker stimulus under sensory ambiguity (i.e., when s_1 and s_2 are close in strengths). Plot shows that $k_{self}=0$ produces greater difference between (mean) responses. Black: $k_{self} = k_{comp}$; red: $k_{self} = 0$.* ***(D)*** *Discriminability (d') of the stronger stimulus from the weaker one in the presence of neural noise (Gaussian). $k_{self}=0$ (red) produces better discriminability of the stronger stimulus.*

However, a uniform back-projection pattern from the Imc to the OT that includes "self"- inhibition (of the OT location providing input), cannot, by definition, implement the proposed computational strategy for robustness. In contrast, a donut-like spatial pattern of inhibition exerted by each Imc neuron, with a "hole" in the back-projection sparing just the portion of the OT providing input, will implement the desired strategy (Fig. 6 and 7AB: if the connections indicated by the dashed lines were weak or absent). Anatomical tracing studies[1] have suggested that such a pattern might exist in the projections between the Imc and the OT. However, no functional evidence exists to date. Perhaps more importantly, whether the indirect, and arguably more potent pathway, involving the Ipc exhibits a donut-like anatomical/functional pattern is not known.

Here, we will directly test the spatial pattern of net functional inhibition from the Imc onto the OTid with an approach that takes into account the contributions of both pathways at once (Fig. 7CD). In addition, we will incorporate these experimental results into a detailed, biologically grounded computational model of the circuit shown in Figure 7 (see Methods). With this model, we will compare the actual efficiency of competitive selection in this circuit in the presence of noise (using ideal observer analysis; d'_{act}), with the theoretically optimal efficiency assuming zero self-inhibition (d'_{opt}).

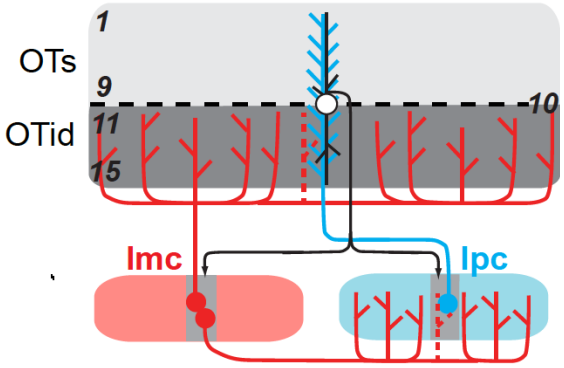

Figure 6. Anatomical connectivity within the isthmo-tectal circuit [1,2]. *Known connectivity between OT (grey), Imc (red), and Ipc (blue) in birds. Dashed lines: connections whose existence is not certain. The GABAergic Imc receives focal input from the OT_{10}, but projects broadly back across the OTid and the Ipc. The cholinergic Ipc receives focal input from OT_{10} and projects back in a focal manner to just the OT location providing input.*

Experimental Design & Methods: General experimental methods will follow previously published procedures [48,56]. Briefly, extracellular neural recordings will be made in passive, but awake, head-fixed barn owls (both genders) using a 5MΩ tungsten electrode. Both visual stimuli (high-contrast looming visual dots) and auditory stimuli (broadband noise bursts) will be used for measurements. The visual looming stimulus will be presented on a computer monitor in front of the owl and its strength controlled by setting its loom speed. The auditory stimulus will be delivered through miniaturized, in-ear microphones, and its strength controlled by setting its auditory binaural level (ABL).

To measure the strength of *self-inhibition* due to the Imc, we will first record extracellularly the responses of OTid neurons to a single sensory stimulus (visual or auditory) inside the RF (Fig. 7C; recording icon). Responses will be measured spatial tuning curves. We will then repeat this measurement while focally blocking the activity of the Imc neurons that also encode the stimulus, i.e., a matched Imc neuron (Fig. 7C, inactivation icons). Blockade of stimulus–evoked Imc activity will be achieved by the iontophoresis of a pan-glutamate receptor blocker (kynurenic acid) using a multi-barrel glass electrode. The difference in OTid responses between the Imc-intact and the Imc-inactivated conditions will estimate the strength of self-inhibition exerted by the Imc neuron. (No change in responses will indicate zero self-inhibition by Imc.)

To measure the strength of "distant", *competitive inhibition* exerted by the same Imc neuron, we will move the OT electrode to a portion of the OTid map that encodes a distant spatial location (Fig. 7D); the Imc electrode will stay in place. We will record the responses of the OTid neuron to a spatial tuning curve centered around its RF, in the absence or presence of a second, competitor stimulus presented simultaneously within the RF of the Imc neuron (Fig. 8A: top vs. bottom panels). Comparing OTid responses in the absence vs. presence of the competitor will yield an estimate of the strength of competitive inhibition due to the Imc neuron in question [9,48]. We will then repeat these measurements following Imc inactivation (Fig. 8E: top vs. bottom panels). This will help verify that the Imc neuron is the source of competitive inhibition (consistent with our published work [48]), and additionally, serve as a positive control to verify that drug iontophoresis works at the Imc site in question. (Experimentally, because finding an OTid site mismatched with the Imc site is easier than finding a matched OTid site, we will first estimate competitive inhibition, and then self-inhibition.)

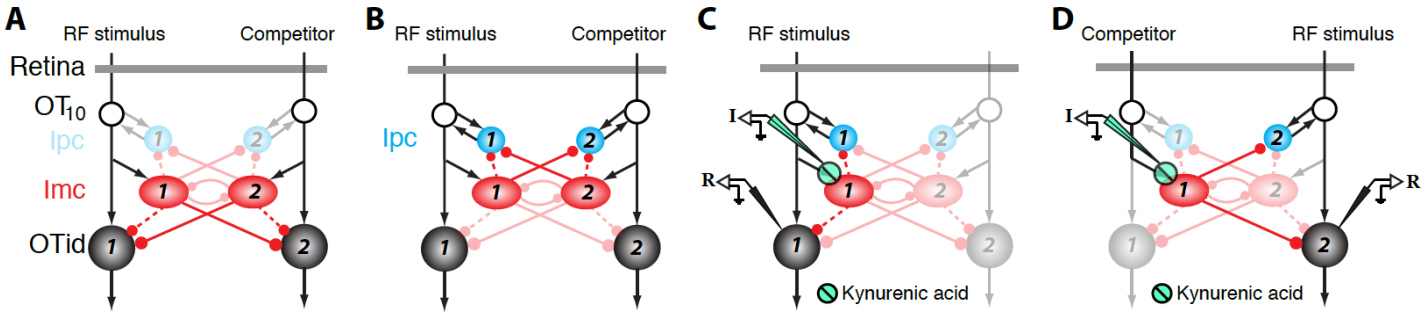

Figure 7. Design of Aim 1: Schematic of the connectivity between the OT, Imc, and Ipc; basis of computational model. *Each column of neurons encodes a different spatial channel; two channels are shown. Black arrows: excitatory input; red arrows: inhibitory input. Dashed lines: connections whose existence is not certain. Ghosted elements: portions of circuit not immediately relevant.* ***(A)*** *Imc-OT connectivity.* ***(B)*** *Ipc connectivity added in.* ***(C)*** *Experimental design for testing "self-inhibition". R: Extracellular recording electrode*

in the OTid; I: Combined iontophoresis + recording electrode in the Imc; filled cyan circle: blockade of excitatory synaptic input to the Imc. Blockade of input to the Imc silences both direct and indirect (Ipc) pathways. ***(D)*** *Experimental design for testing "distant-inhibition". Strengths of RF stimulus in (C) and (D) are identical; strength of competitor = strength of RF stimulus.*

In all cases, the iontophoresis protocol will involve a "baseline" measurement, then a "drug measurement" (starting 10 min after drug ejection is initiated), and a "recovery" measurement (starting 15 min. after drug is turned off). Kynurenic acid at 40mM will be ejected at a current of -400 nA.

The computational model will contain two spatial channels (as shown in Fig. 7), will contain firing rate model neurons with sigmoidal input-output functions whose parameters will be drawn from past experimental measurements in the OTid, Imc and Ipc. The equations describing inhibitory and excitatory synaptic connectivity will be the same as those in our previous published work [57]. Additionally, we will extend that model to both reflect the patterns of connectivity derived from this aim, and to incorporate continuous spatial tuning (our previous model contained only point representations of space). We will simulate model responses to spatial tuning curves without and with a competitor.

Data analysis: Multiunit data (from tungsten as well as iontophoresis electrodes) will first be sorted into individual units using two different software solutions (Chronux Spikesort and Wave_Clus). Two methods are used in order to improve confidence in the identity of the sorted single units. Spike rasters from individual units and spike counts over a fixed window will be analyzed, per procedures outlined previously [9,46,56]. Specifically, responses to the spatial tuning curves (azimuthal or elevational) will be calculated using spike counts over fixed windows and will be fit with Gaussian curves [9].

To calculate the strength of ***self-inhibition*** in the OTid, we will plot the tuning curve responses obtained without vs. with inactivation of the aligned Imc site as a scatter plot: x-axis = responses with Imc inactivated; y-axis = response with Imc intact. We will fit the best straight line to this data. If inactivation has no effect, then the points will all lie on the line of unity (zero intercept, and slope =45°). An increase in the responses following inactivation will cause points to lie *below* the line of unity. The slope of this line (and its intercept) will yield estimates of the strength of divisive (and subtractive) components of self-inhibition.

To calculate the strength of ***competitive inhibition***, we will adopt a similar procedure, with the exception that the two curves being compared will be OTid spatial tuning curves obtained in the absence or presence of a competitor. In the scatter plot, x-axis = responses without the competitor and y-axis = response with the competitor (at the location encoded by the Imc neuron). Again, the slope (and intercept) of the best-fit line will estimate the strength of competitive inhibition.

Expected results & Preliminary data: Pilot data (n=2) suggest that competitive inhibition is strong (Fig. 8D vs. H; k_{comp} = 0.5 = 1-slope factor), but self-inhibition is weak (Fig. 9C; k_{self} = 0.2), thereby supporting the functional-donut hypothesis. Notably, data (not shown) point to a potential anisotropy in the pattern of self-inhibition: self-inhibition along the elevational direction (k_{self} = 0.2) appeared to be weaker than that along the azimuth (k_{self} = 0.3). It will be important to explore the pattern and strength of self- vs. competitive inhibition across the Imc with a thorough sampling of Imc neurons. If the anisotropy emerges as a systematic finding, the computational model will help us explore its implications for competitive signaling by the OTid.

Pitfalls and alternate approaches: Holding a single Imc site while obtaining data at a mismatched OTid site (to measure competitive inhibition), and then moving the OT electrode to obtain data at a matched OTid site (to measure self-inhibition) is very time-consuming: the process can easily take 1.5 hours (this includes time for data acquisition, waiting times for action and clearing, and time for repositioning the electrode). Although our pilot data demonstrate that this approach is feasible (Fig. 8,9), there will likely be cases in which we lose the Imc site after one of the two measurements. In those cases, we will separate out data in which paired measurements were made from those in which only one of the two measurements was made. We will first analyze the paired measurements. Then we will assemble all available "self-inhibition" measurements as well as "competitive inhibition" measurements and run a population-wide comparison. The results in these two cases will reveal whether there is a significant difference between paired vs. population analyses, thereby informing us of the necessity of continuing to aim for the more complicated paired measurements.

Significance: Results from this aim will elucidate the strategy used by the Imc-OT circuit to achieve robust stimulus competition and neural selection of the strongest stimulus. Consequently, it can reveal, for the first time, how the brain implements, through elegant biological circuit design, a core mathematical operation for multisensory competition, namely, the spatial inverse.

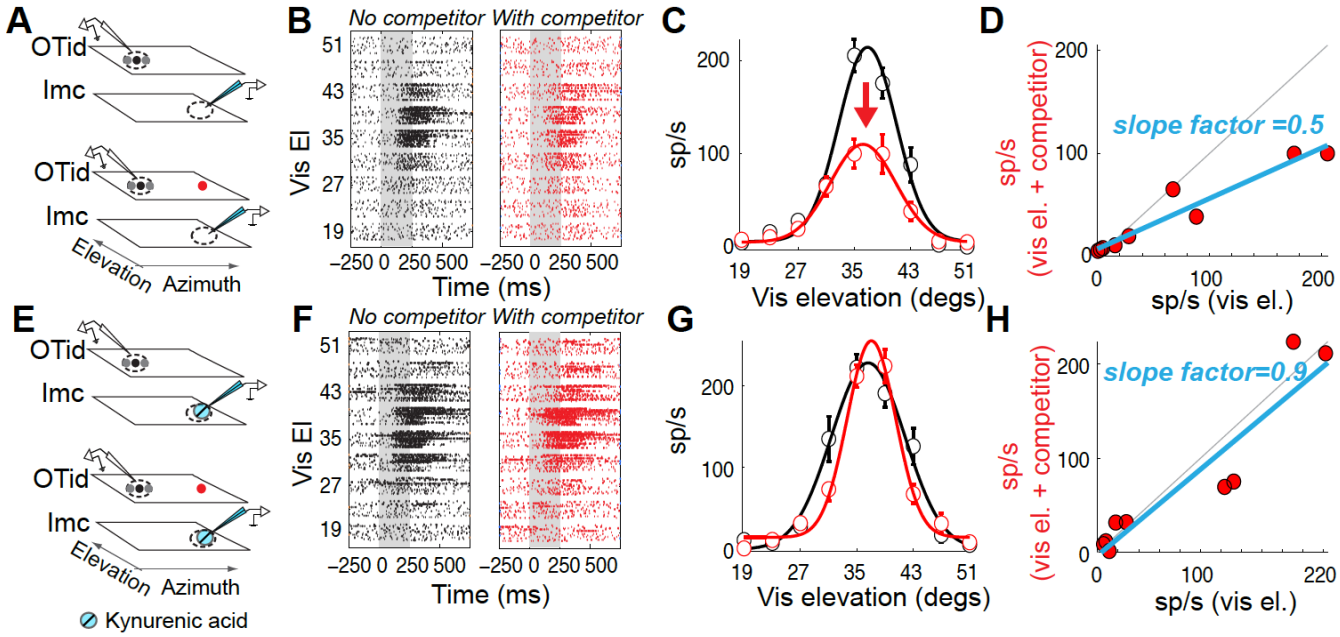

Figure 8. Preliminary data: Estimating strength of competitive inhibition exerted by an Imc neuron. (A-D) *Baseline measurements.* ***(E-H)*** *Measurements after inactivation of Imc site.* ***(A,E)*** *Schematic of experimental and stimulus protocol showing OTid and Imc space maps, location of stimuli and location of electrodes. Note that Imc and OTid sites have <u>mismatched</u> RFs.* ***(B,F)*** *Rasters of OTid responses to elevational tuning curve measured without (black) and with (red) a distant competitor stimulus. Gray shading indicates duration of stimulus presentation.* ***(C,G)*** *Spike counts.* ***(D)*** *Scatter plot showing strength of competitive suppression in baseline condition: k_{comp}=1-slope factor = 0.5 (50%).* ***(H)*** *Competitive inhibition is almost abolished (k_{comp}=0.1; 10%) following Imc inactivation. Not shown: Activity at the Imc site was suppressed by 60% by the drug.*

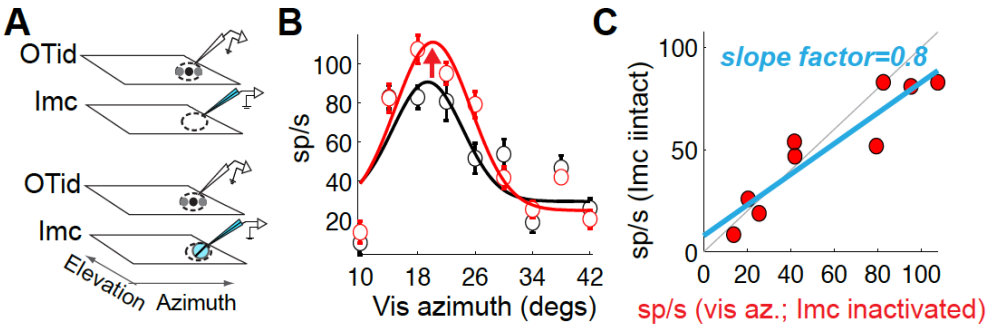

Figure 9. Preliminary data: Estimating strength of self-inhibition exerted by the same Imc neuron. *Conventions similar to Fig. 8.* ***(A)*** *Schematic of experimental and stimulus protocol. Note that the Imc and OTid sites have <u>matched</u> RFs.* ***(B)*** *Azimuthal tuning curves measured in the OTid in the baseline condition (black) and following inactivation of the matched Imc site (red).* ***(C)*** *Scatter plot showing that self-inhibition exerted by this Imc neuron is weak; k_{self} = 0.2 (1-0.8).*

AIM 2. Determine whether Imc neurons show competitive interactions between spatially separated stimuli, and whether these interactions contribute to the categorical signaling of the stronger stimulus by the OTid.

Rationale: Lateral inhibition generated by the Imc is critical for the construction of representations of competing stimuli in the OTid [48](Figs. 4DE). However, it is not known if the Imc passively drives inhibition to the OTid where these representations are constructed, or whether the Imc itself constructs them and conveys the result to the OTid. Immunostaining [2] and slice electrophysiology [63] results from the literature, respectively, indicate that Imc neurons have inhibitory synapses, and that they receive long-range inhibition from other Imc neurons. These suggest that information about distant stimuli (from outside the RF) may already be available for comparison at Imc neurons. In ***<u>Aim 2a</u>****, we will test the hypothesis that Imc neurons themselves express signatures of stimulus competition.* We will do so with recordings in the Imc in conjunction with the competition protocol (Fig. 2A).

Next, we will examine the functional role of putative intra-Imc competition. To aid this effort, we first used our published computational model [57] and simulated OTid CRPs without and with intra-Imc competition. This produced two testable predictions: That competition within the Imc helps set the magnitude of the CRP switch-value, and steepens CRP slopes in the OTid (Fig. 11A). Our past work has demonstrated that switch-values of OTid CRPs are equal to the RF stimulus strength, and that this equality is required for accurate signaling of the stronger stimulus [3,56]. In addition, we have shown that that the narrowness of CRP transition ranges in the OTid plays a critical role in the strength of the categorical signal of the strongest stimulus [3]. Therefore, in ***Aim 2b,*** *we will experimentally test the hypotheses that competition within the Imc controls the accuracy and strength of categorical competitive signaling by the OTid.* We will do so by examining the effect of inactivating stimulus competition within the Imc on the properties of CRPs measured the OTid. Inactivation will be achieved by iontophoresing $GABA_A$ receptor blockers within Imc.

Experimental design: General experimental methods will be same as in Aim 1. Stimulus competition in the Imc will be characterized with the competition protocol (Fig. 2A [56]); both visual and auditory stimuli will be used. Inactivation of competition within the Imc will be achieved by focally blocking inhibitory synapses in the portion of the Imc that encoding the competitor stimulus. This will be done by iontophoresing the $GABA_A$ receptor antagonist gabazine (and in other experiments, bicucullline; Fig. 11B). 5mM of gabazine will be ejected at 10-50nA (or 10mM bicuculline methiodide at 10-50 nA). Other methods same as in Aim 1.

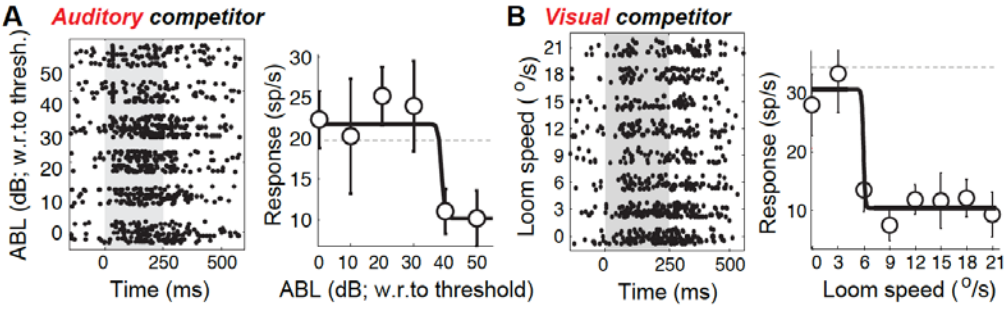

Figure 10. Aim 2a and preliminary data. Measurements of stimulus competition within the Imc using CRP competition protocol from Figure 2A. **A)** CRP measured at an Imc neuron with a visual looming RF stimulus and an auditory competitor. *Left*: raster plot; *right*: spike counts. Responses show switch-like competitive suppression by an auditory competitor. **B)** CRP measured at another Imc neuron with a visual looming RF stimulus and a visual competitor. Responses show switch-like competitive suppression by an auditory competitor.

Data analysis: General analysis methods are as before. To quantify the relative strength-dependence of competition, CRP data will be fit with standard sigmoidal functions. The four parameters of the sigmoid will be extracted as the minimum and maximum response rates, the switch-value and the transition range (Fig. 11A [56]). In addition, we will characterize the maximum value of response suppression observed in the data (as a % of change from responses to the RF stimulus alone).

Expected results & Preliminary data: *Aim 2a*. We expect that Imc neurons will show signatures of stimulus competition. Preliminary data (n=2) show that responses of Imc neurons to an RF stimulus are suppressed by a distant competitor, and this competitive inhibition operates across sensory modalities (Fig. 10). These data are consistent with the hypothesis that Imc already computes competitive representations, and serves as an active computational locus for stimulus competition in the Imc-OT network.

Aim 2b. Our model predicts that CRP switch-values will not be equal to the RF stimulus strength, and that CRP transition ranges will be wider following inactivation of competition within the Imc (Fig. 11A). Our pilot data (n=1) supports both predictions (Fig. 11C). A thorough sampling of Imc neurons (with a complete dataset) will allow us to quantify the detailed effects of spatial location and relative strength of the competitor on competitive suppression in the Imc (as has been done previously in the OTid [9,56]). In addition, the dataset will allow us characterize fully the effects of intra-Imc competition on categorical signaling by the OTid.

Pitfalls and alternate approaches. Although most of the inhibitory input to Imc neurons is due to long-range projections from distant Imc neurons, a small fraction of inhibitory input arrives from nearby (“local”) Imc neurons [63]. Therefore, using GABA receptor blockers to block synaptic inhibition onto Imc neurons would not only turn off long-range competitive inhibition (in a two-stimulus condition), but also, depending on the specific local circuit organization around the Imc neuron, it could result in drastic changes in the pattern of Imc firing (for instance, periodicity, burstiness, epileptiform activity etc). Accurately teasing out the effects of $GABA_A$ blockade on nuanced metrics of stimulus competition from a background of activity barrages could be very difficult. Thus, if the use of a $GABA_A$ blocker at the Imc neuron that encodes the competitor leads to

uninterpretable results, we will adopt a complementary approach motivated by the circuit architecture within the Imc. We will, instead, silence excitatory drive to the Imc neuron that encodes the RF stimulus, thereby disrupting intra-Imc competition. (Experimentally, the former approach of blocking $GABA_A$ receptors is considerably more straightforward, because the OTid and Imc electrodes do not need to be perfectly matched to encode the same portion of space, whereas, in the latter approach, they do. This offers a compelling practical reason to explore $GABA_A$ blockade first.)

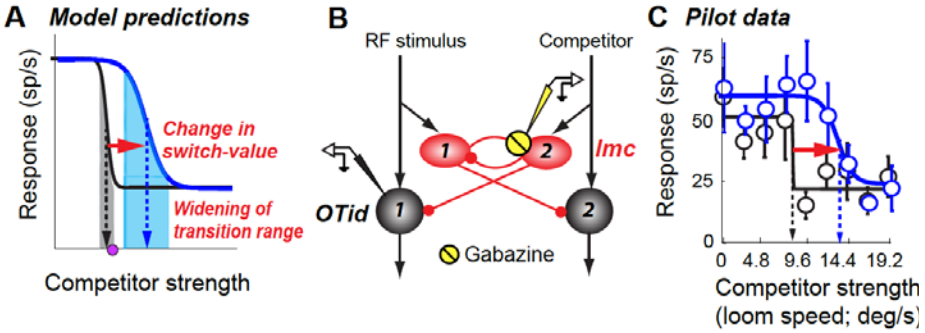

Figure 11. Design of Aim 2b and preliminary data. A) *Computational model predicts that competition within the Imc sets the switch-value and narrows transition ranges of OTid CRPs. Magenta dot: Strength of RF stimulus. Dashed arrow: indicate switch-values. Shaded regions: indicate transition ranges - the range of competitor strengths over which the response drops from 90% of the maximum to 10% of the maximum (transition range is inversely proportional to the maximum slope of the sigmoid; refs:). Black data: OTid CRPs measured competition within Imc intact; blue data: with Imc competition inactivated.* ***B)*** *Simplified schematic of circuit (for ease of visualization) showing the experimental design of Aim 2b: competition within Imc inactivated by focally disrupting inhibition within the Imc.* ***C)*** *Pilot data showing CRPs recorded from one OTid neuron without (black) and with (blue) inactivation of inhibition within the Imc.*

Significance: Finding competitor-driven response suppression in Imc neurons will reveal the Imc as an active computational locus for stimulus competition in the midbrain selection network. Results will also reveal the specific contribution of computations at the Imc to competition in the OTid and reveal a computational rationale for the considerable (additional) biological "cost" involved in creating long-range connections and GABAergic synapses within the Imc. Because representations of competing stimuli in the SC/OT play a critical role in controlling stimulus selection behavior, understanding the circuit implementation and its computational reasons are key to extracting neural principles at play.

AIM 3. Determine how the OTid resolves competition among several (more than two) stimuli.

Rationale: The above aims construct a detailed mechanistic picture of competition between two stimuli. However, sensory environments are typically complex, containing *several* (>2) competing stimuli. The precise algorithms that the brain employs to resolve such competition are not well understood. The SCid/OTid is an excellent site to investigate this issue because studies involving focal inactivation of the SCid (in monkeys) have demonstrated that it is necessary for selection also when several stimuli (upto 4 tested) are presented to the animal [52]. Here we will examine two key questions to uncover the functional logic of the SCid/OTid's role. In ***Aim 3a***, we will investigate what rule the OTid uses to resolve competition and signal the strongest among several competing stimuli. In ***Aim 3b***, we will examine what limitations exist in OTid's ability to do so, i.e., stimulus conditions under which the OTid may be unable to signal the strongest among several competing stimuli. Several past findings (ours as well as others') motivate our approach.

Aim 3a. We have demonstrated [3,56] that OTid neurons resolve competition between two stimuli by signaling categorically whether or not the stimulus inside the RF is the stronger one (Figs. 2C & 3) [3,56]. The experimental readout of this categorical signaling is that the switch-value measured using a CRP is equal to the strength of the RF stimulus (Fig. 2D). Therefore, it is plausible that the same principle extends to the signaling of the strongest among several competing stimuli. Specifically, that OTid neurons continue to categorically signal whether or not the stimulus inside their RF is the strongest, independently of the number of competing stimuli. Consider three competing stimuli (s_A, s_B, and s_C) presented at three locations A, B, and C, with the strength of s_A fixed, the strength of s_B systematically varying from weaker to stronger than s_A, and that of s_C fixed at a value less than the strength of s_A (Fig. 12B). Then,

Hypothesis ***H_0****: For a neuron encoding location A, the switch-value from this 3-stimulus protocol will be the same as its switch-value from a 2-stimulus protocol without s_C* (Fig. 12A).

However, this hypothesis has a potential confound: We have shown that Imc neurons orchestrate mutual competitive inhibition between OTid neurons encoding any two mutually distant locations [9,48,63]. This circuit architecture would predict that with three competing stimuli, the OTid neuron encoding each stimulus would necessarily receive competitive inhibition from the other two (as opposed to from just the one in the 2-

stimulus case). Therefore, the switch value of the neuron would be different in the 2- vs. 3- stimulus conditions, because of the potential difference in the net inhibition to the neuron. Thus:

*Alternate hypothesis **H_1***: *The switch-value of a neuron will depend on the net competitive inhibition arriving at that neuron, i.e., on the number of stimuli. Specifically, the switch-value will be lower in the 3-stimulus case, and potentially, lower still as the number of stimuli increases.*

Corollary to H_1: If *H_1* is true, then decoding the location of the strongest stimulus simply based on the switch-values of individual neurons will be inaccurate (unlike in the 2-stimulus case). We hypothesize that comparison of the responses of neurons across the OTid space map that encode the different competing stimuli will yield accurate, unbiased decoding of the strongest stimulus.

We will test these hypotheses with OTid recordings in conjunction with three stimulus protocols (Fig. 12A-C; see also Methods). In addition, we will also examine whether relative response latencies across the OTid network carry independent information from the relative firing rates for signaling the strongest stimulus. This question is motivated by observations in other systems that response latencies can code critical information about sensory stimuli [64,65].

Aim 3b. Aim 3a can reveal the core principle involved in resolving multi-stimulus competition in the OTid. Two lines of evidence suggest that there may be fundamental limitations to any such principle. Specifically, an upper limit to the number of competing stimuli that the OTid can successfully resolve. The first line of evidence relates to the absolute magnitude of responses. Responses of monkey SCid neurons to multiple competing stimuli progressively (and rapidly) decrease with increasing numbers of stimuli, and more generally, with increasing uncertainty [10]. Consequently, if the number of stimuli is large enough, SCid neurons may be unable to signal the result of competition, simply because they would be completely suppressed (a floor effect). The second line of evidence relates to the magnitude of switch-values. If, per the *H_1* above, switch-values decrease progressively with the number of stimuli, then a large enough number of stimuli would reduce the switch value to zero thereby preventing OTid neurons from resolving relative strengths. Each of these lines of evidence poses a potential limitation to the number of competing stimuli that the OTid can successfully handle. We systematically test both these issues using OTid recordings.

All experiments will be performed with both visual and auditory stimuli.

Finally, for both Aims 3a and 3b, we will employ biologically and experimentally grounded modeling to explore the computational underpinnings of multi-stimulus competition within and across modalities. Specifically, this model will directly test whether (and under what parameter ranges), competitive inhibition at a neuron reaches a steady state value as the number of stimuli is increased. The hypothesis here is that under the right parameter conditions, there will be a balance between the increasing inhibition at any neuron due to the increasing number of stimuli, and reduction in the effective strength of each stimulus because of mutual suppression of each stimulus by all others.

Experimental Design & Methods: *Aim 3a, testing H_0 vs. H_1*. We will record OTid responses with a single-neuron decoding perspective in mind (testing H_0 vs. H_1). To this end, we will measure the responses at individual OTid sites to three different stimulus protocols (Fig. 12A-C). In all three protocols, a stimulus (visual or auditory) of fixed strength will be presented inside the RF, called s_A; (i) In protocol #1, a competitor stimulus (visual or auditory), s_B, will be presented far outside the RF, and its strength will be systematically increased (same as the standard CRP protocol in previous aims), (ii) In protocol #2, a third stimulus, s_C, will additionally

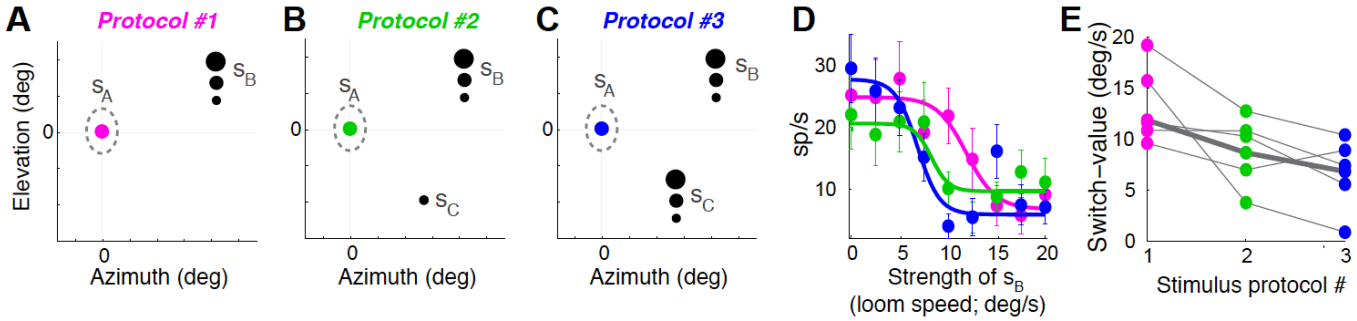

Figure 12. Aim 3a: Protocols and preliminary data testing H_0 vs. H_1. (A-C) *Three stimulus protocols. Dashed oval: RF of OTid neuron. For ease of visualization, the color of stimulus s_A in each protocol matches the protocol number; all stimuli are full contrast dots (black dots on gray backgrounds). Three dots of different sizes indicate that that the corresponding stimulus is one whose strength is systematically varied. Stimuli can be either visual or auditory; here they are visual.* ***(D)*** *Responses from an OTid neuron to the three protocols.* ***(E)*** *Plot of switch-values as a function of protocol number supports H_1 over H_0.*

be presented at a location that is distant from the locations of both s_A and s_B. The strength of s_B will be fixed at a value less than that of s_A, (iii) Protocol #3 will also involve three competing stimuli, but here, s_C will no longer be a fixed-strength stimulus, rather, its strength will vary systematically, and will be coupled to that of s_B.

Aim 3a, testing corollary to H_1. Next, we will record OTid responses with a network-wide decoding perspective in mind. The same three stimulus protocols from Figures 12A-C will be used, with two changes: (a) Stimulus s_A will always be presented in frontal space (-10º ≤ azimuth ≤10º, -10º ≤ elevation ≤10º), stimulus s_B always near the location (45º azimuth, 45º elevation) within a ±10º neighborhood, and stimulus s_C always near (25º azimuth, -45º elevation), within a ±10º neighborhood. (b) Across several experiments, we will sequentially record from individual OTid neurons that encode these three stimulus locations. The combined dataset will yield estimates of the network activity across the OTid in response to the three protocols (see Analysis).

For this experiment, we choose to adopt the sequential recording approach over the significantly more effortful approach of simultaneous recordings at three OTid locations (corresponding to the three stimuli) because it has been used to great effect in several published studies (including our own) and across animal species and brain areas [3,66,67].

Aim 3b. We will record from OTid neurons while using the protocol shown in Figure 14A to explicitly examine the effect of the number of stimuli on the magnitude of responses, and the protocols in Figure 15 to examine the effect of number of stimuli on the switch-value.

Modeling. As in previous aims; with the one modification that several spatial channels will be included.

Data analysis: *Aim 3a, testing H_0 vs. H_1*. To analyze the data from a single-neuron decoding perspective, we will fit the neural responses (spike counts) with sigmoidal functions. The switch-values of neurons obtained using the three protocols (Fig. 12A-C) will be particularly informative. We will test whether switch-values between any two protocols are significantly different by using a model selection approach together with the Akaike Information Criterion, per the procedure in our previously published work [56].

Aim 3a, testing corollary to H_1. To analyze the data from a network-wide decoding perspective, we will assemble the responses of neurons encoding the three locations “A”, “B” and “C” into a matrix. We will then use our previously published method (also illustrated in Fig. 3 [3]) to examine how network activity patterns change as a function of relative stimulus strength (or nominally, the strength of s_B). The result will allow us to examine if, and how, OTid network activity signals the strongest stimulus. In addition, we will use a similar method to examine coding by response latencies across the network.

Aim 3b. Analysis methods as before.

Expected results & Preliminary Data: *Aim 3a, H_0 vs. H_1*. Preliminary data from a few individual OTid neurons support H_1: switch-values from protocol 2 are lower than those from protocol #1, and switch-values from protocol #3 are lower still (Fig. 12DE).

Aim 3a, corollary to H_1. We expect that network-wide responses, but not individual OTid responses, will permit accurate decoding of the strongest stimulus. Specifically, as the strength of s_B is varied,

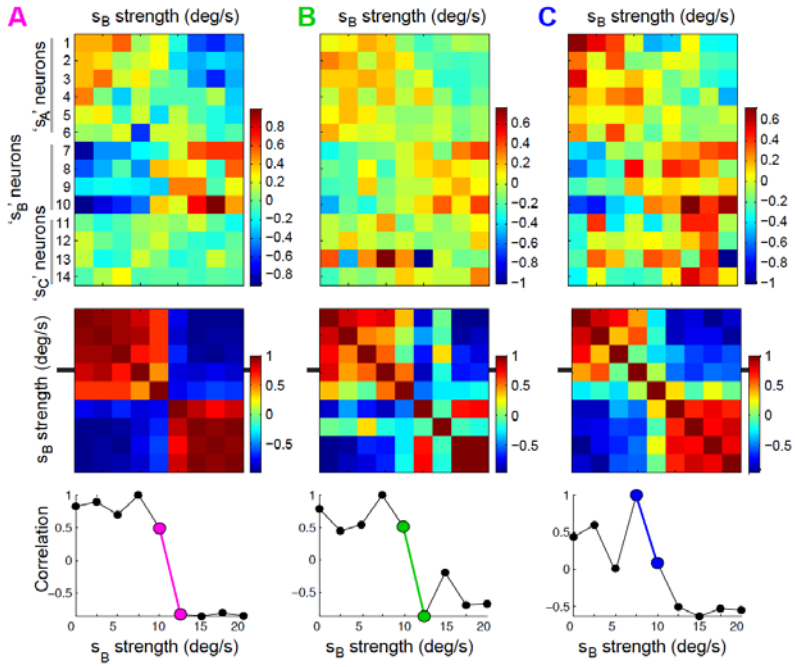

Figure 13. Aim 3a: Preliminary data for network-wide decoding (corollary to H_1). *Data from 6 neurons encoding location A, 4 at location B, and 4 at location C; from sequential recordings across experiments combined into a single matrix. Each row represents a neuron, each column represents the network response pattern corresponding to a particular value of s_B strength. Conventions as in Fig. 3. Strength of s_A = 10 %. **(A)** Neural responses from protocol #1, **(B)** Protocol #2, and **(C)** Protocol #3. **(A-C)** Bottom panels: Colored dots straddle strengths at which response patterns change abruptly, i.e., the categorization boundary. Even with a very small sample, results are consistent with abrupt shifts in network activity patterns when s_B=s_A for both protocols #1 and #2. For protocol #3, the abrupt shift occurs very close to, but not exactly at s_B=s_A; we anticipate that a larger data set will resolve this discrepancy.*

we expect that patterns of network activity will show abrupt shifts in a manner that maps on to the identity of the strongest stimulus in all three protocols. Pilot data from a few neurons across the OTid network support this (Fig. 13A-C). We anticipate that relative response latencies will also allow the decoding of the strongest stimulus. However, any results will be informative.

Aim 3b. Preliminary data indicate that some OTid neurons do suffer from a floor effect in response magnitude (Fig. 14B). However, others do not (Fig. 14C). This allows for a potential reconciliation of both the monkey SCid results of decreasing activity [10], and the necessity of the SCid in multi-stimulus selection [52]. A more thorough sampling of neurons across the OTid space map will reveal a clearer picture of the distribution of these two kinds of responses. We anticipate that the same will hold true regarding the floor effect in switch values. However, any results would be highly informative.

Incorporating these results into a model will elucidate a computational explanation for the resolution of multi-stimulus competition by OTid, and shed light on the properties and dynamics of mutual competitive inhibition that can yield zero (Fig. 14B) vs. non-zero (Fig. 14C) response asymptotes.

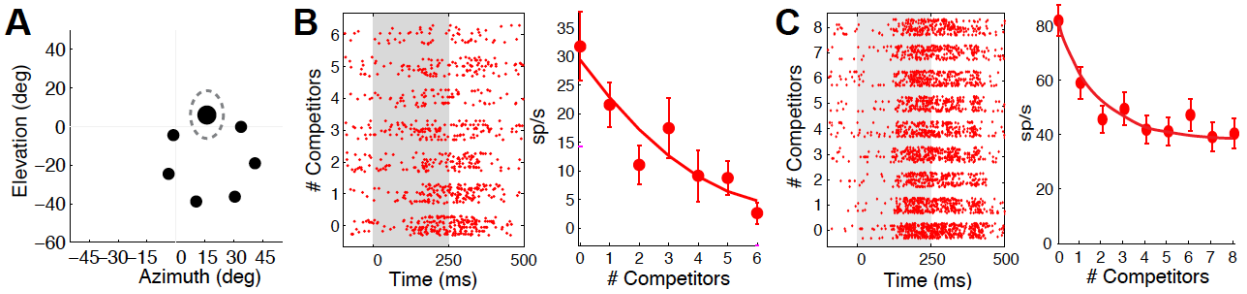

Figure 14. Aim 3b: Effect of number of stimuli on response magnitude. A) Schematic of stimulus protocol. *Dashed oval: RF of OTid neuron. Stimuli are presented in a circular configuration such that each stimulus is at least 20º away from its nearest neighbor. The number of competitors is varied from 1-6. Stimuli can be either visual or auditory; here they are visual.* ***B-C)*** *Rasters and spike counts from the responses of two OTid neurons to the protocol in A.* ***B)*** *Neuron shows a floor effect: responses drop to zero as the number of stimuli is increased.* ***C)*** *Neuron does not show a floor effect: responses asymptote to a non-zero value.*

Potential pitfalls and alternate approaches: In the event that a better estimate of network activity (larger sample size) does not support the preliminary findings from sequential recording experiments, we will turn to simultaneous recordings. We will use multishank silicon probes (Neuronexus), with shanks being 500 um apart and each shank having 4-8 recording hotspots spaced at 50 um from one another. We will repeat the network-wide analyses of relative firing rates and relative latencies with these data.

Significance: Results from this aim can reveal the answer to a long-standing open question: how is competition among several competing stimuli resolved within and across sensory modalities? In addition, it can shed light on the computational limits (if any) of the information encoded by the OTid in multisensory scenes.

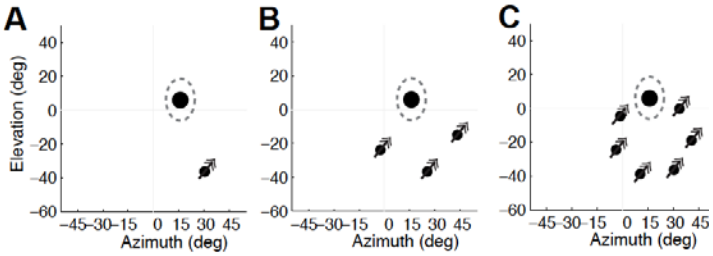

Figure 15. Aim 3b: Effect of number of stimuli on switch-value magnitude. *(A-C) Protocols for measuring the switch-values of a neuron as the number of competitors is increased. Shown are protocols corresponding to 1, 3, and 6 competitors. A dot with an arrow through it indicates that this is a stimulus whose strength is systematically varied. Strengths of all competitors are varied in a coupled manner. Stimuli are either visual or auditory.*

TIMELINE

Year 1: Record from Imc (Aim 2a); Record from OTid (Aim 3a)

Year 2: Record from Imc, analyze data and write paper from Aim 2a (competition in the Imc); Record from OTid (Aim 3a) and create computational model.

Year 3: Start iontophoresis experiments in Imc (Aim 1a); Start iontophoresis experiments in Imc (Aim 2b); Record from OTid (Aim 3b)

Year 4: Iontophoresis experiments in Imc and computational modeling (Aim 1); Iontophoresis experiments in Imc and computational modeling (Aim 2b); Analyze data and write paper from Aim 3 (how OTid resolves competition in cluttered scenes).

Year 5: Analyze data and write paper from Aim 1 (donut-like inhibition and robust OT signaling); Analyze data and write paper from Aim 2b (effect of Imc competition on OT signaling).

VERTEBRATE ANIMALS.

Description of animal use. For the proposed experiments, we will use adult barn owls (*Tyto alba*, both genders) for all the Aims. No gender-based difference has been reported thus far in the owl neurophysiology literature on sensory processing. Nonetheless, we will keep track of the gender and test specifically for gender-based differences in observed results.

Based on past experience and preliminary experiments, experiments in Aim 1 are estimated to need 10-12 barn owls, and experiments in Aims 2 and 3, 10-12 owls per sub-aim; a total of about 50-60 owls over 5 years. This estimation includes the considerations that (a) experiments involving multiple electrodes produce more tissue damage per experiment, necessitating the use of more birds than single electrode experiments, and that (b) training of new personnel on experimental techniques necessitates the use of about 2 owls per mentee. In addition to experimental animals, we will maintain 4 breeding pairs (8 owls) throughout in order to maintain a consistent colony of birds. As a result we will need to house 20 birds each year (10-12 experimental birds + 8 breeding birds).

All animal experiments will be performed in our recently renovated state-of-the art laboratory in [redacted] Animals will be housed in a recently renovated state-of-the-art vivarium [redacted]) which is managed by the Research Animal Resources (RAR) division. All protocols for animal research that are described in this proposal have been fully approved by the ACUC committee.

Surgical procedures. Owls will undergo an initial surgery for the installation of a head bolt. Following that, craniotomies will be performed once on each side and recording chambers installed. The craniotomies will be exposed (by opening the chamber cap) at the start of each experiment, and sealed at the end. Surgeries and craniotomies will be performed in anesthetized owls (isofluorane + nitrous oxide), and physiology experiments in non-tranquilized owls. Birds will be systemically injected with analgesics prior to surgical procedures and with local analgesics at the site of incision. Body temperature will be measured during surgeries and experiments to monitor the state of the birds. Procedures will follow previously published protocols in accordance with NIH regulations [27,6].

Veterinary Care. Johns Hopkins is fully accredited by the American Association for Accreditation of Laboratory Animal Care. Animals are maintained in accordance with the applicable portions of the Animal Welfare Act and the DHHS "Guide for the Care and Use of Laboratory Animals". The Research Animal Resources (RAR) division at Hopkins oversees and manages the housing and care for our animals. Veterinary care is under the direction of a consulting veterinarian who boarded by the American College of Laboratory Animal Medicine. Additional veterinary staff and veterinary technicians (all part of the RAR) provide a complete and comprehensive program of diagnostics, preventive and clinical medicine at our facility.

Procedures to Minimize Pain and Discomfort. The procedures that we need to employ can cause some pain to the animals. However, anesthetics and analgesics are administered to the animals to alleviate the pain and distress and animals are carefully monitored throughout such procedures for nocifensive behaviors (flinching, grasping with talons). In addition, we use the least distressful techniques that are available to achieve our goals. We routinely read the literature that is relevant to our research in order to keep abreast of new findings and new methods. The procedures described are used in other labs around the world (based on literature and on discussions in the SfN annual meetings).

In the event that any bird shows persistent signs of distress, infection, or illness, or has difficulty flying normally or displays abnormal posture, it will be euthanized in consultation with veterinary personnel. At the conclusion of an experimental study, all owls will be euthanized.

Euthanasia. Animals will be euthanized with beuthanasia D (under 4% isofluorane), and perfused with saline followed by a fixative solution (paraformaldehyde) to recover brains for histology and tract tracing. Deaths will be documented in animal inventory records.

Justification for the use of animals. The use of animals in these experiments is essential. In order to uncover the neural circuit bases of stimulus competition and selection, i.e., to uncover how brains represent and process competing information, it is necessary to study brains in live animals exposed to complex, well-controlled sensory environments. Further, in order to test the causal roles of specific neural circuits in mediating attention it is necessary to perform invasive experiments involving inactivation of specific neural

elements, approaches that can only be utilized in animals. For these reasons, the use of animals is essential to this research aimed at revealing how the brain *actually* accomplishes and implements information processing for multisensory competition and selection. Potential alternative approaches that do not use animals at all, such pure computer modeling, or those that involve only non-invasive approaches in animals such as behavioral or psychophysical experiments, are, by themselves, insufficient for the study of the neural underpinnings of sensory processing.

Justification for the use of owls. We study birds because the midbrain circuit architecture that participates in multisensory processing is well characterized and highly organized: specific midbrain nuclei have been implicated in multisensory integration, in stimulus-driven competition, and in the suppression of competing stimuli. Although primates and rodents have equivalent midbrain cell groups, the spatial segregation of the groups in birds permits the activity in these specialized nuclei to be recorded from reliably and independently manipulated. Specifically, the reasons for studying barn owls are that 1) they are multisensory specialists, with extremely well-developed auditory and, interestingly, visual, systems that work cooperatively to process sensory information, 2) being predators, they have a highly developed capacity for spatially accurate stimulus (target) selection, and 3) because most of the recent neurophysiological findings on stimulus competition in birds have come from work done in owls, they stand-out as a powerful system for more sophisticated studies in, such as the ones described in this proposal.

SELECT AGENT RESEARCH.

None.

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