PI: **Sanes, Dan Harvey**	Title: Social learning enhances auditory cortex sensitivity and task acquisition	
Received: 06/04/2021	Opportunity: PA-20-185	Council: 01/2022
Competition ID: FORMS-F	FOA Title: NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)	
1R01DC020279-01	Dual: HD	Accession Number: 4585480
IPF: 5998301	Organization: [redacted]	
Former Number: 1R01NS126434-01	Department: [redacted]	
IRG/SRG: AUD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: [redacted]	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Dan Sanes PhD	[redacted]	PD/PI

OMB Number: 4040-0010
Expiration Date: 12/31/2022

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

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 2021-06-04

Application Identifier

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: [redacted]
Department:
Division:
Street1*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: [redacted] Middle Name: Last Name*: [redacted] Suffix:
Position/Title: Sr. Director of OSP
Street1*: [redacted]
Street2:
City*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

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*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Social learning enhances auditory cortex sensitivity and task acquisition

12. PROPOSED PROJECT
Start Date* 04/01/2022
Ending Date* 03/31/2027

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Dan Middle Name: H. Last Name*: Sanes Suffix: PhD

Position/Title: Professor

Organization Name*: [redacted]

Department: [redacted]

Division: [redacted]

Street2:

City*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: 10003-6603

Phone Number*: [redacted] Fax Number: [redacted] Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]

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

[redacted] Middle Name: Last Name*: [redacted] Suffix:

Position/Title*: Sr. Director of OSP

Organization Name*: [redacted]

Department: OSP

Division: [redacted]

Street2:

City*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*

[redacted]

Date Signed*

06/04/2021

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:0_SF424_Cover_Letter__SL__v21035305011.pdf

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

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: [redacted]

[redacted]

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: [redacted]

Project/Performance Site Congressional District*: [redacted]

Additional Location(s) File Name:

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 _ 7 _ 8

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:

Animal Welfare Assurance Number A3317-01

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*	7_R_R_Project_Summary__SL__v11035304999.pdf
8. Project Narrative*	8_R_R_Project_Narrative__SL__v11035305000.pdf
9. Bibliography & References Cited	9_R_R_Bibliography__SL__v31035305001.pdf
10.Facilities & Other Resources	10_R_R_Facilities___Resources__SL_1035305002.pdf
11.Equipment	11_R_R_Equipment__SL__v11035305003.pdf

PROJECT SUMMARY

Skill acquisition can be facilitated by social experience, usually through exposure to a conspecific performing a well-defined behavior. In fact, social learning (**SL**) is pivotal to the acquisition of many core behaviors, including aural communication. Although the neural bases for auditory SL remain uncertain, one plausible hypothesis is that social experience may induce experience-dependent plasticity in auditory cortex (**AC**), as found for many forms of learning, thereby facilitating auditory task acquisition. Social learning may also have implications for developmental hearing loss (**HL**), a prevalent sensory impairment that is associated with persistent deficits in speech and language acquisition, especially since social factors are thought to facilitate language acquisition in children with HL. Three Aims test predictions that emerge from this hypothesis: Aim 1 first demonstrates the positive impact of SL on task learning: Naïve Observer gerbils receive five days of exposure to a trained Demonstrator performing an amplitude modulation rate discrimination task. An opaque divider separates Observer and Demonstrator, such that visual cues are absent. Observer gerbils are then permitted to practice the auditory task, and the rate of learning assessed. To test the prediction that AC activity is required, AC will be inactivated during social experience. Aim 1 will go on to test the prediction that dopaminergic neuromodulation within AC is be necessary for social learning. We will first determine whether dopamine is released in AC during social experience, using fiber photometry and a genetically expressed dopamine sensor. We will then block dopamine receptors in AC during social exposure to determine whether the benefits of social experience are diminished. Aim 2 tests the prediction that AC neuron sensitivity to auditory cues will be enhanced during SL. Gerbils will be instrumented with electrode arrays in AC, and recorded during five days of social exposure. Single neuron and population responses to auditory task stimuli will be assessed to determine if improved neural sensitivity during observation can explain the rate of task acquisition rate during practice. To test the contribution of an auditory social cue (i.e., Demonstrator vocalizations), recordings will be obtained from Observers exposed to auditory task cues plus playback of demonstrator vocalizations. Aim 3 tests the prediction that SL will improve task acquisition in hearing loss-reared animals. Juvenile gerbils will receive either permanent (malleus removal) or transient (earplugs) conductive HL. Animals will then be instrumented with electrode arrays in AC, and assessed as in Aim 2. Innovations in this proposal are to: (i) extend current auditory learning paradigms to include social cues, (ii) use wireless recordings during learning to make within-animal comparisons of neural and behavioral sensitivity, and (iii) shift the current emphasis in HL research from a focus on degraded sensory processing to one that considers how social factors may facilitate auditory skills. *If successful, the project will identify a CNS mechanism that mediates socially-enhanced auditory learning, and provide a novel approach to remediate sensory and cognitive barriers in children with HL.*

PROJECT NARRATIVE

The acquisition of new skills, including aural communication, can be facilitated when an observer is exposed to a conspecific performing a well-defined behavior (i.e., social learning). Since the neural bases for auditory social learning remain uncertain, this proposal will evaluate the idea that social cues induce experience-dependent plasticity in auditory cortex, thereby facilitating the acquisition of an acoustic task. The long-term impact of this research will be to test whether social experience can facilitate auditory learning in animals reared with developmental hearing loss, a condition that is associated with long-lasting aural communication deficits.

FACILITIES AND OTHER RESOURCES

Scientific Environment: The [redacted] contains 28 Core and 58 Associated faculty with interests ranging from cellular neuroscience to perception and learning to computational neuroscience. Within the department there is a strong focus on sensory neuroscience, including labs that study auditory processing, development, and learning. In the past, our lab has collaborated intensively with [redacted] faculty on a variety of projects. For example, I have collaborated with: (1) [redacted] to examine whether hearing loss-induced changes to synapse function are attributable to changes in the ultrastructural localization of glutamate and GABA receptors (Kotak et al., 2005; Sarro et al., 2008), (2) [redacted] to study auditory brainstem and cortical processing and development, including the effects of hearing loss (Sanes et al., 1998; Thornton et al., 1999; Ter-Mikaelian et al., 2007; Rosen et al., 2010; Ter-Mikaelian et al., 2013; von Trapp et al., 2016, 2017), (3) [redacted] to study cellular neurophysiology and theoretical models of auditory brainstem processing (Svirskis et al., 2002, 2004; Jercog et al., 2010; Gai et al., 2014), (4) [redacted] to study the development and dysfunction of tonotopic map formation in the inferior colliculus (Yu et al., 2005, 2007, 2008), (5) [redacted] to study human envelope processing (Overath et al., 2012), (6) [redacted] to study auditory decision-making (Yao et al., 2020), and (6) [redacted] to study context-specific cortical encoding of gerbil social vocalizations (unpublished).

Principle Investigators' Laboratory: My laboratory occupies a 1200 ft^2 space on [redacted] University's [redacted] campus. The principal facilities within the laboratory include: (1) Two integrated systems for simultaneous acquisition of behavioral and neural responses in awake-behaving animals, each housed in a sound attenuation booth, (2) a system for acquisition and analysis of auditory brainstem responses, (4) a surgical suite in which to perform BSL-1 injections, (5) acoustic calibration equipment, (6) a station for electrode fabrication, and (7) general equipment, including refrigerators, freezers, balance, stirrer/hotplates, networked computers, and laser printers. There is separate office space for all personnel.

Animal Facility: The [redacted] University [redacted] program of Animal Care and Use is accredited by AAALAC international and meets or exceeds federal, state, and local regulations and guidelines related to the humane and ethical care and use of animals in research. The institution holds a current Animal Welfare Assurance with the Public Health Service (PHS) and is registered as a research facility with the United States Department of Agriculture (USDA). The Office of Veterinary Resources (OVR) is responsible for overseeing operation of the animal facilities. The Director of OVR is a Board Certified Laboratory Animal Veterinarian with over 20 years experience. OVR is staffed with 3 experienced Lab Animal Veterinarians, a Facilities Manager, Supervisor, technicians certified as Veterinary and or Laboratory Animal Technicians and additional trained cage washing staff. OVR technical staff include specialists in animal welfare, behavior, environmental enrichment as well as experimental surgery. The [redacted] Research Animal Facilities was expanded in 2020, and now occupies approximately 24,000 ft^2, containing ample administrative support, central resources, caging, supplies, equipment, and staffing to support the current accredited program of Animal Care and Use.

Technical Facilities: The [redacted] maintains several research support facilities that are available to all scientists. (1) Computer and Internet: The [redacted] and Department of Psychology share an IT staff who support PC, Mac, and Unix based systems, as well as local and cloud data storage. (2) Mechanical: Our building houses a 4000 ft^2 machine shop and two full time machinists are available for all custom design and mechanical construction. (3) Histology: A shared histology laboratory contains a cryostat, a paraffin microtome, an ultratome, a sledge microtome, perfusion hoods, a -80° freezer, refrigerators, vibratomes, hoods, and balances. (4) Digital Imaging: We have a shared facility housing our microscopes and imaging output devices. The digital imaging facility contains a Leica SP8 confocal microscope, a Neurolucida morphometry system, a Zeiss photomicroscope, an Olympus VS120 high resolution slide scanner, a large format poster printer, a color laser printer, and a high resolution scanner.

Office and Computer: Each member of the lab has office space that includes a desk, with ample storage space and computers equipped with Microsoft Office, Matlab, JMP statistics package, and custom written software for data analysis. Data, analyses, and documents on these computer are backed up daily via a Synology DiskStation DS1515+80TB. In addition, the laboratory is equipped with a number of dedicated and personal workstations, which provide additional access to software. All computers are tethered to a network

that provides the same software on each machine. Personal accounts are located and backed up on a central server run through [redacted] University Academic Computing Facilities. Personal accounts can be opened on any computer attached to the network facilitating the ease of data analysis and manuscript preparation. Each electrophysiology and behavior rig has a dedicated computer for both the acquisition and analysis of data. All machines are provided with network access by the Academic Computing Facility.

The [redacted] maintains an office staff including personnel who handle ordering, budgetary considerations, grants management, mail, and other general functions. All manuscripts are produced within the laboratory.

All of the requisite services which typically support basic research laboratories are present on the [redacted] University grounds. These include university and departmental libraries, grants administration, postal services, a communications department, a supply stockroom, and a bookstore.

EQUIPMENT

Equipment necessary to carry out the proposed project is available on site.

Awake-Behaving Recording (2 systems)

Training cages
Speakers
Triangle Biosystems 64 channel wireless recording systems
Acoustic isolation booths (one IAC and one GretchKen)
Tucker-Davis Technologies sound generation and data acquisition hardware (RZ5 and RZ6)
Pellet dispensers (Med Associates)
Webcams
PC computers & monitors
Custom Matlab-based software [redacted]
Bruel & Kjaer acoustic calibration system (microphones, amplifiers, Pulse acquisition hardware and software)

Auditory brainstem responses (ABRs)

Grass P15 preamplifier
Brownlee Precision Model 440 filter and amplifier
Harvard homeothermic blanket
Needle electrodes
Data acquisition hardware utilized in awake behaving studies will also be used for acquiring ABRs
Python scripts for data acquisition, stimulus generation and offline analysis (developed in [redacted] laboratory [redacted]

Surgery suite for BSL-1 injections

Stereo Microscope (Olympus)
Isoflurane / O_2 regulator
Thermal blanket
Model 900 small animal stereotaxic instrument & micromanipulators (Kopf)
Stereo Microscope Fluorescence Adapter (Nightsea)
K5Plus dental drill (Kavo)
Auto-Nanoliter Injector (Nanoject II)

Other

Water purification (Gen Pure)
Fume Hood for perfusions
Micropipette puller (Brown-Flaming)
Laminar flow hood
Vibratome (Pelco)
Chemical and perfusion hood
Microbalance (Mettler)
Heater / Stirrer
Peristaltic pumps (Rainin)
Refrigerator
Freezer
Micropipeters (Pipetman)
pH meter
Laser printer

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Dan Middle Name H. Last Name*: Sanes Suffix: PhD

Position/Title*: Professor
Organization Name*: [redacted]
Department: [redacted]
Division: [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

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

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

Degree Type: PHD Degree Year: 1984

Attach Biographical Sketch*: File Name: RR_KP_1_Biosketch_Sanes__SL__v61035305004.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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: Dan H. Sanes

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

POSITION TITLE: Professor

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
University of Massachusetts, Amherst MA	B.S.	05/1978	Zoology
Princeton University, Princeton NJ	Ph.D.	05/1984	Biology
University of Virginia, Charlottesville VA	Postdoctoral	05/1986	Auditory Science
Yale University Medical School, New Haven CT	Postdoctoral	08/1987	Neurobiology

A. Personal Statement

There are three attributes that support my role as PI of this proposal: **First**, I have a 35 year background in the hearing sciences. My research program initially focused on the developmental plasticity of inhibitory connections, from auditory brain stem to cortex, and discovered that developmental hearing loss leads to a profound reduction of inhibitory synapse strength (*Lateral Superior Olive*: Kotak & Sanes, 1996; *Inferior Colliculus*: Vale & Sanes, 2000, Vale et al., 2003; *Medial Geniculate*: Mowery et al., 2019; *Auditory Cortex*: Kotak et al., 2005, Takesian et al., 2010, 2012). In fact, even a brief period of mild hearing loss can induce a long-term reduction of inhibition when it occurs during a well-defined developmental "critical period" (Mowery et al., 2015, 2017). This work culminated in the hypothesis that hearing loss-induced perceptual deficits are, in part, caused by the loss of central inhibition. This led us to incorporate an auditory psychophysical approach. Thus, we demonstrated that transient hearing loss causes perceptual deficits (Caras & Sanes, 2015), and then experimentally restored central inhibitory synapse strength which led to the recovery of normal perceptual thresholds (Mowery et al., 2019). This work is currently funded (R01DC011284). **Second**, I have an extensive background studying the relationship between central auditory processing and perceptual skills. Like most neuroscientists of my generation, I initially studied sound encoding with acute single neuron recordings in anesthetized animals using closed field stimulation (Sanes et al., 1998). To overcome some the limitations of anesthetized preparations, we establish a freely-moving, awake-behaving preparation with which to evaluate the real-time correlations between auditory cortex processing and psychometric performance. Using this approach, we have discovered two auditory cortex mechanisms that may contribute to perceptual sensitivity: (1) a behaviorally-gated reduction of spontaneous discharge that improves signal-to-noise ratio at the expected stimulus time (Buran et al., 2014b), and (2) a decline in trial-to-trial response variability that can improve signal detection (von Trapp et al., 2016). We have also taken advantage of this approach to ask whether developmental hearing loss-induced perceptual deficits can be explained, in part, by degraded central auditory processing (Yao & Sanes, 2018). **Third**, and most relevant to this proposal, I have established a research program that explores the mechanisms that support auditory learning, including its development and the impact of hearing loss. Thus, our lab discovered that auditory learning is poorer in developing animals (Sarro & Sanes, 2010), similar to human studies (Huyck & Wright, 2011). However, we also showed that juvenile training leads to a unique, long-term improvement in adult perceptual skills (Sarro & Sanes, 2011). More recently, we extended this work to study the neural basis of perceptual learning in adolescents and adults (Caras & Sanes, 2017, 2019). These studies segued into a new avenue of research, and the primary topic of this proposal: the impact of social experience on auditory learning. Specifically, we have established a new paradigm to study auditory social learning (Paraouty et al., 2020), permitting us to

address some of the underlying mechanisms. Our research on learning also has implications for hearing loss: thus, developmental hearing loss is a risk factor for learning delays (Caras & Sanes, 2015; von Trapp et al., 2017; Anbuhl et al., doi.org/10.1101/2021.04.12.439537), a primary motivation for the final Aim of this proposal. **Finally**, I have strong record of mentorship and scholarship. Since establishing my lab, I have trained and mentored 42 undergraduates, 10 doctoral students and 16 postdoctoral fellows. All of my doctoral students have graduated with publications, and 15 postdoctoral students have continued independent research or teaching careers in academic settings. Further evidence of my commitment to undergraduate education comes from a widely adopted undergraduate textbook that I co-author ("*Development of the Nervous System,*" 4th Edition, Academic Press).

1) von Trapp G, Buran BN, Sen K, Semple MN, Sanes DH (2016) A decline in response variability improves neural signal detection during auditory task performance. J Neurosci 36:11097-11106. PMCID: PMC5098844
2) Caras ML, Sanes DH (2017) Top-down modulation of sensory cortex gates perceptual learning. Proc Natl Acad Sci USA. 114:9972-9977. PMCID: PMC5604044.
3) Mowery TM, Caras ML, Hassan SI, Wang DJ, Dimidschstein J, Fishell G, Sanes DH (2019) Preserving inhibition during developmental hearing loss rescues auditory learning and perception. J Neurosci 39:8347-8361.
4) Paraouty N, Charbonneau JA, Sanes DH (2020) Social learning exploits the available auditory or visual cues. Sci Rep 10:14117. PMCID: PMC7445250

B. Positions, Scientific Appointments, and Honors

Positions

2000-	Professor, [redacted] Psychology, and Biology, [redacted]
1998-2004	Director, [redacted]
1993-2000	Associate Professor, [redacted] Biology, [redacted]
1991-1993	Assistant Professor, [redacted] and Biology, [redacted]
1987-1991	Assistant Professor, Otolaryngology and Physiology & Biophysics, [redacted] School of Medicine
1986-1987	Postdoctoral Fellow, Molecular Neurobiology, Yale University School of Medicine
1984-1986	Postdoctoral Fellow, Department of Otolaryngology, University of Virginia School of Medicine

Scientific Appointments

2021-	BRAIN Initiative Multi-Council Working Group
2020	Member, NIDCD Intramural Research Program Blue Ribbon Panel
2019-	NDCD Advisory Council
2016-	Senior Editor, Journal of Neuroscience
2016-	Scientific Advisory Board, HCN Training Program, University of Southern California
2015-	External Advisory Board, CEBH Training Program, University of Maryland
2014-	Board of Trustees, Virginia Merrill Bloedel Hearing Research Center
2012-2016	Reviewing Editor, Journal of Neuroscience
2010-2013	Councilor, Association for Research in Otolaryngology
2010-2014	Member, AUD Study Section, NIH
2009-2012	Section Editor, Hearing Research

Honors

2010	Fellow, American Association for the Advancement of Science
2007	Visiting Scholar, University of Munich
2006	Hugh Knowles Visiting Professor, Northwestern University
2002	[redacted] Golden Dozen Teaching Award
1988-1990	Sloan Foundation Fellow

C. Contributions to Science

1. Development and disruption of auditory learning

As a developmental neuroscientist, my research has always been directed at understanding how environmental experiences influence neural function. Ultimately, I seek to understand how beneficial and adverse experiences regulate synaptic function, cortical encoding, and the behaviors that they support. During the past decade, I have increasingly studied auditory learning, including the deleterious effect that attends developmental hearing loss. At the behavioral level, we found that a brief period of training during development dramatically improves adult

perceptual skills, suggesting a critical period for skill learning (Sarro & Sanes, 2011). At the cellular level, we demonstrated auditory cortex inhibitory strength transiently declines when animals first improve on both aversive and appetitive auditory tasks (Sarro et al., 2015). At the systems level, we showed that auditory cortex activity is necessary for perceptual learning, and the improvement in behavioral thresholds is accompanied by a proportional improvement in single neuron sensitivity to the task cues (Caras & Sanes, 2017). These cortical mechanisms mature slowly: the average rate of cortical improvement is significantly slower in adolescents and offers one explanation for reduced skill learning at this age (Caras & Sanes, 2019). These normative studies intersect with our research on developmental hearing loss, in which we find significant delays in both procedural and perceptual learning (Caras & Sanes, 2015; von Trapp et al., 2017; Anbuhl et al., doi.org/10.1101/2021.04.12.439537). Finally, our general interest in learning mechanisms, and their dysfunction following hearing loss, led us to consider the role of social factors. Thus, we established a new paradigm to study auditory social learning (Paraouty et al., 2020), and have recently used it to address mechanistic questions (Paraouty et al., doi: https://doi.org/10.1101/2021.03.03.433719). Together, these findings motivate this proposal which examines whether auditory cortex is necessary for auditory social learning.

1) Sarro EC, Sanes DH (2011) The cost and benefit of juvenile training on adult perceptual skill. J Neurosci 31: 5383–5391. PMCID: PMC3090646
2) Sarro EC, von Trapp G, Kotak VC, Mowery TM, Sanes DH (2015) Auditory task learning is associated with diminished cortical inhibition. J Neurosci 35:6318-6325. PMCID: PMC4405553
3) Caras ML, Sanes DH (2019) Neural variability limits adolescent skill learning. J Neurosci 39:2889-2902. PMCID: PMC6462443
4) Paraouty N, Rizzuto CR, Sanes DH. Dopaminergic signaling supports auditory social learning. bioRxiv 2021.03.03.433719; doi: https://doi.org/10.1101/2021.03.03.433719

2. Relationship between central auditory processing and perceptual skills

A primary goal of systems neuroscience is to understand the neural basis of perceptual skills. Thus, I have explored the mechanisms of binaural processing in the auditory brain stem (Sanes and Rubel, 1988; Sanes, 1990; Grothe & Sanes, 1994; Jercog et al., 2010), virtual motion processing by auditory midbrain neurons (Sanes et al., 1998; Thornton et al., 1999), and amplitude modulation and vocalization processing by auditory cortex neurons (Rosen et al., 2010; Ter-Mikaelian et al., 2013). We now routinely record from auditory cortex while animals perform psychometric tasks, and have discovered that spontaneous discharge is transiently reduced at the moment animals initiate a trial (Buran et al., 2014b), explored how cortical response variance declines during task performance (von Trapp et al., 2016), and described how cortical population activity can account for envelope discrimination versus categorization (Yao & Sanes, 2021). More recently, we have extended our analysis to parietal cortex, a region downstream of auditory cortex that mediates auditory decision-making (Yao et al., 2020). These findings motivate Aim 2 of this proposal which examines whether auditory cortex encoding is modified by social learning, and can account for behavioral performance.

1) Rosen MJ, Semple MN, Sanes DH (2010) Exploiting development to evaluate auditory encoding of amplitude modulation. J Neurosci 30: 15509-15520. PMCID: PMC3073556
2) Buran BN, von Trapp G, Sanes DH (2014b) Behaviorally-gated reduction of spontaneous discharge can improve detection thresholds in auditory cortex. J Neurosci 34:4076-4081. PMCID: PMC3951702
3) Yao JD, Gimoto J, Constantinople CM, Sanes DH (2020) Parietal cortex is required for the integration of acoustic evidence. Curr Biol 30:3293-3303.e4. PMCID: PMC7483995
4) Yao JD, Sanes DH (2021) Temporal encoding is required for categorization but not discrimination. Cer Cortex Jan 12:bhaa396. [Online ahead of print].

3. The impact of developmental hearing loss on auditory processing and perception

Those of us who work on synapses seek to understand how their properties permit networks to encode auditory cues and, ultimately, impact auditory perceptual skills. Thus, a major challenge is to design a strategy for exploring how the synaptic changes induced by early hearing loss perturb sensory coding and behavioral performance. Towards this end, we have studied both auditory cortex processing and auditory perception in normally developing gerbils, and those reared with diminished sensory experience (Sarro and Sanes, 2010; Rosen et al., 2010; Rosen et al., 2012; Buran et al., 2014a; Ihlefeld et al., 2016). We have found that even a transient period of sensory deprivation is a risk factor for diminished performance (Caras and Sanes, 2015). Our most recent works provides evidence that cortical encoding deficits contribute to diminished perceptual performance in hearing loss-reared animals (Yao and Sanes, 2018). Furthermore, both perceptual and learning

deficits persist, even after normal hearing is restored, and are closely associated with auditory cortex population coding (Anbuhl et al., doi: https://doi.org/10.1101/2021.04.12.439537). These findings motivate Aim 3 of this proposal which examines social learning in hearing loss-reared animals.

1) Caras ML, Sanes DH (2015) Sustained perceptual deficits from transient developmental deprivation. J Neurosci 35:10831-10842. PMCID: PMC4518056
2) von Trapp G, Aloni I, Young SK, Semple MN, Sanes DH (2017) Developmental hearing loss impedes auditory procedural learning and performance. Hearing Res 347:3-10. PMCID: PMC5391307
3) Yao JD, Sanes DH (2018) Developmental deprivation-induced perceptual and cortical processing deficits in awake-behaving animals. eLife 2018; 7:e33891. PMCID: PMC6005681.
4) Anbuhl KL, Yao JD, Hotz RA, Mowery TM, Sanes DH. Auditory processing remains sensitive to environmental experience during adolescence. bioRxiv 2021.04.12.439537; doi: https://doi.org/10.1101/2021.04.12.439537

4. Long-term inhibitory synaptic plasticity

A characteristic feature of our research has been a concentration on long-term inhibitory synaptic plasticity. Inhibitory synapses are essential to every computation performed by the central nervous system, and their dysfunction has increasingly been tied to developmental disorders such as autism. For example, we showed that - like excitatory systems - inhibitory projections become more precise during development, and this process is activity-dependent (Sanes and Siverls, 1991; Sanes and Takacs, 1993). In fact, our subsequent research uncovered some of the cellular mechanisms that control the strength of developing inhibitory synapses, and which may support the refinement of these contacts in response to auditory experience (Kotak and Sanes, 2000; Kotak et al., 2001; Kotak and Sanes, 2002; Chang et al., 2003; Kotak & Sanes, 2014). When it became clear that inhibitory synapse function is influenced by the auditory environment, I was motivated to explore the implications for hearing loss. In fact, developmental hearing loss leads to a significant decrease of inhibitory synaptic strength in the lateral superior olive, inferior colliculus, medial geniculate, auditory cortex, and auditory striatum (Kotak and Sanes, 1996; Vale and Sanes, 2000; Vale et al., 2003, 2004; Kotak et al., 2005, 2008; Takesian et al., 2010, 2012, 2013; Mowery et al., 2015, 2017, 2019). This line of research culminated in a recent study showing that auditory perceptual deficits can be remediated by restoring normal inhibitory synapse strength in hearing loss-reared animals (Mowery et al., 2019). Finally, we have discovered that the synaptic mechanisms commonly thought to support learning (i.e., long-term potentiation) do not mature properly in the auditory cortex following early hearing loss (Kotak et al., 2007; Xu et al., 2010). This cellular finding was a motivating factor in our decision to study the impact of hearing loss on learning.

1) Kotak VC, Breithaupt AD, Sanes DH (2007) Developmental hearing loss eliminates LTP in the auditory cortex. Proc Natl Acad Sci USA 104: 3550-3555. PMCID: PMC1805556
2) Xu H, Kotak VC, Sanes DH (2010) Normal hearing is essential for cortical inhibitory long-term potentiation. J Neurosci 30: 331-341. PMCID: PMC2823134
3) Takesian AE, Kotak VC, Sanes DH (2010) Presynaptic GABA(B) receptors regulate experience-dependent development of inhibitory short-term plasticity. J Neurosci 30: 2716-2727. PMCID: PMC3842473
4) Mowery TM, Penikis KB, Young SK, Ferrer CE, Kotak VC, Sanes DH (2017) Sensory striatum is permanently impaired by developmental deprivation. Cell Reports 19:2462-2468. PMCID: PMC5577933.

5. Textbook in Neural Development

For the past 20 years, I have co-authored an undergraduate textbook on neural development, in collaboration with Tom Reh and Bill Harris. Some of the chapters I write (e.g., Refinement of Synaptic Connections, Behavioral Development) are relate directly to this proposal. My co-authors and I recently completed the Fourth Edition.

1) Sanes DH, Harris WA, Reh TA (2000) Development of the Nervous System, Academic Press.
2) Sanes DH, Harris WA, Reh TA (2006) Development of the Nervous System, 2nd Edition, Academic Press.
3) Sanes DH, Harris WA, Reh TA (2012) Development of the Nervous System, 3rd Edition, Academic Press.
4) Sanes DH, Harris WA, Reh TA (2019) Development of the Nervous System, 4th Edition, Academic Press.

MyNCBI Bibliography: https://www.ncbi.nlm.nih.gov/myncbi/16KahxvZsaxAp/bibliography/public/

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **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 .	Dr.	Dan	H.	Sanes	PhD	PD/PI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
2	Post Doctoral Associates	19			[redacted]	[redacted]	[redacted]
1	Graduate Students	12			[redacted]	[redacted]	[redacted]
	Undergraduate Students						
	Secretarial/Clerical						
3	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 1**

C. Equipment Description

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

Equipment Item	**Funds Requested ($)***
1 . White Matter wireless 128 channel headstage	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total funds requested for all equipment listed in the attached file	
Total Equipment	[redacted]

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	[redacted]
[redacted]	
[redacted]	[redacted]

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

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Costs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus RESEARCH	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Sanes_R01_Budget_Just_v61035488648.pdf (Only attach one file.)

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **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 .	Dr.	Dan	H.	Sanes	PhD	PD/PI	0.00		3	3	[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
2	Post Doctoral Associates	24			[redacted]	[redacted]	[redacted]
1	Graduate Students	12			[redacted]	[redacted]	[redacted]
	Undergraduate Students						
	Secretarial/Clerical						
3	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 2**

C. Equipment Description

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

Equipment Item	**Funds Requested ($)***
1 . White Matter wireless 128 channel headstage	[redacted]
Total funds requested for all equipment listed in the attached file	
Total Equipment	[redacted]

Additional Equipment: File Name:

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

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

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Costs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus RESEARCH	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Sanes_R01_Budget_Just_v61035488648.pdf (Only attach one file.)

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **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 .	Dr.	Dan	H.	Sanes	PhD	PD/PI	0.00		3	3	[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
2	Post Doctoral Associates	24			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]
	Undergraduate Students						
	Secretarial/Clerical						
3	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **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)	[redacted]
2. Foreign Travel Costs	
Total Travel Cost	[redacted]

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

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 3**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Costs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Total Other Direct Costs	[redacted]

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . On Campus RESEARCH	[redacted]	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency DHHS, [redacted]
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	**Funds Requested ($)***

K. Total Costs and Fee	**Funds Requested ($)***
	[redacted]

L. Budget Justification*	File Name: Sanes_R01_Budget_Just_v61035488648.pdf (Only attach one file.)

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **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 .	Dr.	Dan	H.	Sanes	PhD	PD/PI	0.00		3	3	[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
2	Post Doctoral Associates	24			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]
	Undergraduate Students						
	Secretarial/Clerical						
3	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **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)	[redacted]
2. Foreign Travel Costs	
Total Travel Cost	[redacted]

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

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Costs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus RESEARCH	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Sanes_R01_Budget_Just_v61035488648.pdf (Only attach one file.)

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **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 .	Dr.	Dan	H.	Sanes	PhD	PD/PI	0.00		3	3	[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
2	Post Doctoral Associates	24			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]
	Undergraduate Students						
	Secretarial/Clerical						
3	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **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)	[redacted]
2. Foreign Travel Costs	
Total Travel Cost	[redacted]

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

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Costs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus RESEARCH	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Sanes_R01_Budget_Just_v61035488648.pdf (Only attach one file.)

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

Tracking Number: GRANT13382552 Funding Opportunity Number: PA-20-185 . Received Date: 2021-06-04T16:48:01.000-04:00

BUDGET JUSTIFICATION

Senior Personnel

[redacted] Ph.D., *Principal Investigator*
3 academic months and 3 summer months
[redacted] will be responsible for the overall direction and supervision of the project. He is able to carry out any aspect of the proposed behavior, pharmacological, and awake-behaving electrophysiology experiments, and he will participate on each of these in collaboration with graduate and postdoctoral students. The salary requested of NIH in each grant year is to cover 3 academic and 3 summer months.

[redacted] Postdoctoral Research Scientist
7 calendar months in Year 1, and 12 calendar months thereafter
[redacted] is currently completing her doctoral thesis [redacted] and will join the laboratory in July of 2021. [redacted] thesis research employed behavioral training, pharmacological manipulation, electrophysiological recordings, and molecular assays to study the mechanisms that support long-term memory in the auditory system. Therefore, her intellectual and technical background is ideal for this project, and will perform many of the awake-behaving recordings (Aim 2), as well as hearing loss experiments (Aim 3). [redacted] will join the project in month 6 of the first year, after she has completed her initial project in my laboratory.

[redacted] Postdoctoral Research Scientist
12 calendar months
As an undergraduate in the [redacted] Lab (University [redacted]), [redacted] studied dopamine signaling in a learning paradigm, and designed drivable 64-channel tetrode arrays and optical fiber assemblies for chronic implantation. As a graduate student in the [redacted] lab [redacted], [redacted] studied the cortical mechanisms associated with noise-induced hearing loss, including the reduction of inhibitory drive and chemogenetic activation of inhibitory interneurons to alleviate behavioral deficits. Therefore, his technical intellectual and technical background is ideal for this project, and he will perform many of the pharmacological manipulations of auditory cortex and awake-behaving photometry recordings (Aim 1).

[redacted] Graduate Student
12 calendar months
I have recruited a new graduate, [redacted] to participate on this proposal. [redacted] performed a rotation in our lab, working on gerbil auditory behavior in a naturalistic environment, and is currently learning to perform awake-behaving recordings form auditory cortex. His has a primary interest is in auditory cortex encoding during social interactions, and the effects of developmental hearing loss, and I expect him to contribute to both Aims 2 & 3.

Fringe Benefits
The fringe benefit rate for the PI and staff is [redacted] as per [redacted] agreement with DHHS dated September 17, 2020. Graduate Research Assistants receive tuition remission in lieu of fringe benefits.

EQUIPMENT

Year 1
Purchase of equipment to construct a new in vivo awake-behaving recording system is requested during the first year. The proposed new system will consist of TDT hardware for stimulus deliver and data acquisition [redacted], and a photometry system (Doric Lenses, [redacted], and a PC computer & monitor [redacted]. I have already purchased a wireless 128 channel amplifiers and headstage system that permits for recordings from up to 4 animals. However I will require additional amplifiers and controller units (which remain with each implanted animal throughout an experiment) so that sufficient animals can be run concurrently (White Matter, [redacted].

Year 2
To complete the proposed experiments, it will be essential to have 2 contemporary systems for the scientists involved. During the second year, we will purchase additional wireless 128 channel amplifiers and a headstage system (White Matter, [redacted]

For All Years

SUPPLIES

+ Surgical: For several of the Aims, surgical procedures are used to expose the central nervous system for viral vector injections, cannula implantation, and electrode array implantation. The procedures require isoflurane and isoflurane scavenger filters, Palacos dental cement, heating blankets, sterile PPE, surgical drape material, bone wax, silicone mixing wells, Kwil-sil adhesive, sutures, antibiotics, optical ointment, sterile Normasol, syringes and needles, sharps containers, analgesics, surgical instruments, autoclave bags, and medical grade Oxygen [redacted]
+ Pharmacological agents: In Aim 1 experiments, it will be necessary to infuse auditory cortex with specific pharmacological agents, including a GABA receptor agonist (muscimol), a D1/D5 agonist (SFK-38393), and a D1/D5 antagonist (SCH-23390) [redacted] and incremented [redacted] in subsequent years).
+ Data storage: The short- and long-term storage of electrophysiology data require both local hard disk backups using a Synology system within our lab. To accommodate new data storage on the Synology system, we will purchase four 16 Tb hard disks in year 1 [redacted], six 16 Tb hard disks in Year 2 [redacted] in year 2), and ten 16 Tb hard disks in years 3-5 [redacted] in year 3, and incremented [redacted] in subsequent years), and cloud storage which is provided [redacted]
+ Histology: Tissue processing will be required to localize the position of cannulae, electrode arrays, and GRAB-DA injections. This will require paraformaldehyde and tissue mounting supplies ([redacted] in year 1, incremented [redacted] in year 3, and incremented [redacted] subsequent years).
+ In vivo electrophysiology: In Aims 2 and 3, we record from auditory cortex using 64 channel electrode arrays (Neuronexus) which are currently priced at [redacted] each when ordered with contact activation to permit low impedance recordings (13 electrodes in years 1 and 2: [redacted] 30 electrodes in year 3: [redacted] and incremented [redacted] in years 4 and 5).
+ Drug infusion: To infuse drugs directly into auditory cortex, we will require implantable cannulae and associated pieces from P1 Technologies, Hamilton gastight syringes and needles, and PE tubing ([redacted] in year 1, and incremented [redacted] in subsequent years).
+ Virus: A viral vector expressing the dopamine reporter, GRAB-DA1h, will be constructed by Penn Vector Core ([redacted] in year 1, and incremented [redacted] in subsequent years).
+ Optic fibers: Fiber optic cannulae will be implanted for photometric imaging ([redacted] in year 1, and incremented [redacted] in subsequent years).
+ Procedure cages: Animal running cages are made of plastic and due to animal chewing, must be restored and replaced ([redacted] in year 3, and $[redacted] in years 4 and 5).
+ Food pellets: All behavioral experiments require Dustless Precision 20 mg Pellets which are accuratedly dispensed and counted. At a bulk rate of 12 or more boxes, the cost is [redacted] each [redacted] in year 1, and incremented [redacted] in subsequent years).

ANIMAL PURCHASE AND CARE

For gerbils, the cost of procuring 8 breeding pairs (16 animals) each year is [redacted] (Charles River) ([redacted] in year 1, and incremented [redacted] in subsequent years). The animal care cost at New York University will be [redacted] /cage/day. With breeders and experimental animals, 50 cages will be used in year 1 ([redacted]), 55 cages in year 2 [redacted], and 85 cages in Years 3-5 [redacted] year 3, and incremented [redacted] in subsequent years), as the pace of experiments increases.

TRAVEL

Funds are requested for travel to 2 meetings in the United States (Society for Neuroscience Annual Meeting, Association for Research in Otolaryngology Winter Meeting) by the Principal Investigator and two students. The cost of travel, lodging, registration, and meals is approximately [redacted] per person per meeting, depending on the location and available housing. This cost assumes round trip airfare of [redacted] a nightly hotel charge of [redacted] for 4 days (shared room), and meal charges of [redacted] per day for 4 days. Registration is approximately [redacted] (3 investigators x 2 trips per year = 6 trips: [redacted] in year 1, and incremented [redacted] in subsequent years).

OTHER EXPENSES

1) Publication: The average cost of preparing manuscripts, including page charges has averaged [redacted] Estimating future publications from our publication rate over the past 5 years, [redacted] will be required in year 1 (incremented by [redacted] in subsequent years)

2) Maintenance: Much of the electrical, computer, and general lab equipment used in the proposed study is only serviceable by the manufacturer, and much of it is out of warranty. Therefore, funds are requested to maintain this equipment in working condition. [redacted] in year 1, and incremented by [redacted] in subsequent years)

3) Tuition Remission: Tuition remission costs are charged at [redacted] of the graduate student salary. [redacted] in year 1).

Facilities and Administration

In accordance with the DHHS agreement dated 9/17/2020, indirect costs are calculated on a modified total direct cost (MTDC) base. Indirect costs are [redacted] of MTDC, excluding tuition remission, capital equipment $[redacted] or greater, and subcontracts in excess of [redacted].

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)
Section A, Senior/Key Person	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
1. Domestic	[redacted]
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	[redacted]
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Section G, Direct Costs (A thru F)	[redacted]
Section H, Indirect Costs	[redacted]
[redacted]	[redacted]
Section J, Fee	
Section K, Total Costs and Fee (I + J)	[redacted]

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OMB Number: 0925-0001

Expiration Date: 02/28/2023

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*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)

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3. Human Embryonic Stem Cells Section

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

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, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ❍ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ❍ Yes ❍ No

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

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

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Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	2_RP_Specific_Aims__SL__v121035305005.pdf
3. Research Strategy*	3_RP_Research_Strategy__SL__v131035488534.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	8_RP_Vertebrate_Animals__SL__v11035305007.pdf
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	Letter_of_Support_[redacted]_1035305008.pdf
10. Resource Sharing Plan(s)	13_Resource_Sharing_Plan__SL__v11035305009.pdf
11. Authentication of Key Biological and/or Chemical Resources	Authentication_of_Key_Resources_Plan1035305010.pdf
Appendix	
12. Appendix	

SPECIFIC AIMS [Abbreviations: **AC**, auditory cortex; **DA**, dopamine; **HL**, hearing loss; **SL**, social learning]

Skill acquisition can be facilitated by social experience, usually through exposure to a conspecific performing a well-defined behavior (Bandura, 1971). In fact, social learning (**SL**) is pivotal to the acquisition of many behaviors, including aural communication (Kuhl, 2007). Although the neural bases for auditory SL remain uncertain, one plausible idea is that social cues induce experience-dependent plasticity in auditory cortex (**AC**). Support for this idea draws from AC's role in many forms of learning (Recanzone et al., 1993; Polley et al., 2006; Aizenberg and Geffen, 2013; Caras and Sanes, 2017), including those that rely on social experience (Marlin et al., 2015). Therefore, this proposal asks whether social experience induces a form of AC plasticity that serves to facilitate auditory task acquisition. Three advances make this goal viable:

First, we developed a SL paradigm (Paraouty et al., 2020) in which auditory task acquisition is facilitated in naïve Observer gerbils that are exposed to a Demonstrator gerbil performing an auditory Go-Nogo task across an opaque divider (Figures 1 & 2A). Second, we found that SL is supported by dopamine (**DA**) signaling (see Figure 6), similar to reward learning. Third, Demonstrator gerbils vocalize at trial onset, and the number of Demonstrator vocalizations predicts an Observer's rate of task acquisition (see Figure 3).

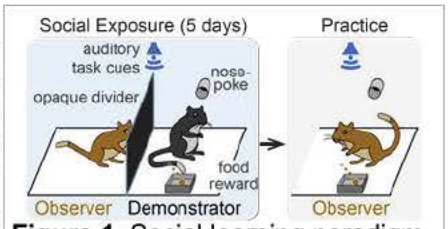

Figure 1 Social learning paradigm.

Finally, auditory SL may have implications for developmental hearing loss (**HL**), a prevalent sensory impairment that is associated with persistent deficits in perception, speech, and language processing (see Significance). For example, social factors may facilitate language acquisition in children with HL (e.g., Ambrose et al., 2015). Therefore, the proposal concludes by testing whether SL can facilitate auditory learning in HL-reared animals.

Together, these observations motivate the core hypothesis that *social exposure to a Demonstrator performing a sound discrimination task induces auditory cortex plasticity that is causally related to an Observer's enhanced rate of task acquisition*. Three Aims test predictions that emerge from this hypothesis:

AIM 1 *ARE AUDITORY CORTEX ACTIVITY & PLASTICITY NECESSARY FOR SOCIAL LEARNING OF AN AUDITORY TASK?*

Prediction 1A: If the hypothesis is correct, then inactivating AC during Social Exposure will diminish learning.

Design: To determine whether AC is necessary for SL, naïve littermates will be instrumented bilaterally with cannulae in AC, and receive either muscimol (to inactivate AC) or saline infusions during the five days of exposure to a trained Demonstrator performing an amplitude modulation rate discrimination task. An opaque divider separates the Observer and Demonstrator, such that visual cues are absent. Observer gerbils will then be permitted to practice the auditory task, and the rate of learning assessed. AC inactivation during exposure to Task Cues Only, without a Demonstrator, will serve as the control condition (see Figure 2C).

Prediction 1B: If the hypothesis is correct, then neuromodulation within AC will be necessary for social learning.

Design: Systemic manipulation of DA signaling regulates SL (see Figure 6). Therefore, we will first determine whether DA release occurs in AC during SL, using fiber photometry to measure DA signaling in AC with a genetically expressed dopamine sensor (GRABDA). To determine whether DA signaling is necessary for SL, DA receptors will be pharmacologically blocked or activated in AC during the observation period, using cannulae.

AIM 2 *IS AUDITORY CORTEX PLASTICITY SUFFICIENT TO EXPLAIN SOCIAL LEARNING OF AN AUDITORY TASK?*

Prediction: If the hypothesis is correct, then AC sensitivity to auditory cues will be enhanced by Social Exposure.

Design: To determine whether AC neuron stimulus encoding is altered during Social Exposure, naïve littermates will be instrumented with electrode arrays in AC, and recorded during five days of Social Exposure (as in Aim 1). Recordings will continue while Observers subsequently practice the auditory task. Single neuron and population responses to Go and Nogo stimuli will be assessed to determine if improved neural sensitivity during Social Exposure correlates with task acquisition rate during practice. To determine the effect of non-social cues, recordings will be obtained from naïve Observers that are exposed to auditory Task Cues Only (no conspecific). To test the contribution of a specific auditory social cue, Demonstrator vocalizations (Figure 3), recordings will be obtained from naïve Observers exposed to auditory task cues plus playback of Demonstrator vocalizations.

AIM 3 *DOES SOCIAL LEARNING IMPROVE THE ACQUISITION OF AN AUDITORY TASK FOLLOWING DEVELOPMENTAL HL?*

Prediction: If the hypothesis is correct, then Social Exposure should normalize learning in HL-reared animals.

Design: HL-reared gerbils display delayed auditory learning (e.g., von Trapp et al., 2017). To determine whether Social Exposure enhances task acquisition and perceptual learning, gerbils will receive either bilateral malleus removal, earplugs, or sham treatment at P10. Animals will be instrumented with electrode arrays in AC, and tested on the SL paradigm. Both procedural and perceptual learning rate will be assessed. For comparison, separate groups will be trained and tested with Task Cues Only, or task cues plus vocalizations (as in Aim 2).

The long-term impact of this research will be to identify a CNS mechanism that mediates socially-enhanced auditory learning, and provide a novel approach to overcome sensory and cognitive barriers in children with HL.

RESEARCH STRATEGY

a. **SIGNIFICANCE** [Abbreviations: **AC**, auditory cortex; **DA**, dopamine; **HL**, hearing loss; **SL**, social learning]

"Does the project address an important problem?" "How will scientific knowledge be improved?"

Auditory perceptual skills can improve with practice, requiring many forms of learning (Saffran et al., 2006; Ortiz and Wright, 2009; Wright et al., 2010). However, mechanistic studies of auditory learning have largely bypassed a cardinal attribute that facilitates skill acquisition: social experience. This proposal addresses the problem by exploring neural mechanisms that support auditory social learning (**SL**). *Aim 1* tests whether auditory cortex (**AC**) activity and plasticity are required for social learning. *Aim 2* tests whether social exposure improves AC neuron stimulus encoding, thereby accelerating learning. *Aim 3* asks whether social exposure is sufficient to improve the rate of auditory learning in animals with developmental hearing loss (**HL**). This Aim is a departure from most basic research on HL which has focused on sensory processing deficits. Successful completion of this proposal will improve scientific knowledge by providing evidence for an AC mechanism that may explain the benefits of SL, both in normal hearing and HL-reared animals. Below, I present the logic that motivates this proposal:

SOCIAL LEARNING IS A PREVALENT BEHAVIORAL MECHANISM THAT FACILITATES SKILL ACQUISITION

WHAT IS SOCIAL LEARNING?: *Social learning* typically occurs when a naïve animal experiences a conspecific performing a well-defined behavior and, as a consequence, acquires that behavior more rapidly than would occur without the social element, and despite the absence of reinforcement (Zajonc, 1965; Bandura, 1971; Zental & Galef, 1988; Heyes, 1994; Zentall, 2012; Carcea & Froemke, 2019). SL is found throughout the animal kingdom, and can be mediated by all sensory modalities. Thus, gerbils and rats acquire dietary preferences by smelling or tasting food on the mouths of familiar conspecifics (Laland and Plotkin, 1993; Valsecchi et al., 1996), chimpanzees and cockatoos learn tool use to obtain food by watching a conspecific demonstrator (Auersperg et al., 2017; Vale et al., 2017), blue tits learn to associate a vocalization with antipredator behaviors by listening to heterospecific great tits (Keen et al., 2020), and bats can learn to avoid a poisonous toad species through social observation of an acoustic prey cue (Page & Ryan, 2006). Despite its pervasive impact, most auditory learning experiments study the neural mechanisms of operants, and would be enriched by inclusion of social experience.

WHAT IS THE RATIONALE FOR STUDYING AUDITORY SOCIAL LEARNING?: While SL through visual experience is better-studied (Carlier and Jamon, 2006; Petrosini et al., 2003; Saggerson and Honey, 2006), the acquisition of complex behaviors often involves acoustic cues. In fact, a practical attribute of auditory cues is that animals can accurately localize objects in the dark or in any spatial position (Payne, 1971; Fuzessery et al., 1993; Caldwell and Bee, 2014). For example, blind gerbils evade capture by owls as effectively as those with vision (Lay, 1974). Since gerbils retain a representation of their environment when vision is occluded (Ellard and Eller, 2009), it is likely that they continuously track sound location. In principle, this information may be relayed to hippocampal 'social place cells' and facilitate SL (Omer et al., 2018; Teruko et al., 2018).

A second rationale for studying auditory SL draws from its role in aural communication. Thus, while juvenile songbirds can learn a species-specific vocalization from playback alone, learning is facilitated by social exposure to a tutor (Eales, 1989; Derégnaucourt et al., 2013; Chen et al., 2016). Social experience with an alien species can even override a preference for learning the conspecific song (Immelmann, 1969; Baptista and Petrinovich, 1986). Similarly, learning to discriminate between songs is enhanced by social exposure to a demonstrator that is performing the task (Narula et al., 2018). In human infants, the ability to discriminate between foreign speech sounds is lost by one year, while exposure to a live foreign speaker, but not an audiovisual recording, restores this ability (Kuhl et al., 2003). Although it is commonly assumed that rodents do not learn vocal behavior, naked mole-rats - which live in cooperative groups, like gerbils - learn colony-specific vocalizations (Barker et al., 2021). Thus, animals attend to social acoustic cues, and learn from them, which motivate the study of auditory SL.

ARE GERBILS A FAVORABLE SPECIES IN WHICH TO STUDY AUDITORY SOCIAL LEARNING?: Like other rodents, gerbils have an elaborate repertoire of social behaviors (Hurtado-Parrado et al., 2015). However, gerbil also displaying significant vocal communication in the audible range (Ter-Mikaelian et al., 2012) which is likely to be integral to social behaviors. Gerbils live in dark, complex underground burrows, as families of ~15 animals, in multi-family neighborhoods with strictly enforced territorial boundaries (Swanson and Lockley, 1978; Ågren et al., 1989; Scheibler et al., 2004, 2006a, 2006b). In fact, our pilot findings show that gerbil families produce thousands of vocalizations per day (Figure 4), suggesting that SL is a plausible element of its natural repertoire.

AUDITORY CORTEX PLASTICITY IS CAUSALLY ASSOCIATED WITH MANY FORMS OF LEARNING

Sound encoding by AC neurons can be modified, both by chronic environmental stimuli and by learning (reviews: Weinberger, 2007; Sanes and Bao, 2009; Schreiner and Polley, 2014). For example, learning to detect or discriminate a spectral cue causes a persistent shift of single AC neuron response properties towards the

conditioned spectrum, and an expansion of its topographic representation (Recanzone et al., 1993; Blake et al., 2002; Blake et al., 2006; Polley et al., 2006; Keeling et al., 2008; Shepard et al., 2016). Similar forms of plasticity are found for temporal or sound level cues (Beitel et al., 2003; Bao et al., 2004; Polley et al., 2004). Moreover, the magnitude of AC plasticity correlates with both learning magnitude and its resistance to extinction (Rutkowski and Weinberger, 2005; Bieszczad and Weinberger, 2010). At mechanistic level, learning-induced AC plasticity may be gated by synaptic inhibition (Letzkus et al., 2011; Sarro et al., 2015; Aizenberg et al., 2015), which may influence context-dependent processing (Phillips et al., 2017). Since AC plasticity is observed in anesthetized animals, after learning has occurred, it is likely to include long-term changes to ascending or local connections.

There is also evidence that AC plays a causal role in auditory learning: AC inactivation during training leads to diminished learning even though animals can perform the task (Aizenberg and Geffen, 2013; Caras and Sanes, 2017). Similarly, NMDA receptor blockade during the sensory acquisition phase diminishes song learning in juvenile birds (Aamodt et al., 1996; Basham et al., 1996). Our pilot data suggests that AC plays a similar role during SL (Figure 5). *Together, this literature supports a strategy that targets AC as a site that may support auditory SL (Aim 1), and explores whether task-specific information is, indeed, stored there (Aim 2).*

A PLAUSIBLE NEURAL MECHANISM TO ACCOUNT FOR AUDITORY-BASED SOCIAL LEARNING

The neural mechanisms that govern SL are manifold (Olsson et al., 2020). Therefore, this proposal targets a theoretical framework that draws support from reward learning mechanisms. Explicit rewards, such as food, can reinforce behaviors and facilitate learning, in part by engaging dopamine (**DA**) signaling (Schultz et al., 1997; Bromberg-Martin et al., 2010; Schultz, 2013; Gottlieb et al., 2014). Specifically, DA neuron activity in substantia nigra pars compacta and the ventral tegmental area is correlated with reward anticipation and presentation, and is thought to guide learning through D1 receptor-dependent long-term potentiation (Speranza et al., 2021).

Dopamine also plays a key role in auditory-based vocal learning (discussed above). DA release in the cortical nucleus, HVc, is selectively activated by a live, singing tutor. Eliminating DA signaling during tutoring prevents song learning (Tanaka et al., 2018). In fact, DA innervation is found throughout the mammalian auditory pathway, including the AC (Harris et al., 2021). Thus, DA is released in gerbil AC during auditory learning, and DA receptor activation facilitates stimulus-evoked responses in AC for up to 45 mins (Stark and Scheich, 1997; Happel et al., 2014; Brunk et al., 2019; Deliano et al., 2020). Furthermore, DA afferent activity can induce long-term plasticity of tone-evoked responses in AC (Bao et al., 2001). Finally, DA-induced AC plasticity is associated with learning: systemic activation of D1/D5 receptors facilitates auditory discrimination learning in gerbils, while local blockade of this receptor in AC impairs the retention of the auditory task (Schicknick et al., 2008, 2012). Our preliminary findings are consistent with a role for DA signaling during social learning (Figure 6).

A second rationale for studying dopaminergic modulation is that social signals are thought to constitute an *implicit* reward that acts through DA signaling (Trezza et al., 2011; Panksepp and Lahvis, 2017; Dölen et al., 2013; Gunaydin et al., 2014; Hung et al., 2017). For example, fluctuations in DA levels occur in rat nucleus accumbens when naïve animals observe the delivery of an explicit reward to a conspecific (Kashtelyan et al., 2014). Furthermore, DA has been shown to play a pivotal role in the social transmission of food preferences and aggressive behaviors (Rodriguiz et al., 2004; Choleris et al., 2011; Suzuki and Lucas, 2015; Matta et al., 2017). DA signaling has even been causally associated with the pleasure evoked by music, or by the experience of successfully learning new words without explicit rewards (Ripollés et al., 2018; Ferreri et al., 2019). Therefore, DA signaling is a plausible mechanism for explaining social facilitation of auditory learning, assessed in Aim 1.

The mechanistic framework described here will likely expand as the project matures. For example, cingulate cortex receives a direct projection from AC and processes social signals, including vocalizations (Budinger et al., 2000; Johnstone et al., 2006: Allsop et al., 2018; Burgos-Robles et al., 2019; Smith et al., 2021). Lesions to gerbil cingulate diminish social behaviors (Ellard et al., 1990). We will also consider other neuromodulators that have been implicated in SL (Dölen et al., 2013; Hung et al., 2017; Moreno et al., 2018; Carcea et al., 2020).

SOCIAL EXPERIENCE MAY COUNTERACT BEHAVIORAL DEFICITS INDUCED BY DEVELOPMENTAL HEARING LOSS

DEVELOPMENTAL HEARING LOSS IMPACTS SENSORY & COGNITIVE PROCESSING: Developmental HL is the most common birth defect and sensorineural impairment, posing a risk for deficits in speech and language acquisition (Schonweiler et al., 1998; Psarommatis et al., 2001; Morton & Nance, 2006; Aithal et al. 2012; Svirsky et al. 2004; Kishon-Rabin et al., 2015). One explanation for these deficits is that degraded *sensory processing* causes perceptual impairments. Both clinical and basic research support this framework: both perceptual and central neural deficits can persist even after a transient period of HL (*human perception*: Pillsbury et al. 1991; Wilmington et al., 1994; Hall & Grose 1994; Hall et al. 1995; Hogan et al. 1996; Hall et al. 1998; Hogan & Moore 2003; Whitton & Polley 2011; McKenna Benoit et al., 2018; *human neural*: Folsom et al. 1983; Haapala et al.

2013; *non-human perception*: Knudsen et al., 1984; Caras & Sanes, 2015; *non-human neural*: Knudsen, 1985; Popescu & Polley, 2010; Polley et al. 2013; Mowery et al., 2015, 2016, 2017). In fact, restoring normal synaptic function can rescue normal perception in HL-reared gerbils (Mowery et al., 2019).

A second explanation for speech and language deficits is that HL can delay or impair *cognitive processing* skills, including attention, working memory, and learning (*verbal IQ & math*: Teele et al., 1990; *phonological skills*: Briscoe et al., 2001; Wake et al., 2006; Park and Lombardino, 2012; *attention*: Yucel and Derim, 2008; Barker et al. 2009; *working memory*: Pisoni and Cleary, 2003; Pisoni et al., 2011; Burkholder and Pisoni, 2003; *learning*: Bennett & Furukawa, 1984; Pittman et al. 2005; Conway et al. 2011; Kronenberger et al. 2014; *executive function*: Beer et al. 2014). Similarly, developmental HL is associated with learning delays in gerbils (von Trapp et al., 2017), even after audibility returns to normal (Caras & Sanes, 2015; Anbuhl et al., bioRxiv, see Bibliography).

RELEVANCE OF SOCIAL EXPOSURE TO DEVELOPMENTAL HEARING LOSS RESEARCH: While many studies assess the effects of auditory training on the performance of a perceptual task, they are typically conducted in the absence of a social context. Thus, individual practice on a task leads to improved performance across many auditory dimensions (Wright et al., 1997; Mossbridge et al., 2006; Kacelnik et al., 2006; Sabin et al., 2012; Caras & Sanes, 2017). However, social factors can enable or facilitate learning, as discussed above. In fact, there are many qualitative studies that document an impact of social factors on language acquisition in children with HL, including active parental language input (Erbasi et al., 2018; Nittrouer et al., 2019). Thus, measures of parent performance as a "Demonstrator" (e.g., lexical repetition) correlate with language acquisition in their children with cochlear implants (Wang et al., 2020). In fact, coaching parents to serve as better Demonstrators can improve language acquisition in children with HL (Lund, 2018). The basic research literature also reveals an effect of social experience: social isolation reduces starling AC call-selective neurons, even when birds experience the adult conspecific songs (Cousillas et al., 2006). *Together, these results support Aim 3 in which the SL paradigm is tested for its capacity to ameliorate HL-induced learning delays.*

SCIENTIFIC RIGOR: The cited studies, and our preliminary results, have used proper control groups. However, most do not implement a double-blind procedure for acquisition and analysis. Our study attempts to address this by: (1) blinding the experimenter to treatment group, (2) comparing data collected by two experimenters, and (3) coding and analyzing raw data by a blind third experimenter. Furthermore, we will control for the key biological variables, sex and age. An equal number of male and female subjects will be used, and we will consider the influence of sex in the interpretation of our results. Since our research program has focused on developmental HL, we will restrict our manipulations and analyses to a well-established age range during which HL induces neural and behavioral deficits, as discussed above.

b. **INNOVATION**

To determine whether AC plasticity supports social learning, a key set of issues must be addressed: First, we must determine whether there is a causal relationship between AC activity and social learning. Second, we must establish whether AC neuron coding properties are modified by social experience. Third, it would be advantageous to test whether SL is a viable strategy to facilitate auditory learning in a developmental HL model. Here, we describe the innovations that address these challenges:

(i) *"seeks to shift current research paradigms"*: Current research paradigms that focus on perceptual skills and learning, including our own, have relied on experimenter-controlled animal training procedures to shape an animal's behavior (Bouton, 2016). In contrast, this proposal emphasizes a role for conspecific social cues which are often pivotal to naturally acquired behaviors. In fact, gerbils learn an auditory task more rapidly when they are previously exposed to a Demonstrator that performs the task (Paraouty et al., 2020). Thus, the proposal seeks to shift current auditory learning paradigms from their current focus on classical or operant conditioning paradigms, to one that incorporates socially-mediated cues that facilitate learning.

(ii) *"novel approaches or methodologies, and advantages over existing"*: Studies on the neural bases of learning typically compare neurophysiological measurements between trained versus untrained animals, often after the behavioral assay is completed. In contrast, we can record wirelessly from animals during the period of learning (Caras and Sanes, 2017, 2019), permitting us to (1) explore the kinetics of practice-induced changes to neural processing, and (2) make within-animal comparisons of neural and behavioral performance. We now extend this approach to social experience, thereby removing an essential barrier to studying the neural mechanisms of SL.

(iii) *"new application of theoretical concepts"*: Theoretical concepts of HL, including our own, have emphasized a sensory framework, whereby degraded sensory processing leads to perceptual impairments. In contrast, this proposal will focus on social signals that may facilitate skill acquisition. Thus, the proposal will expand our current concept of sensory performance to include a more realistic assessment of socially-mediated task learning.

c. **APPROACH**

PRELIMINARY RESULTS

Here, we present feasibility studies and pilot data in support of the three Specific Aims.

A PARADIGM FOR STUDYING THE NEURAL BASES FOR AUDITORY SOCIAL LEARNING

(1) **A social learning paradigm in gerbils that facilitates auditory task acquisition** (Paraouty et al., 2020): We developed a social learning paradigm in which gerbils acquire an auditory task more rapidly when previously exposed to a trained conspecific that is performing the task accurately (Paraouty et al., 2020). During 5 daily sessions, naïve Observer gerbils experience a trained Demonstrator perform an auditory Go-Nogo task on the other side of an opaque divider to eliminate visual cues (Figure 2A): The Demonstrator (1) initiates trials by nose-poking, which (2) triggers either a Go or Nogo sound cue; the Go cue is 12 Hz amplitude modulated noise and the Nogo is 4 Hz amplitude modulated noise, and (3) seeks a food reward on Go trials or returns to the nose-poke on Nogo trials. After the 5th day of Social Exposure, the Observer begins to practice the task. Figure 2B shows that Observers learn to perform the Go-Nogo task by 5 days at a criterion of d'=1.5 (thin lines: individual animals; thick line & shading: $\bar{x}$ ± SE). Paraouty et al. (2020) also established that Observer gerbils with no prior Social Exposure take 14.5 days to acquire the task (Figure 2B, gray line). To control specifically for social cues, naïve Observer gerbils experienced the Task Cues Only: 4 and 12 Hz amplitude modulated stimuli, and delivery of pellets to the food tray (Figure 2C). These controls subsequently acquired the task in 8.5 days, significantly longer than with Social Exposure (Figure 2D; social learning curve from Fig 2B shown for comparison). The learning observed following exposure to Task Cues Only is consistent with human findings that acoustic exposure can facilitate learning (Wright et al., 2010; 2015), and rat experiments showing a facilitatory effect of passive stimulation (Sakai & Kudoh, 2005; Fleming et al., 2019).

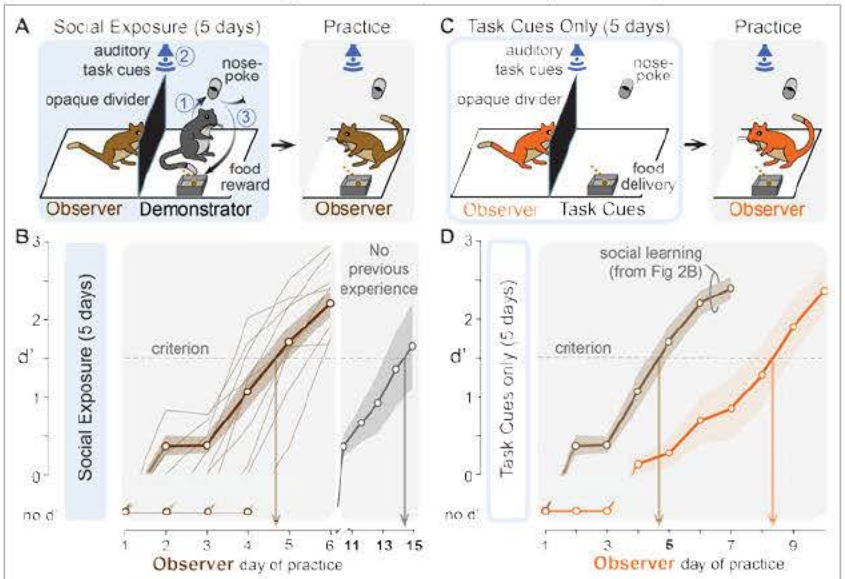

Figure 2 (A) Observer gerbils are exposed to a Demonstrator that is performing an auditory task during 5 daily sessions. (B) The Observers subsequently practice and acquire the task in ~5 days (brown arrow). Controls with no previous experience take ~14.5 days (gray arrow) (C) A separate group of Observer gerbils experienced only auditory task cues. (D) These gerbils took ~8.5 days to acquire the task (orange arrow).

(2) **Demonstrator vocalizations are a candidate social cue** (Paraouty et al., bioRxiv): A fundamental question for SL studies concerns the sensory cue(s) that convey social information. To address this, we obtained audio recordings from Observers and Demonstrators during Social Exposure. Figure 3A illustrates that a *transparent* divider attenuated vocalizations such that they could be assigned to each gerbil (Paraouty et al., bioRxiv, see Bibliography). Figure 3B shows an example sonogram of the 12 Hz Go stimulus (blue), and ultrasonic vocalizations at ~30 kHz (gray arrows) that occur just before and after the nose-poke. Figure 3C plots Demonstrator vocalization time as a function of sound onset. In fact, Demonstrator gerbils emitted 60% of their vocalizations within ±0.5 s of initiating trials. Figure 3D shows that a larger number of Demonstrator vocalizations were correlated with a faster rate task acquisition by the Observer. This finding motivates a test of whether Demonstrator vocalizations facilitate SL, especially for HL-reared animals.

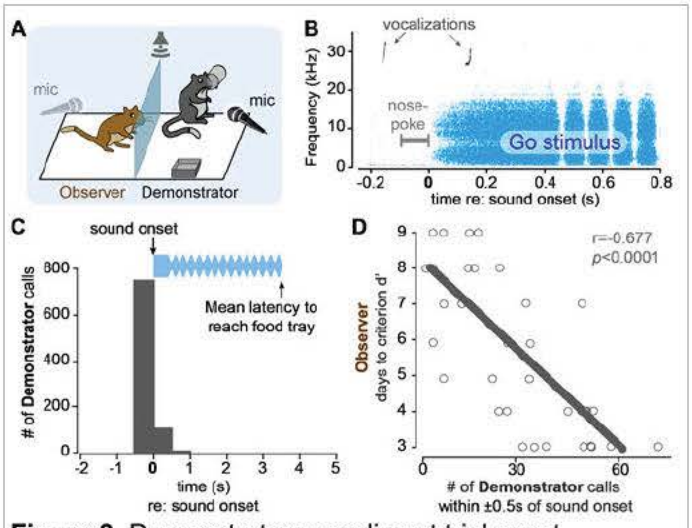

Figure 3 Demonstrators vocalize at trial onset.

(3) **Gerbil vocal communication in social settings** (pilot results): A separate project in our laboratory examines vocal communication, using continuous audio and video recordings in gerbil families over 3-4 weeks. Figure 4A

schematizes the setup, Figure 4B shows four example vocalizations, and Figure 4C is a circadian plot of vocalizations/hour (note: averaged across 20 days of recording, which conceals periods of zero vocal activity). These pilot data suggest that gerbil aural communication is robust in social settings, and may be a plausible social cue in our paradigm (see Figure 3).

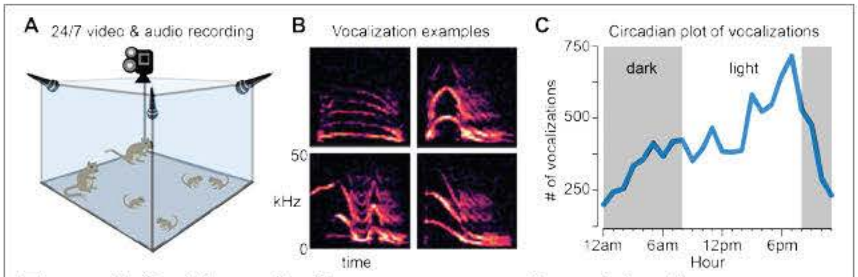

Figure 4 Gerbil vocalizations are common in social settings.

TESTING THE ROLE OF AUDITORY CORTEX IN A SOCIAL LEARNING PARADIGM (SUPPORT FOR AIM 1)

(4) A role for auditory cortex during social learning (pilot results): To ask whether AC activity is necessary during Social Exposure, we implanted naïve Observer gerbils bilaterally with cannulae in the AC (Figure 5A), and delivered bilateral infusions of muscimol during the 5 days of Social Exposure. Controls were infused with saline vehicle. No drugs were delivered during the subsequent practice sessions. Figure 5B shows that naïve Observer gerbils infused with saline (n=6; gray) required 5.2 ± 0.3 days to perform the task at a criterion d' of 1.5 which did not differ from the unmanipulated Observer gerbils shown in Figure 2B (Wilcoxon rank sum test, $X^2(1)=0.65$, p=0.517). This indicates that neither surgery nor saline infusions impact learning. A second group of naïve Observers received muscimol infusions during Social Exposure (n=6; red), and these animals required 9.4 ± 0.4 days to reach criterion performance. This rate of task acquisition was significantly delayed, as compared to the saline-infused animals (Wilcoxon rank sum test, $X^2(1)=2.70$, $p=0.007$), suggesting that AC is necessary for social learning.

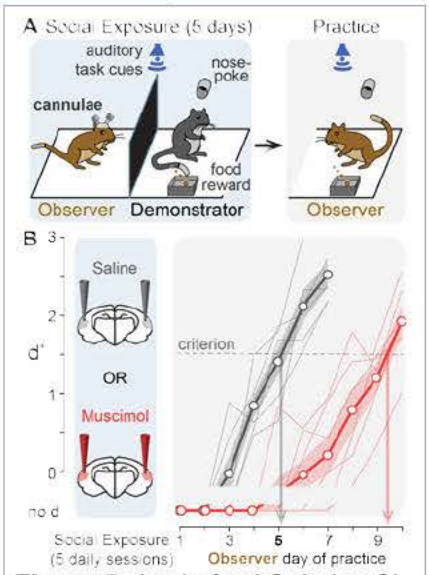

Figure 5 A role for AC during SL.

(5) A role for dopamine signaling during social learning (Paraouty et al., bioRxiv): Dopamine signaling has been postulated to support SL, similar to reward learning. To address whether DA signaling played a role in our paradigm, we blocked or activated D1/D5 DA receptors in gerbils during Social Exposure, but not subsequent practice (Paraouty et al., bioRxiv, see Bibliography). As shown in Figure 6, three groups of naïve Observer gerbils were exposed to a Demonstrator that performed the task on the other side of a *transparent* divider on 5 successive days: the first group received daily saline injections, the second group received daily D1/D5 agonist injections (5 mg/kg SFK-38393), and the third group received daily D1/D5 antagonist injections (0.025 mg/kg SCH-23390). Saline-injected Observers (gray line) subsequently learned the task in 5.6 ± 0.3 days (at a criterion performance of d'=1.5). D1/D5 agonist injected Observers (green lines) subsequently learned the task in 4.2 ± 0.2 days, significantly faster than saline-treated controls (Wilcoxon rank sum test, $X^2(1)=9.84$, $p=0.0017$). D1/D5 antagonist injected Observers (red lines) subsequently learned the task in 8.3 ± 0.2 days, significantly slower than saline-treated controls (Wilcoxon rank sum test, $X^2(1)=13.81$, $p=0.0002$). These findings do not exclude other neuromodulatory systems (Significance), but they do motivate a test for DA signaling in Aim 1.

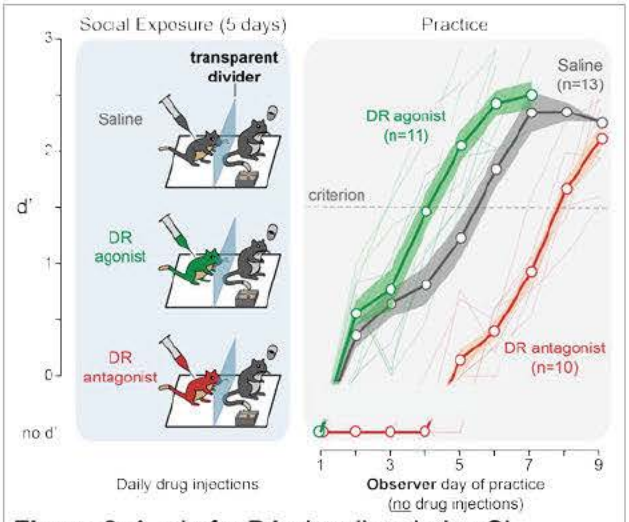

Figure 6 A role for DA signaling during SL.

PLASTICITY OF AUDITORY CORTEX CODING PROPERTIES MAY CONTRIBUTE TO SOCIAL LEARNING (SUPPORT FOR AIM 2)

(6) Social exposure can induce an improvement in auditory cortex neural sensitivity (pilot results): To address whether central auditory function is modified by social experience, we obtained pilot recordings from the AC of naïve Observer gerbils. Wireless recordings were obtained from 64 channel arrays that were implanted in left AC, and spike sorting was used to isolate single neurons (see General Methods). Figure 7A shows waveforms recorded on 8 contact sites (left), and a principal component analysis from 2 channels (orange) that was used to isolate 2 neurons (right). Figure 7B shows Go- and Nogo-evoked responses for 2 exemplar neurons. Using this approach, AC recordings were obtained from two groups: (1) during exposure to Task Cues Only,

consisting of experimenter-triggered Go and Nogo stimuli and food delivery (n=4 animals; Figure 7C), or (2) during Social Exposure to a Demonstrator performing the auditory task (n=6 animals, Figure 7D). To analyze whether either experience modified AC neuron encoding, we first calculated neuronal d' for all multiunits recorded during early exposure (days 1-2 of Social or Task Cue Only) and late exposure (days 4-5 of Social or

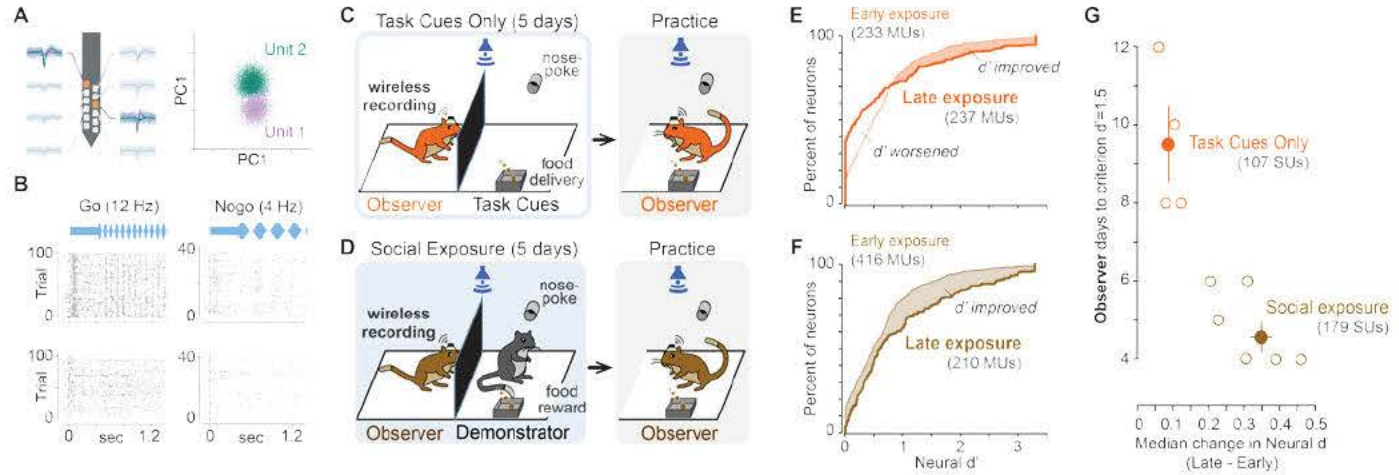

Figure 7 AC neuron stimulus discrimination increases during Social Exposure (see text for details).

Task Cue Only). Figure 7E plots cumulative distributions of neural d' for recordings obtained during early (thin line) and late (thick line) exposure to Task Cues Only, and shows both a worsening (white shading) and improvement in d' values (orange shading). In contrast, Figure 7F shows a net increase in neural d' during the 5 days of Social Exposure (brown shading). This pilot result suggests that neural d' increases more for Social Exposure, as compared to Task Cues Only exposure. To explore whether an improvement in neural d' could plausibly account for an Observer's subsequent task acquisition, we plotted the rate at which Observers acquired the task (days to criterion d'=1.5) against the median change in neural d' during the 5 days of exposure. Here, only single units were analyzed. Figure 7G shows that Social Exposure led to faster learning and a larger increase in neural d', as compared to exposure to Task Cues Only. These data motivate the experiments proposed in Aim 2.

SOCIAL LEARNING IN HEARING LOSS-REARED GERBILS (SUPPORT FOR AIM 3)

(7) **Developmental HL is associated with learning delays** (Anbuhl et al., bioRxiv, see Bibliography): Hearing Loss-reared gerbils display slower task acquisition and perceptual learning on the perceptual task used in this proposal, amplitude modulation rate discrimination (von Trapp et al., 2017). Furthermore, we recently found that perceptual learning is delayed by a transient period of HL during adolescence (Anbuhl et al., bioRxiv, see Bibliography). Figure 8A shows the simple Go-Nogo task used to assess AM depth detection thresholds. Figure 8B compares the amount of improvement over 10 days of practice: Controls (black) improved significantly more than transient HL (red) animals (ANCOVA; initial threshold as a covariate; adjusted means shown; df=1, F=6.5769, p=0.0177)). These data motivate Aim 3 which tests whether Social Exposure facilitates learning following HL.

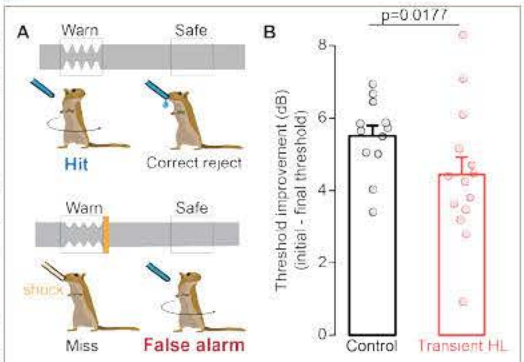

Figure 8 (A) AM detection task. (B) Transient HL diminishes learning.

(8) **HL-reared animals may benefit from Social Exposure** (pilot): To determine whether HL-reared animals displayed normal learning in our SL paradigm, we monitored the performance of gerbils reared with a permanent conductive HL (General Methods). HL-reared Observer gerbils were exposed to trained Demonstrators for 5 successive days, as described above (Figure 2A). As shown in Figure 9, HL-reared animals (n=5; red dashed lines) displayed variable performance with 2 animals learning *faster* than normal hearing animals, 2 animals learning at a similar rate, and 1 animal learning more slowly. Although these are pilot observations, they suggest that Social Exposure provides an advantage for HL-reared animals, and permits them to learn, on average, at the same pace as normal hearing animals. These pilot data motivate the experiments proposed in Aim 3.

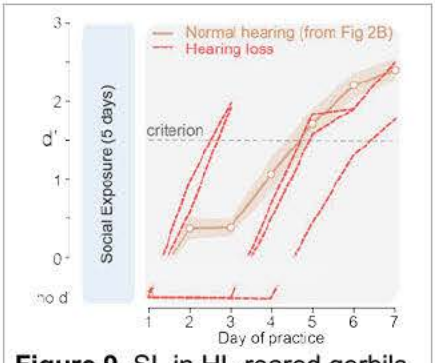

Figure 9 SL in HL-reared gerbils.

GENERAL METHODS

Species (see Vertebrate Animals): Advantages of the gerbil (*Meriones unguiculatus*) include an extensive, contemporary literature on the cochlea, CNS, perception, development, and HL (e.g., *cochlear development*: Harris & Dallos, 1984; Johnson et al., 2009; *audiogram & perception*: Ryan, 1979; von Trapp et al., 2017; Ferreiro et al., 2020; Yao et al., 2020; *VCN*: Keine et al., 2017; *MSO*: Scott et al., 2010; Myoga et al., 2014; *LSO*: Sanes & Rubel 1988; Franken et al., 2018; *IC*: Kreeger et al., 2021; *AC*: Buran et al., 2014b; Pachitariu et al., 2015; Yao & Sanes, 2021; *HL & cochlear implant*: Caras & Sanes, 2015; Wrobel et al., 2018; *anatomy & atlas*: Budinger et al. 2009; Radtke-Schuller et al. 2016). Gerbils are sensitive to low frequencies, and display a natural social structure (Significance). Animals are weaned at P30, and Observers are P80-90 at the start of the experiment.

Social learning (SL) paradigm (Paraouty et al., 2020): Testing equipment: Gerbils are placed in a plastic test cage housed in a sound attenuation booth. The cage contains a pellet dispenser (Med Associates) connected to a food tray, and a nose-poke. Visits to the nose-poke and food tray are detected with IR emitters and sensors. Stimuli, food delivery, and data acquisition are controlled on a PC with custom MATLAB scripts, and an RZ6 multifunction processor (TDT). Auditory stimuli: Sounds are delivered from a calibrated free-field tweeter positioned 1 m above the cage. For the amplitude modulation (AM) discrimination task, the Go stimulus is 12 Hz AM and the Nogo stimulus is 4 Hz AM (100% mod depth, broadband noise carrier, 25 dB roll-off 3.5-20 kHz, 55 dB SPL). Demonstrator gerbils are placed on controlled food access, and trained on the AM task by an experimenter, using an appetitive conditioning paradigm (Yao & Sanes, 2021). Demonstrators sequentially learn to approach the food tray, receive food pellets when a Go stimulus is presented, and initiate Go trials with a nose-poke. When Demonstrators reliably perform Go trials, the Nogo stimulus is introduced in a randomized order. To qualify as a Demonstrator, animals are required to perform the task with a d' > 1.5.

Social Exposure (Figure 2A): The Demonstrator and naïve Observer gerbils are placed on controlled food access. The SL paradigm begins with 5 daily *Social Exposure* sessions, during which an Observer is placed on one side of an opaque divider, and a Demonstrator that performs the AM task is placed on the other side. The Observer experiences the Demonstrator perform ≥ 60 Go trials and 20 Nogo trials during each exposure session.

Task Cue Only exposure (Figure 2C): In a second paradigm, naïve Observer gerbils are separated from an unoccupied compartment by an opaque divider, and experience only non-social task cues. The experimenter manually triggers: (1) Go and Nogo stimuli, (2) "virtual false alarm" trials in which house lights are extinguished, and (3) "virtual Hit trials" during which pellets are delivered to the food tray. There are no social cues.

Practice & Task Learning: After the 5th day of exposure, the naïve Observer gerbil is allowed to *practice* the task. The Observer is provided with ≤ 5 experimenter-triggered Go trials during practice day 1 & 2, which are initiated when an animal touches the nose-poke. Except for these, all Go trials are initiated by the Observer. For all animals, Nogo trials are introduced once an Observer is initiating Go trials and obtaining ≥ 25 Hits.

Psychometric analysis: On Go trials, responses are scored as a Hit when animals break an IR light beam at the food tray within a 5 s window. Failing to break the beam is scored as a miss. On Nogo trials, responses are scored as a False Alarm (FA) when animals incorrectly break the light beam at the food tray. Failing to break the beam is scored a correct reject. A performance metric, d', is calculated for each session as a z-transform of Hit and FA values: d' = z(Hit rate) – z(FA rate) (Green & Swets, 1966).

Rate of Task Acquisition: The number of days for each animal to reach a criterion performance of d'=1.5 during practice session serves as the standard metric of task learning, and is used for between group comparisons.

Audio and Video recordings (Paraouty et al., bioRxiv, see Bibliography): Vocalizations are captured with microphones (Dodotronic Ultramic 384K_BLE) placed on opposite sides of the opaque divider in the cage. Vocalizations are identified offline using DeepSqueak (Coffey et al., 2019). The vocalizations can be attributed to either the Observer or Demonstrator because the opaque divider attenuates calls significantly. Videos are captured with a webcam (Logitech c270-HD; 30 fps), and animal position is tracked with DeepLabCut (Mathis et al., 2018), using a trained gerbil network (10^6 iterations; 10^3 labeled frames; Paraouty et al., 2020).

Cannula implantation & drug infusions (Caras & Sanes, 2017): Following anesthesia, craniotomies are made above each AC, and cannulae (26 g, 3 mm; P1 Technology) are positioned just dorsal to AC. Animals recover for at least 1 week before being placed on controlled food access. Drugs are infused bilaterally under isoflurane anesthesia: (1) Muscimol (Abcam; 0.2 µL/hemisphere), (2) SFK-38393, a D1/D5 agonist (Sigma-Aldrich; 0.06 µg/µL; 0.5 µL/hemisphere), (3) SCH-23390, a D1/D5 antagonist (Sigma-Aldrich; 2.4 µg/µL; 0.5 µL/hemisphere; Schicknick et al., 2012), or (4) vehicle (0.9% NaCl). Animals recover for 30 min prior to behavioral testing.

Malleus removal (Rosen et al., 2012): Following anesthesia at P10, the tympanic membrane is punctured, the malleus removed, and the procedure repeated on the other side. Sham surgery consists of anesthesia and a skin incision. The resulting conductive HL is relatively flat, and does not affect peripheral tuning (Ye et al., 2021).

Earplugs (Caras & Sanes, 2015; Anbuhl et al., bioRxiv): At P11, earplugs are inserted into each canal. Animals are checked daily, and earplugs adjusted to accommodate growth. Earplugs produce a threshold shift of 15-50 dB, depending on frequency, and are completely reversible.

Electrode implantation & ***Awake-behaving electrophysiology*** (von Trapp et al., 2016; Yao & Sanes, 2021): Surgery is conducted under isoflurane anesthesia in a dedicated suite (Vertebrate Animals). A 64 channel electrode array (Neuronexus) is affixed to a microdrive, and inserted through a craniotomy above left AC using stereotactic coordinates that permit sampling across the tonotopic axis. Wireless recordings are obtained during exposure and practice sessions (TBSI). Raw waveforms are thresholded offline, imported to Matlab, and sorted by cluster analysis routines (Fee et al. 1997; Hill et al. 2011). At the experimental endpoint, animals are deeply anesthetized and perfused with 4% paraformaldehyde. Brains are extracted, vibratome-sectioned and mounted.

Neurophysiology analyses (Yao & Sanes, 2018; 2021): Primary measures: Matlab routines are used to obtain standard measures of discharge magnitude and pattern, including: (1) spontaneous and evoked firing rates, (2) power ((spikes/s)^2/Hz) at the AM rate, (3) vector strength, and (4) coefficient of variation. Spike pattern classifier: Figure 10 schematizes the classifier used to index single neuron sensitivity (neural d'). Test trials consist of a randomly selected spike train from a Go trial (12 Hz), and one from a Nogo trial (4 Hz). Each template is composed of all trials other than the test trial. The test trial is assigned to the Go or Nogo template based on the Euclidean distance (van Rossum, 2001). The procedure is repeated 1,000 times to minimize selection biases. Go test trials are "Hits" if they are assigned to the Go template (Fig 10, green), and Nogo test trials are False Alarms (FA) if they are assigned to the Go template (Fig 10, red). Population decoder: Figure 11 schematizes the linear classifier readout procedure used to assess AM rate discrimination across a population of AC single units. Figure 11A shows hypothetical population responses for single trials of a Go (black) and Nogo (gray) stimulus. Specifically, spike count responses from *N* neurons are counted to *T* trials. Figure 11B illustrates the support vector trials and the support vector machine (SVM; MATLAB: "fitcsvm" & "predict") procedure used to fit a linear hyperplane to each training data set. Figure 11C shows that classification performance is assessed on single trials across 500 iterations. Figure 11D shows that individual Go trials are correctly classified as "Hits" or misclassified as "Misses," and Nogo trials are correctly classified as "Correct Rejects" (CR) or misclassified as FAs. Alternatively, the SVM can be given access to spike pattern information. Decoder performance is converted to d', and can be assessed as a function of the number of single units.

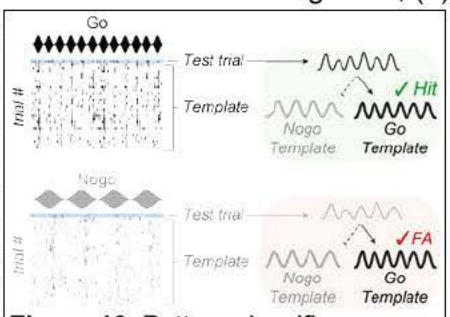

Figure 10 Pattern classifier.

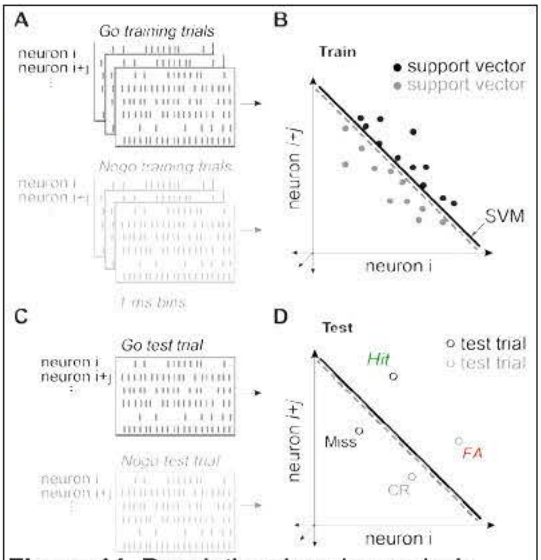

Figure 11 Population decoder analysis.

Viral injections *(Mowery et al., 2017)* ***& Photometry***: Following anesthesia, a craniotomy is made above AC, and a glass pipette is used to microinject (Nanoject) virus (AAV1-hSyn-GRABDA1h) at 2 nL/sec. An optic fiber (flat 400 µm core, 0.48 NA, Doric Lenses Inc.) will be inserted to 0.2 mm above the injection site. During behavior, an optic fiber patch cable will be routed through a rotary joint (Doric Lenses) mounted above the animal. Fluorescence signals will be acquired (Exc/Emis: 490/510 nm; Doric minicube; TDT RZ6), digitized, and movement artifact subtracted. Data will be bandpass filtered (0.05-2.25 Hz) and analyzed with an open-source package (PMAT; Bruno et al., 2021). Towards this goal, we obtained the guidance of a CNS colleague who has an expertise in the neural mechanisms that support value-based decisions, including DA imaging (Dr. Christine Constantinople, see Letter of Support).

Auditory brainstem response (ABR) (Rosen et al. 2012, Caras & Sanes, 2015; Yao & Sanes, 2018): ABRs are obtained under anesthesia (Vertebrate Animals) to assess peripheral function. Tone-evoked responses are averaged, amplified, filtered (0.3-3 kHz), and digitized (TDT), using a custom Python script.

Statistical analyses: Statistical tests for distribution and significance are performed with JMP v9. We first determine whether observations are normally distributed (Shapiro-Wilk W Test). If so, values are given as mean ± SEM, and one- or two-way ANOVA tests are followed by a Tukey-Kramer HSD Test to control for multiple comparisons. If not normally distributed, values are given as median ± quartile, and a Kruskal-Wallis Rank Sum test is followed by a nonparametric Steel-Dwass All Pairs Test.

SPECIFIC EXPERIMENTS

CORE HYPOTHESIS

Social experience is pivotal to the acquisition of many core behaviors, including the auditory task used in this proposal (Paraouty et al., 2020). Thus, our core hypothesis is that *social exposure to a Demonstrator performing a sound discrimination task induces AC plasticity that is causally related to an Observer's enhanced rate of task acquisition*. Three Specific Aims test predictions that emerge from the hypothesis:

***AIM 1** ARE AUDITORY CORTEX ACTIVITY & PLASTICITY NECESSARY FOR SOCIAL LEARNING OF AN AUDITORY TASK?*

PREDICTION 1A

If AC activity is causally linked to social learning, then decreasing AC activity during Social Exposure will diminish the rate of task acquisition during practice.

APPROACH 1A

Figure 12 shows the experimental design of Approach 1A, which asks whether AC activity is necessary for social learning. Naïve littermate Observer gerbils will be instrumented bilaterally with cannulae in AC, and receive 5 daily exposures to a Demonstrator that is performing an amplitude modulation (AM) rate discrimination task on the opposite side of an opaque divider. As illustrated in Figure 12A, the Demonstrator (1) nose-pokes to initiate each trial, (2) hears either a Go (12 Hz AM) or Nogo cue (4 Hz AM), and (3) seeks a food reward on Go trials or re-pokes on Nogo trials. Immediately before each daily exposure to a Demonstrator, the Observer will receive an infusion of either:

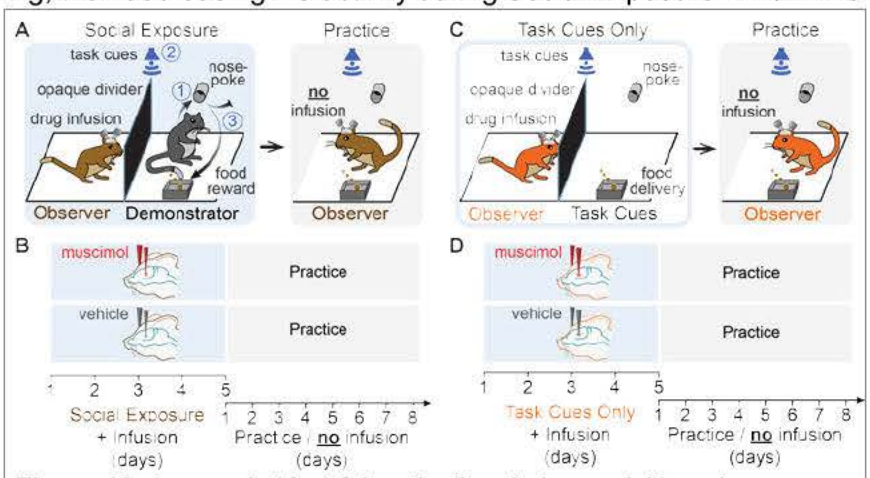

Figure 12 Approach 1A: AC inactivation during social learning.

(i) muscimol, a $GABA_A$ receptor agonist (1.0 mg/mL; 1 µL/hemisphere, 0.2 µL/min; Caras & Sanes, 2017), or
(ii) vehicle, 0.9% saline which is the solvent for delivery of muscimol.

Beginning immediately after the 5th day of exposure, Observers begin to practice the auditory task, and their learning rate is assessed. If an Observer does not reach a sensitivity of d' ≥ 1.5 by 15 days, then its practice sessions are concluded. As illustrated in Figure 12C,D, the specific impact of social cues will be evaluated by studying a second group of naïve Observer gerbils that experience 5 daily sessions of Task Cues Only (i.e., experimenter-triggered 4 and 12 Hz AM signals, pellet delivery into the food tray, and extinguishing of the house lights to simulate FA trials, but no Demonstrator). Observers that experience Task Cues Only will also receive daily AC infusions of muscimol or vehicle.

Data collection & analysis (see General Methods for details)

Behavioral measures: Three types of dependent variables will be collected and analyzed:

- Hits and FAs will be acquired during practice sessions, d' computed (z(Hit) - z(FA)), and performance tracked over practice days. The number of days to reach a criterion d' ≥ 1.5 will be recorded.
- Video recordings will be obtained of during each session and analyzed with DeepLabCut (Mathis et al., 2018). We will measure distance traveled, head orientation, and dwell time as a function of cage position.
- Audio recordings will be obtained during each session and analyzed with DeepSqueak (Coffey et al., 2019). Vocalization times are plotted as a function of trial initiation, sound onset, and arrival at food tray.

For each dependent variable, statistical comparisons will be made across the four treatment groups.

Controls: For this and all subsequent experiments, data collection and/or analyses will be performed by experimenters who are blind to drug treatment group. Animals from a single litter will be split between two conditions (e.g., muscimol vs vehicle), and data will be collected from ≥ 3 litters to avoid litter-specific biases.

Possible outcomes & interpretations

Effect of Demonstrator: If the rate of task acquisition is significantly slower only in muscimol-treated animals with Social Exposure (Fig 12A), then we will conclude that AC is necessary for social learning. If an identical effect is observed for animals that experience Task Cues Only (Fig 12C), then we will conclude that AC is also necessary for learning that depends on non-social cues. However, these experiments do not exclude the possibility that AC inactivation prevents regions downstream of AC from receiving afferent drive and undergoing plasticity.

Effect of Demonstrator Vocalization: If Demonstrator vocalizations during Social Exposure with an opaque divider (Fig 12A) correlate with Observer task acquisition, then we will have a strong rationale for testing the facilitatory

effect of vocalizations in Aim 2. This effect has been established for transparent divider conditions (Figure 3).

Potential problems and alternative strategies

The proposed inactivation procedures are implemented and published (Caras & Sanes, 2017). However, potential off-target effects may include disrupted motor function. Therefore, we will measure the effect of muscimol on locomotion during the 5 day exposure period. If motor effects are observed, then we will use a DREADDs inactivation procedure that we have implemented (Yao et al., 2020) to seek confirmatory evidence.

PREDICTION 1B

If auditory cortex plasticity is causally related to social learning due to a reward signal, then dopamine release should occur within AC during Social Exposure.

APPROACH 1B

Figure 13 illustrates the experimental design for Approach 1B, which will determine whether DA release occurs in AC during Social Exposure, or Task Cues Only. Fiber photometry will be used to measure DA signaling in AC with a genetically expressed dopamine sensor. Gerbils will receive an injection of AAV1-syn-GRABDA1h-IRES-mCherry into left AC, along with an optic fiber positioned above the injection. This vector expresses a sensor, GRABDA1h, that responds to DA in the physiological range (10-100 nM; Sun et al., 2018). The AAV1 serotype efficiently transfects gerbil AC (Mowery et al., 2017), the synapsin 1 promotor permits expression in all AC neurons, and mCherry gives a fluorescent reference for signal intensity. After a 2-3 week recovery to permit expression, we will attach an optic fiber patch cable routed through a rotary joint above the cage, and record DA-evoked fluorescent signals from AC while animals experience either Social Exposure to a Demonstrator (Figure 13A) or Task Cues Only (Figure 13B). Control animals will receive a virus injection and optic lens implant, but will only experience the test cage Observer compartment on 5 successive days.

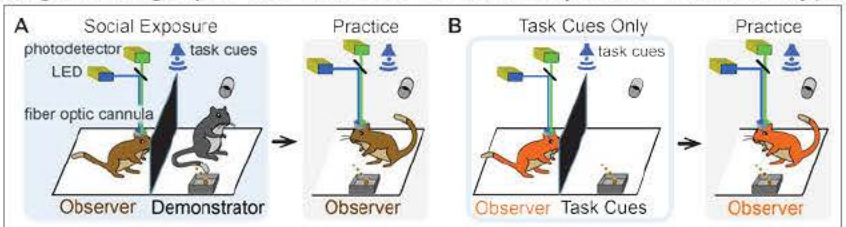

Figure 13 Approach 1B: DA imaging in auditory cortex.

Data collection & analysis (see General Methods for details)

Behavioral measures: The behavioral data to be collected and analyzed are identical to Approach 1A.

Photometric signal: Fluorescence signals will be acquired, digitized, and movement artifact subtracted (Exc/Emis: 490/510 nm; TDT RZ6). The bandpass filtered (0.05-2.25 Hz) signal will be analyzed with an open source package (pMAT; Bruno et al., 2021). Signal will be acquired continuously while animals experience Social Exposure or Task Cues Only, and subsequently during practice. Analyses of DA sensor fluorescence will include: (1) baseline fluorescence in the cage during a 5 min pre-exposure period, (2) transient changes in fluorescence that are latency locked to auditory input (e.g., AM stimuli, Demonstrator vocalizations or locomotion-associated sound) and motor action (e.g., Observer's movement and position obtained from DeepLabCut metrics), and (3) long-term changes in fluorescence that persist for the entire exposure period. Similar measures will be obtained from animals during practice sessions. Statistical comparisons will be made across the four treatment groups.

Possible outcomes & interpretations

If DA sensor fluorescence increases during Social Exposure (Fig 13A), but not in control animals that experience the cage only, then we will conclude that context can induce DA release. If a similar increase occurs during Task Cues Only (Fig 13B), then we will conclude that DA signaling does not require social cues. If no changes are recorded, we will conclude that neither social, nor non-social, context cues induce DA release in AC.

Potential problems and alternative strategies

We have used viral vectors for optogenetics or DREADDs (Mowery et al., 2017; Yao & Sanes, 2020), and have implemented calcium imaging with fluorescent indicators (Lo et al., 1998). However, since we have not yet implemented photometric recordings, we have obtained the guidance of a consultant in our department (Dr. Christine Constantinople, see Letter of Support) to help with any implementation questions. In addition, I have recruited a postdoctoral scientist, Dr. Masri, who has experience with optical fiber assemblies (see Budget).

PREDICTION 1C

If AC plasticity is causally related to social learning due to a reward signal, then intracortical up- or down-regulation of DA signaling will enhance or diminish the rate of task acquisition, respectively.

APPROACH 1C

Figure 14 illustrates the experimental design for Approach 1C, which will determine whether DA signaling within AC is necessary for social learning, and can facilitate it. To test this idea, D1/D5 DA receptors will be pharmacologically manipulated within AC using bilateral cannulae (Figure 14A). Immediately before each daily

exposure, the Observer will receive an infusion of either:
(i) SCH-23390, a D1/D5 antagonist (0.5 µL of 2.4 µg/µL), or
(ii) SFK-38393, a D1/D5 agonist (0.5 µL of 0.06 µg/µL), or
(iii) vehicle, 0.9% saline which is the solvent for both drugs.
Both drugs affect SL when injected systemically (Figure 6), and modulate gerbil AC function when infused locally (Schicknick et al., 2012). Observers recover for 30 min prior to behavioral testing. Following the 5 days of Social Exposure or Task Cues Only, Observers will be permitted to practice the auditory task, and the rate of learning assessed.

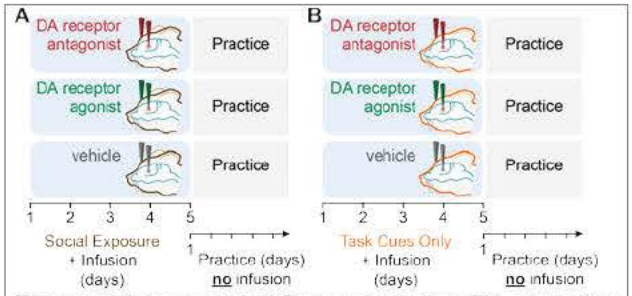

Figure 14 Approach 1C: manipulating DA signaling.

Data collection & analysis
Behavioral measures: The measures and analyses are identical to those described above for Approach 1A.

Possible outcomes & interpretations
If infusion of the DA receptor antagonist during Social Exposure delays subsequent task acquisition, then we will conclude that DA signaling within AC is necessary for the effect of social and/or non-social cues. If a similar effect is obtained for exposure to Task Cues Only, then we will conclude that DA signaling is associated with non-social cues. A similar set of conclusions can be drawn for outcomes of the DA receptor agonist.

Potential problems and alternative strategies
The cannula and infusion procedures are published (Caras & Sanes, 2017). However, potential off-target effects include disrupted motor function. Therefore, we will measure the effect of each drug on the rate of locomotion during the 5 day exposure period. If motor effects are observed, then we will use a DREADDs inactivation procedure that we have implemented (Yao et al., 2020) to seek confirmatory evidence.
Together, the experiments in Aim 1 will test whether AC plays an pivotal role in auditory social learning.

AIM 2 IS AUDITORY CORTEX PLASTICITY SUFFICIENT TO EXPLAIN SOCIAL LEARNING OF AN AUDITORY TASK?

PREDICTION
If the hypothesis is correct, then AC neuron sensitivity to auditory task cues will be enhanced by Social Exposure.

APPROACH
Figure 15 illustrates the experimental design for Aim 2, which will determine whether AC neuron stimulus encoding is altered by Social Exposure. Naïve gerbil will be instrumented with electrode arrays in AC, and recorded during 5 days of Social Exposure (Figure 15A). Recordings continue while Observers subsequently practice the auditory task. To determine the contribution of non-social cues, recordings will be obtained from naïve littermate Observers that are exposed to Task Cues Only (Figure 15B). To test the contribution of an auditory social cue (i.e., Demonstrator vocalizations; Figure 3), recordings will be obtained from Observers exposed to Task Cues plus playback of Demonstrator vocalizations that are *time-locked to trial onset* (Figure 15C).

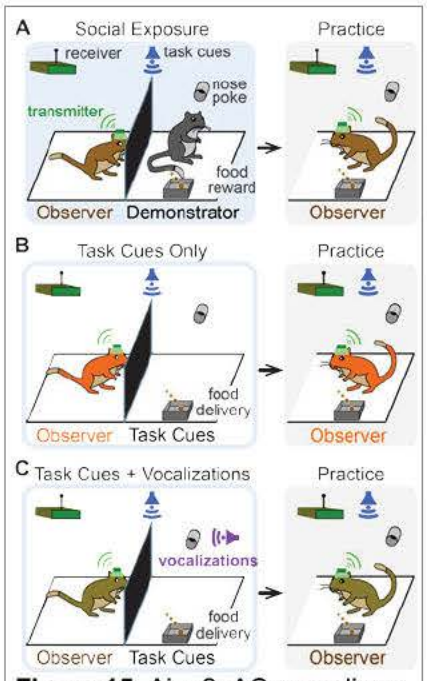

Figure 15 Aim 2: AC recordings.

Data collection & analysis (see General Methods for details)
Behavioral measures & analyses: Identical to those described in Aim 1.
Neurometric analyses (Yao & Sanes, 2021): AC neuron responses will be digitized and analyzed offline. To determine whether any of the 3 paradigms induce functional changes to AC neurons, we will use a pattern classifier (Figure 10) to assess each neuron's capacity to discriminate between Go and Nogo stimuli (Figs 7E,F). We will also use a support vector machine to assess the sensitivity of AC sub-populations recorder within a session (Figure 11).
Comparison of psychometric and neurometric findings: The magnitude by which neural sensitivity improves during observation sessions will be correlated to that animal's subsequent task acquisition rate. Only neurons held across recording sessions will be used, as assessed with spike sorting (Figure 7G).

Possible outcomes & interpretations
If neural sensitivity improves as a function of day-of-exposure for any of the three paradigms (Fig 15A-C), then we will conclude that AC plasticity is induced by the experience. If there is a greater increase in neural sensitivity when either a Demonstrator is present, or when Demonstrator vocalizations are presented, then we will conclude that social cues facilitate AC plasticity. If the magnitude of improved neural sensitivity correlates with an individual animal's rate of task acquisition (Fig 7G), then we will conclude that social experience-induced AC plasticity is a

plausible mechanism that could contribute to social learning.

Potential problems and alternative strategies

Awake-behaving recordings: Awake-behaving recording techniques and neurometric analyses are routinely used (e.g., *perception*: Yao & Sanes, 2021; *learning*: Caras & Sanes, 2017; *hearing loss*: Yao & Sanes, 2018).

Social cues: Social cues could include olfactory recognition of a conspecific, or spatial cues generated by a Demonstrator's movements. Therefore, if replay of Demonstrator vocalizations (Fig 15C) does not influence subsequent task acquisition, we will move forward with a test of these alternative social cues. For example, the Observer's nares can be plugged before each Social Exposure session to test the role of olfactory cues.

Aim 2 will test whether AC encoding is altered by social experience, and predicts subsequent task acquisition.

AIM 3 DOES SOCIAL LEARNING IMPROVE THE ACQUISITION OF AN AUDITORY TASK FOLLOWING DEVELOPMENTAL HL?

PREDICTION

If the hypothesis is correct, then Social Exposure will improve the rate of learning in HL-reared animals.

APPROACH

Figure 16 shows the experimental design for Aim 3, which will test whether social cues facilitate learning in HL-reared animals. Our previous findings suggest that HL is a risk factor for delayed auditory procedural and perceptual learning (Caras & Sanes, 2015; von Trapp et al., 2017; Figure 8). Here, *procedural learning* refers to the acquisition of a specific perceptual judgement (e.g., discriminating 4 vs 12 Hz AM), whereas *perceptual learning* refers to an improvement in the specific perceptual judgement (e.g., the just noticeable difference between 4 Hz and another AM rate). To test the effect of Social Exposure on animals reared with HL, four groups will be studied (Figure 16A): littermate gerbils receiving bilateral malleus removal (permanent conductive HL) or sham surgery at P10, and littermate gerbils receiving either bilateral earplugs (transient conductive HL) or sham treatment from P11-80. At P80, all animals will be instrumented with AC electrode arrays and, after a week recovery, will be tested on one of the three experimental paradigms used in Aim 2 (Figure 16B). In addition, after animals reach a criterion performance of d'=1.5 on the procedural task (i.e., 4 Hz Nogo vs 12 Hz Go), all animals will be tested in a perceptual learning stage to determine their AM rate detection thresholds (von Trapp et al., 2017).

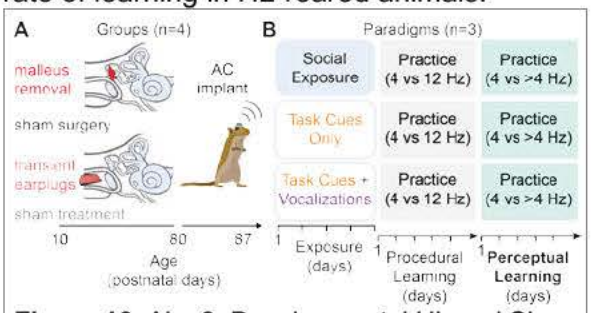

Figure 16 Aim 3: Developmental HL and SL.

Data collection & analysis (see General Methods for details)

Identical to those described in Aim 2, with the addition of ABR measures at the termination of the experiment.

Possible outcomes & interpretations

The most pivotal comparison addresses whether Social Exposure offers a relative advantage to HL-reared animals. As schematized in Figure 17A, the *positive effect of social experience with a Demonstrator* is the difference between rate of task acquisition following Social Exposure versus Task Cues Only (Fig 2; Paraouty et al., 2020). As shown in Figure 17B, if the *positive effect of Social Exposure* is relatively greater for HL-reared animals than sham-treated controls, then we will conclude that SL can compensate for the deleterious impact of developmental deprivation. A similar set of interpretations can be drawn for perceptual learning and AC neuron plasticity.

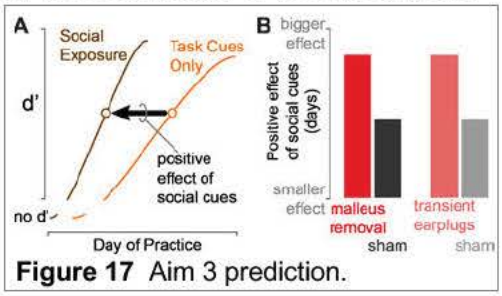

Figure 17 Aim 3 prediction.

Potential problems and alternative strategies

In addition to the caveats described for Aim 2, it is also possible that Observers with permanent HL will fail to hear the social cues. This is one reason for adopting the transient HL model. However, we will also be prepared to increase the salience of Demonstrator vocalizations, by playing them at an elevated sound level.

Together, the significance of this proposal is to identify a CNS mechanism that contributes to auditory social learning, and assess its applicability to animals reared with HL.

SCHEDULE based on a priori analyses of animals required to establish significance (Vertebrate Animals).

	Aim 1	Aim 2	Aim 3
Year 1	Test necessity of AC for SL	AC recording: Task Cues Only	
Year 2	Record DA signaling in AC	AC recording: Social Exposure	Permanent HL: SL paradigms
Year 3	Manipulate DA signaling in AC	AC recording: Social Exposure	Permanent HL: SL paradigms
Year 4		AC recording: +Vocalizations	Transient HL: SL paradigms
Year 5			Transient HL: SL paradigms

OMB Number: 0925-0001

Expiration Date: 02/28/2023

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	❍ Yes ● No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	❍ Yes ● No
Is the Project Exempt from Federal regulations?	❍ Yes ❍ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

VERTEBRATE ANIMALS

1. Description of Procedures

Male and female Mongolian gerbils (*Meriones unguiculatus*), aged postnatal (P) days 10-550, will be used for breeding or as experimental subjects. All animals are weaned at P30, and all Observer gerbils will be between P80-90 at the beginning of an experiment.

To study the effect of auditory cortex activity on SL (Aim 1, Approach 1A), animals will be anesthetized and undergo bilateral cannula implants into auditory cortex. A subset will receive daily infusions of muscimol or vehicle (saline, control) during the 5 daily sessions of social exposure to a demonstrator gerbil performing an auditory task. For this, and all subsequent experiments, the demonstrators will be hand-trained by the experimenter. A second subset will receive daily infusions of muscimol or vehicle (saline, control) during the 5 daily sessions of task cue exposure. All animals will subsequently practice the auditory task without drug infusions. Aim 1A calculation of animal number used: This experiment will have 4 gerbil treatment groups and a group of experimenter trained demonstrator gerbils. Based on mean behavioral values observed during our previous use of muscimol (Caras & Sanes, 2017), and previous collection of the behavioral dependent variables (Paraouty et al., 2020), a power analyses indicate that a minimum of 10 observer animals per group will be needed to establish significance. Since each demonstrator animal can be used for two different observers (when groups are run sequentially), only 5 demonstrators per group will be needed. To collect data in this experiment, 60 gerbils will be needed ([4 groups * 10 observers/group] + [4 groups * 5 demonstrators/group]).

To study whether social exposure causes dopamine (DA) released in auditory cortex (Aim 1, Approach 1B), animals will be anesthetized and receive bilateral injection of the virally expressed DA sensor (GRAB-DA) into auditory cortex, and an optic fiber will be lowered through the craniotomy to 0.2 mm above the injection site. After a 2-3 week recovery to permit expression, the optic fiber will be attached to a photometry system while implanted animals experience either 5 daily sessions of social exposure or 5 daily sessions of exposure to Task Cues Only. We will continue to collect photometric data when animals subsequently practice the auditory task. Aim 1B calculation of animal number used: This experiment will have 2 gerbil treatment groups and a group of experimenter trained demonstrator gerbils. Based on literature-derived dependent variables (Sun et al., 2018), a power analyses indicate that a minimum of 10 observer animals per group will be needed to establish significance. Since each demonstrator animal can be used for two different observers (when groups are run sequentially), only 5 demonstrators per group will be needed. To collect data in this experiment, 30 gerbils will be needed ([2 groups * 10 observers/group] + [2 groups * 5 demonstrators/group]).

To study the effect of increasing or decreasing D1/D5 dopamine receptor activity in auditory cortex on SL (Aim 1, Approach 1C), animals will be anesthetized and undergo bilateral cannula implants into auditory cortex. A subset will receive daily infusions of a D1/D5 agonist (SFK-38393), or a D1/D5 antagonist (SCH-23390), or vehicle (saline, control) during the 5 daily sessions of social exposure to a demonstrator gerbil performing an auditory task. A second set of three groups will receive daily infusions of SFK-38393, SCH-23390, or vehicle during the 5 daily sessions of exposure to Task Cues Only. All animals will subsequently practice the auditory task without drug infusions. Aim 1C calculation of animal number used: This experiment will have 6 gerbil treatment groups and a group of experimenter trained demonstrator gerbils. Based on mean behavioral values observed during our previous use of D1/D5 agents delivered systemically (Paraouty et al., bioRxiv, see Bibliography), and previous collection of the behavioral dependent variables (Paraouty et al., 2020), a power analyses indicate that a minimum of 10 observer animals per group will be needed to establish significance. Since each demonstrator animal can be used for two different observers (when groups are run sequentially), only 5 demonstrators per group will be needed. To collect data in this experiment, 90 gerbils will be needed ([6 groups * 10 observers/group] + [6 groups * 5 demonstrators/group]).

To study auditory cortex functional plasticity (Aim 2), animals will be anesthetized and undergo electrode array implants into auditory cortex. After a one week recovery, implanted animals will be divided into three groups, and wireless recordings will be obtained. The three groups are: (1) 5 daily sessions of social exposure to a demonstrator gerbil performing an auditory task, (2) 5 daily sessions of exposure to Task Cues Only, or (3) 5 daily sessions of exposure to Task Cues plus recorded demonstrator vocalizations. Recordings will continue for all implanted animals when they subsequently practice the auditory task. Aim 2 calculation of animal number used: This experiment will have 3 gerbil treatment groups and a group of experimenter trained demonstrator gerbils. Based on mean neural values observed during our previous study of amplitude modulation processing (Yao & Sanes, 2021), and previous collection of the behavioral dependent variables

(Paraouty et al., 2020), a power analyses indicate that a minimum of 10 observer animals per group will be needed to establish significance. Since each demonstrator animal can be used for two different observers (when groups are run sequentially), only 5 demonstrators per group will be needed. To collect data in this experiment, 45 gerbils will be needed ([3 groups * 10 observers/group] + [3 groups * 5 demonstrators/group]).

To study the effect of social learning on the acquisition of auditory tasks by hearing loss-reared animals (Aim 3), littermates will be anesthetized and receive either of four treatments: (1) bilateral malleus removal at age P10, leading to permanent conductive hearing loss, (2) sham surgery used during malleus removal, (3) bilateral earplug insertion from P11-80, leading to transient conductive hearing loss throughout the critical period and adolescence, and (4) sham treatment used during earplug placement. At P80, animals will be anesthetized and instrumented with electrode arrays in auditory cortex. After a one week recovery, animals in each group will and tested on the social learning paradigm. For comparison, separate groups will be trained and tested with the task cues only paradigm. Aim 3 calculation of animal number used: This experiment will have 8 gerbil treatment groups and a group of experimenter trained demonstrator gerbils. Based on mean neural values observed during our previous study of amplitude modulation processing in control and hearing loss-reared animals (von Trapp et al., 2017; Yao & Sanes, 2018; Yao & Sanes, 2021), and previous collection of the behavioral dependent variables (Paraouty et al., 2020), a power analyses indicate that a minimum of 10 observer animals per group will be needed to establish significance. Since each demonstrator animal can be used for two different observers (when groups are run sequentially), only 5 demonstrators per group will be needed. To collect data in this experiment, 120 gerbils will be needed ([8 groups * 10 observers/group] + [8 groups * 5 demonstrators/group]).

Euthanasia: At the experimental endpoint for each of the above experiments, animals will be given an overdose of Euthasol (150 mg/kg body weight, IP) and, when fully anesthetized, will be perfused transcardially with fixative such that the anatomical positions of cannulae, optic fibers, or electrodes can be histologically verified. Breeding pairs will be euthanized after their 8th litter, but not later than P550, using CO_2, followed by decapitation. These methods of euthanasia are consistent with recommendations of the Panel of Euthanasia of the American Veterinary Medical Association Guidelines on Euthanasia.

2. Justifications

Species: The Mongolian gerbil (*Meriones unguiculatus*) is an easily bred rodent with an audiogram that resembles that of humans (i.e. low threshold frequency responses below 1.5 kHz). Therefore, it is a favorable system in which to perform functional and developmental studies of the auditory system, and is now amenable to genetic manipulations (Zorio et al., 2019). Most importantly for this proposal, there is a rich literature on auditory behavior, CNS physiology, and anatomy. There is an equally strong literature on the effects of developmental hearing loss. There is no substitute method for animal experimentation, either to manipulate social interactions, or to obtain perceptual measures, or to obtain multisite neural responses from the central auditory system. Breeders will be obtained commercially (Charles River) or generated from lab-reared animals, and will be cared for in [redacted] facilities, and checked daily for new litters. All procedures related to the maintenance and uses of animals will be in accordance with the IACUC Handbook and approved by the University Animal Welfare Committee.

The research goals cannot be accomplished using an alternative model (e.g. computational model, invertebrate species, in vitro neuronal culture) because none include all of the independent variables that are essential for studying the auditory cortical mechanisms that support socially-mediated auditory learning.

3. Minimization of Pain and Distress

Auditory psychophysics: Gerbils will be tested using an appetitive procedure to determine their responses to auditory signals. While participating in a behavior experiment, each gerbil will obtain its entire food supply inside of a testing cage. To minimize distress, food consumption, body weight, and level of hunger will be monitored daily during periods of testing. Body weight will be maintained at a level that is never less than 80% of the pre-training weight.

Surgery for cannula or electrode implants: Surgery will be conducted under sterile conditions in a dedicated surgery suite. Anesthesia (1-3% isoflurane) and analgesia (ketoprofen) will follow the IACUC-approved Standard Operating Procedure for Gerbil survival surgery, anesthesia, and analgesia. Once a surgical plane of anesthesia has been achieved, the head will be stabilized in a stereotaxic device (Kopf) and isoflurane and oxygen will be delivered via a nosecone for the duration of the procedure. An incision will be made in the scalp

to expose the rostral skull at the midline. A head cap will be secured with bone screws and a small amount of acrylic, and a craniotomy will be made above temporal cortex to allow for tangential insertion of either an electrode array (NeuroNexus) or an infusion cannula (P1 Technologies). The skin incisions will be sutured or sealed, if necessary, to form secure margins around the implants. During the first 3 days post-surgery, animals will be given analgesic (ketoprofen), Normosol or lactated Ringers (30-60 mL/kg, subcutaneous). On the first day post-surgery, animals will also be given an anti-inflammatory (dexamethasone, 0.35 mg/kg, subcutaneous). Animals will be observed daily to confirm that recovery is progressing normally, including the maintenance of adequate body weight. These surgical procedures have been used in our laboratory previously to successfully record from auditory cortex in an awake-behaving preparation (Buran et al. 2014b; von Trapp et al., 2016; Yao & Sanes, 2018; Yao & Sanes, 2021), or to infuse drugs into auditory cortex (Caras & Sanes, 2017; Yao et al., 2020).

Permanent hearing loss (malleus removal): Gerbils are anesthetized with isoflurane such that there is a complete lack of responses to nociceptive stimuli. The fur on each side of the head will be shaved, and the skin will be scrubbed, alternating with Betadine and 70% ethanol soaked gauze sponges. A postauricular incision is made to expose the external auditory canal, the tympanic membrane punctured, and the malleus removed with a forceps. The small wound is closed with surgical glue. The surgical procedure is repeated on the other side. Control animals receive a sham operation consisting of anesthesia and a skin incision. The local anesthetic, bupivicaine (0.5% or 0.25% 0.01 ml), will be applied topically to the surgery area and the small wound (˜2-3 mm in length) is closed with cyanoacrylate glue, and heals within 1-2 days. Following surgery, the animal is permitted to recover for 40 minutes on a warm pad (28 C), and then returned to its cage when full motility returns. There are no signs of pain or distress following recovery. Meloxidyl will be given as an analgesic. If the pups appear to be receiving less than adequate feeding during the first 72 hours, we inject a 0.1 mL Normosol-R subcutaneous bolus on each day. Conductive HL is relatively flat across the gerbil audible frequency range, and does not affect peripheral frequency tuning (Rosen et al., 2012; Ye et al., 2021).

Transient hearing loss (earplug insertion): Animals up to age P21 are restrained by hand, and the pinna is manipulated to allow for a clear view of the external auditory meatus, and curved, blunt forceps are used to insert each earplug. Animals older than P21 will be briefly placed under isoflurane anesthesia such that there is a complete lack of responses to nociceptive stimuli, and the ear canal and tympanic membrane visualized under a stereomicroscope (Olympus). Earplug removal is also carried out under isoflurane anesthesia via blunt forceps. Full removal of the earplug takes 20-60 seconds. Sham littermates receive identical handling and pinna manipulation, but without earplug insertion. This manipulation produces a threshold shift of 15-50 dB, depending on frequency, as measured with auditory brainstem responses (Caras and Sanes, 2015), and ~25 dB at 4 kHz as measured behaviorally (Mowery et al., 2015). There is no associated pain or distress. If the pups appear to be receiving less than adequate feeding during the first 72 hours, we inject a 0.1 mL Normosol-R subcutaneous bolus on each day.

Viral injections and optic fiber implant: Surgery will be conducted under sterile conditions in a dedicated IACUC-approved surgery suite that is also approved for BSL-1 injections. Anesthesia and analgesia will follow the IACUC-approved Standard Operating Procedure for Gerbil survival surgery anesthesia/analgesia. Once a surgical plane of anesthesia has been achieved (2-3% isoflurane), the head will be stabilized in a stereotaxic device (Kopf) and isoflurane and oxygen will be delivered via a nosecone for the duration of the procedure. Craniotomies will be made at predetermined, stereotaxic coordinates in the temporal bon to target auditory cortex (Mowery et al., 2017). A small incision will be made in the dura to allow the virus-filled glass pipette to penetrate the brain (see General Methods). Glass electrodes are loaded with viral vector or a fluorescent protein (control) and a Nanoject (Drummond) is then used to deliver 2 nL/s of virus (Mowery et al., 2017). A fiber optic will then be lowered to 0.2 mm above the injection site and secured with dental cement. The craniotomy is covered with Kwik-Sil Adhesive (WPI), the surgical site closed with sutures, and the animal allowed to recover for 2-3 weeks prior to *in vivo* recording.

Auditory brainstem response (ABR): Animals are sedated (ketamine, 30 mg/kg; IP) and anesthetized xylazine (5 mg/kg) and placed in a sound attenuation booth. Respiration rate and response to toe-pinch are monitored regular intervals and supplemental anesthesia is delivered, as needed. Recordings are made with subdermal needle electrodes inserted at the apex of the skull (positive electrode), the nape of the neck (inverting electrode; caudal to right pinna), and ground in hind leg. At the termination of these recordings, animals are euthanized (described above).

Veterinary Care: The [redacted] University [redacted] Campus [redacted] program of Animal Care and Use is accredited by AAALAC international and meets or exceeds federal, state, and local regulations and guidelines related to the humane and ethical care and use of animals in research. The institution holds a current Animal Welfare Assurance with the Public Health Service (PHS) and is registered as a research facility with the United States Department of Agriculture (USDA). The Office of Veterinary Resources (OVR) is responsible for overseeing operation of the animal facilities. The Director of OVR is a Board Certified Laboratory Animal Veterinarian with over 25 years experience. OVR is staffed with 3 experienced Lab Animal Veterinarians, a Facilities Manager, Supervisor, technicians certified as Veterinary and or Laboratory Animal Technicians and additional trained cage washing staff. OVR technical staff include specialists in animal welfare, behavior, environmental enrichment as well as experimental surgery. The [redacted] Research Animal Facilities recently expanded and now occupies approximately 24,000 Sq. Ft. and contain ample administrative support, central resources, caging, supplies, equipment, and staffing to support the current accredited program of Animal Care and Use.

Humane Endpoints: For animals with malleus removal surgery, if there is significant (i.e., greater than 20%) reduction in body weight compared to animals of a similar age, excess circling, or ataxia, then euthanasia will be performed. For animals that have received chronic electrode implants or cannula implants or viral injections with optic fiber implants, if there is significant reduction in body weight following surgery (greater than 20%) compared to animals of a similar age, or ataxia, then euthanasia will be performed. If an animal loses surgically implanted instrumentation, then it will be euthanized immediately.

Performance site: All experiments will be performed in the PI's laboratory within the [redacted] University's [redacted]

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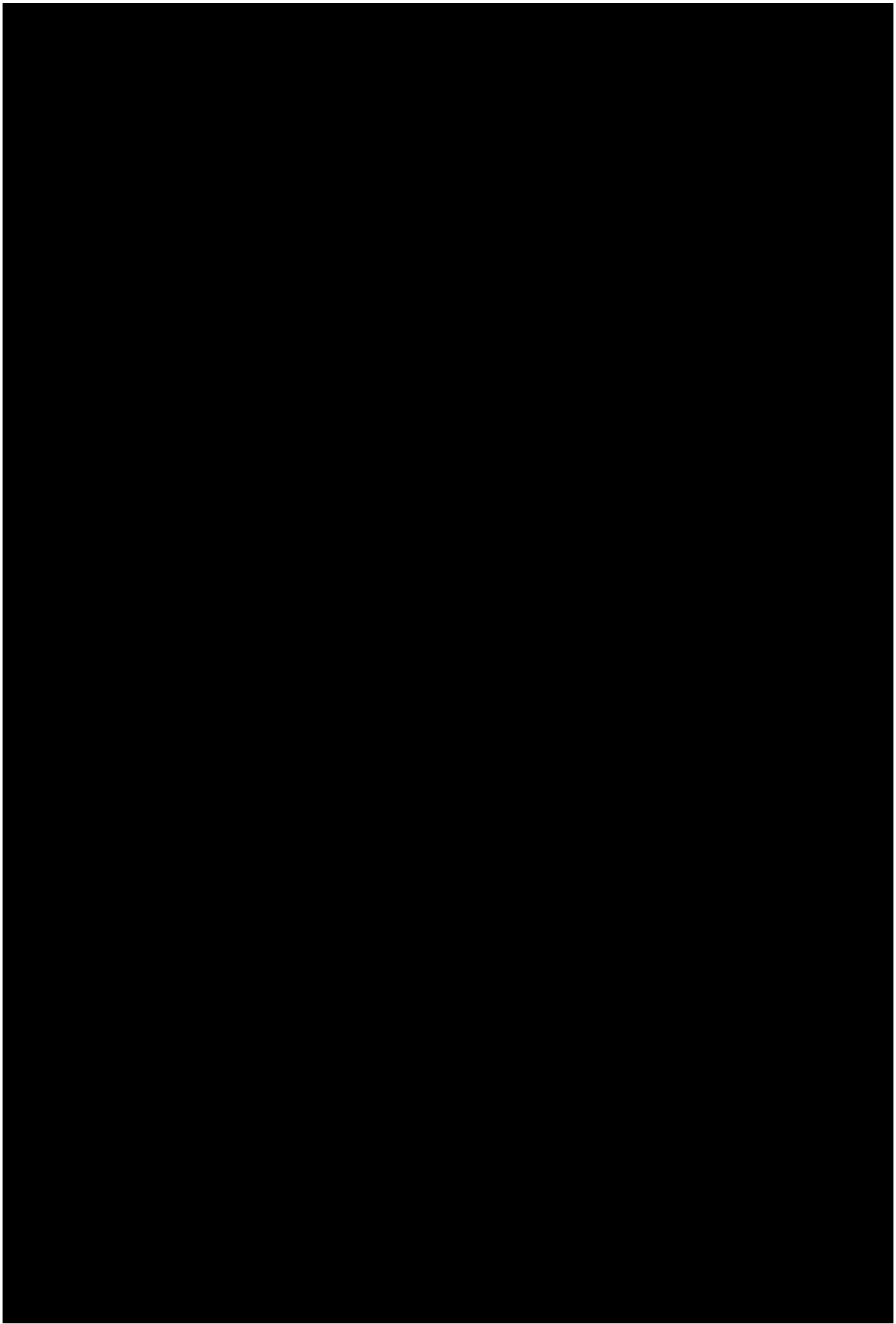

Let

Data Management Plan

A. Type of Data Generated

This project will involve (i) auditory behavioral data from naïve animals, drug- or sham-treated animals, and animals reared with permanent or transient hearing loss, (ii) *in vivo* electrophysiological data from naïve animals, and animals reared with permanent or transient hearing loss performing an appetitive Go-Nogo auditory task, and (iii) photometry data from naïve animals performing an appetitive Go-Nogo auditory task. Electrophysiological and behavioral data will be stored in Matlab format (.mat files). Other information related to the experimental animals will be filed.

B. Storage of Data

All raw data will be stored in multiple secure locations at [redacted] to maximize data integrity. After collection, raw data will be moved from the PC host machines to individual experimenter workstations, and also backed up to a centralized lab server (Synology DiskStation DS1515+80TB). In addition, the server is backed up to a cloud repository (Google Drive) with read only access. Records of experimental animals will be filed in the lab and separately in the Office of Veterinary Resources [redacted]. Only the researchers on the project will have access to the data on servers. All digital files will be stored indefinitely (with the absolute minimum being at least 5 years). Any paper materials will be stored for at least 5 years following publication, following American Psychological Association guidelines. All histological samples will be stored for at least 5 years following publication.

C. Sharing of Data

Immediately following publication of any paper, all associated data files and analysis code will be available in an online repository hosted by [redacted] University [redacted] In addition, should any qualified investigator contact the PI to request additional data related to the project, the PI will make every effort to comply to the extent that it is practically and ethically appropriate. Data together with necessary instructions to interpret the files will be shared.

D. Sharing of model organisms

The proposed experiments will not aid in the production of a new model organism, and will not contain a genome wide association study.

Authentication of Key Resources Plan

The primary biological resource to be used in the proposed study is a recombinant adeno-associated virus that restricts expression of a genetically-encoded fluorescent dopamine (DA) sensor (GRABDA1h) to auditory cortex neurons (AAV1-syn-GRABDA1h-IRES-mCherry). The pAAV-hSyn-GRAB_DA1h plasmid was developed in the laboratory of Dr. Yulong Li at Peking University (Sun et al., 2018), and was uploaded to the Addgene geneback, making it universally available for packaging. We will authenticate the use of the AAV1-syn-GRABDA1h-IRES-mCherry vector by injecting the virus into gerbil auditory cortex, waiting a minimum of 2 weeks for viral expression to plateau, and then using in vivo imaging to perform photometry in transfected auditory cortex and non-transfected auditory cortex neurons. Fluorescent signal will be collected (Exc/Emis: 490/510 nm) during freely moving behavior, and following IP injection of a dopamine transporter blocker (methylphenidate) to increase endogenous DA levels.