SUMMARY STATEMENT

(Privileged Communication)

PROGRAM CONTACT:
[redacted]

Release Date: **11/03/2021**
Revised Date:

Application Number: **1 R01 DC020279-01**
Formerly: **1R01NS126434-01**

Principal Investigator

SANES, DAN HARVEY

Applicant Organization: [redacted]

Review Group: **AUD**
Auditory System Study Section

Meeting Date: **10/21/2021**
Council: **JAN 2022**
Requested Start: **04/01/2022**

RFA/PA: **PA20-185**
PCC: **HR61**
Dual IC(s): **HD**

Project Title: **Social learning enhances auditory cortex sensitivity and task acquisition**

SRG Action: **Impact Score:10 Percentile:1**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01DC020279-01 Sanes, Dan

RESUME AND SUMMARY OF DISCUSSION: This new R01 application from an established investigator addresses the hypothesis that social experience induces experience-dependent plasticity in auditory cortex (AC) that facilitates the acquisition of skills, such as conspecific communication. Experiments will test the role of AC activity and dopaminergic neuromodulation in naive gerbils learning an auditory discrimination task via a trained demonstrator gerbil, in both normal and hearing loss conditions. If successful, these experiments would demonstrate a mechanism for social enhancement of auditory learning that could potentially inform interventions for children with hearing loss. Reviewers were unanimous in their strong support for this innovative, elegant, and highly significant application. The scientific premise for the role of AC and dopamine in social learning is established through compelling preliminary data, and the experimental design is both conceptually and technically innovative. The principal investigator and the intellectual environment [redacted] are outstanding. The rigorous approach (which includes blinding and consistency checks across multiple observers) will allow clear interpretation of the results. Weaknesses were considered to be negligible; inactivation by muscimol is imprecise (but plans for chemo- and optogenetic refinements are in the works), analysis of multielectrode array recordings is not well described, and the rationale for deafening the animals in Aim 3 is not clearly defined. A question arose during discussion as to whether social learning is really distinct from other forms of learning that are already known to involve changes in AC, and the panel ultimately agreed that social reinforcement (such as that which underlies language learning) may well be distinct from the operant conditioning typically used in the laboratory, and the proposed experiments will provide the answer. Given the myriad strengths and insignificant weaknesses, the committee considered this to be an exceptional application with a high impact on our understanding of how social learning enhances AC plasticity and acquisition of auditory skills.

DESCRIPTION (provided by applicant): 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 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 application 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.

PUBLIC HEALTH RELEVANCE: 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 application 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.

CRITIQUE 1

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 1
Environment: 2

Overall Impact: A terrific grant application on the study of the role of the auditory cortex in social learning. The principal investigator lays out convincingly the case for potential role of AC in social learning and proposes a series of innovative experiments to systematically test whether AC is necessary for social learning, whether and how dopamine (DA) within AC contributes to social learning, and whether social learning improves the outcomes of hearing loss. Combined, this is an elegant set of experiments that will move our field forward. The experimenter is an established investigator with experience in behavior and auditory physiology, as well as pharmacological manipulations of neuronal activity.

Significance:

Strengths

- Social learning is a burgeoning field, and the role of auditory cortex in social learning is poorly understood.
- Convincing preliminary data support the main hypotheses of the grant application.
- The behavioral experiments with gerbils are combined with electrophysiology and pharmacology for identification of the underlying mechanisms.
- Addressing the effect of hearing loss on social learning will allow for direct translation of the results to therapeutics.

Weaknesses

- The application stops short of identifying the underlying mechanisms with cellular-level perturbation studies.

Investigator(s):

Strengths

- Established auditory neuroscientist with decades of experience.
- Highly productive investigator who has trained a new generation of scientists.

Weaknesses

- None noted

Innovation:

Strengths

- Conceptually, the project is innovative in that the role of audition in social learning is poorly understood.
- Exploring the transformation in neuronal responses during learning allows for within-animal comparisons.

Weaknesses

- More specific manipulation tools are available, and described as an alternative, potentially offering a richer set of hypotheses to explore.

Approach:

Strengths

- The preliminary data support the notion that gerbils indeed do exhibit social learning, and that the demonstrators produce vocalizations that can be used for social learning. Furthermore, suppressing AC reduces social learning and dopamine manipulation bi-directionally changes learning.
- The use of signal detection theory will help compare behavior across subjects and to neurometric estimates.
- Bi-directional DA manipulation will allow for identifying a direct role in a more convincing fashion than suppression or activation alone. Alternative strategy of using DREADDs or optogenetics may allow for more circuit-specific manipulations.
- Assaying for hearing loss will be performed with multiple different manipulations (e.g., malleus removal or ear plugs) allowing to test for generalization of the findings.

Weaknesses

- None noted

Environment:

Strengths

- [redacted] provides for a great environment with supportive colleagues and the laboratory is fully equipped to carry out proposed research.

Weaknesses

- None noted

Protections for Human Subjects:
Not Applicable (No Human Subjects)

Vertebrate Animals:
YES, all criteria addressed

Biohazards:
Not Applicable (No Biohazards)

Resource Sharing Plans:
Acceptable

Authentication of Key Biological and/or Chemical Resources:
Acceptable

Budget and Period of Support:
Recommend as Requested

CRITIQUE 2

Significance: 1
Investigator(s): 2
Innovation: 1
Approach: 1
Environment: 2

Overall Impact: This application seeks to understand the neural mechanisms of social learning on an auditory task. They will use gerbils as the animal model as this species lives in large social groups and the auditory system is a major way that they communicate with each other. Social learning is little studied so the results from these studies should provide a novel and important impact on the field of perceptual learning. Additionally, the role of dopamine will be investigated at a level that should also significantly impact the learning field. Finally, cortical plasticity and hearing loss studies will also present a significant impact to the field. The principal investigator is excellent and well qualified to perform these experiments in a very collegial and intellectually strong environment, all added strengths to the application. There are only very few minor concerns with the approach that the principal investigator should be able to easily overcome. Overall, there is a great deal of enthusiasm for this application.

Significance:

Strengths

- Social learning is key to much of human learning, particularly language skills, yet is little studied.
- Establishing the gerbil as an animal model of social learning should provide a framework for further studies.
- Cortical plasticity and the role of dopamine in a rigorous experimental paradigm will shed new light on the potential role of cortex for a variety of perceptual abilities.

Weaknesses

- None noted

Investigator(s):

Strengths

- The principal investigator has a long and established history of productivity.
- The principal investigator is well qualified to perform these studies.

Weaknesses

- None noted

Innovation:

Strengths

- Social learning for many species under certain contexts, including language acquisition in humans, is not well studied, and the principal investigator has a novel behavioral paradigm that can address this issue.
- Aside from the behavioral task, the methods are well proven to be effective, so the innovation here is in the application to SL paradigms, which strengthens the rigor of the experiments.
- Inclusion of the hearing loss study will extend these experiments into a new realm.

Weaknesses

- None noted

Approach:

Strengths

- Investigators blind to the condition of the animals increases rigor.
- The appropriate controls are well described and can account for all non-social factors.
- The experimental design is straightforward and will provide solid data that will allow for rigorous interpretations.

Weaknesses

- It is not clear how well the effectiveness of the muscimol will be assessed. If an animal does not seem to have an inactivation effect, can the lack of infusion or inappropriate location of the cannula be excluded? DREADD was suggested as an alternative if motor confounds become apparent, so that should be considered here as well.

Environment:

Strengths

- The laboratory has much of the necessary equipment in place.
- The proposed experiments can be accomplished in the principal investigator's facilities.
- The intellectual environment [redacted] is outstanding.
- There are established collaborations among the principal investigator and colleagues [redacted].

Weaknesses

- New equipment must be purchased, which is a minor concern.

Protections for Human Subjects:
Not Applicable (No Human Subjects)

Vertebrate Animals:
YES, all criteria addressed

Biohazards:
Not Applicable (No Biohazards)

Resource Sharing Plans:
Acceptable

Authentication of Key Biological and/or Chemical Resources:
Acceptable

Budget and Period of Support:
Recommend as Requested

CRITIQUE 3

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 3
Environment: 1

Overall Impact: This is a thoughtfully written and creative new R01 submission from a productive and influential senior investigator. The goal of the application is to determine whether social experience causes AC to become more plastic in ways which facilitate acquisition of auditory tasks. The importance of social learning in humans is easy to recognize, and the mechanisms really have not been studied much in animal models, so these experiments are likely to fill an important conceptual gap. The preliminary data convincingly shows that gerbils learn an auditory task far faster when they are allowed to hear other gerbils performing the task and receiving rewards. The data suggest that gerbils vocalize during the task and that vocalizations are correlated with social learning, that AC inactivation and DA receptor antagonism impair this learning, and that AC sound representations evolve during this process (some results are from a modified paradigm in which gerbils could see as well as hear each other).

Based on these data, Aim 1 is to use the task variant in which the gerbils can only hear each other but not see each other to determine whether AC inactivation during the observation period prevents social learning, and use fiber photometry in the same paradigm to determine whether DA is released in AC during social learning. The lab doesn't have experience in fiber photometry but has recruited a consultant and postdoc who do.

Aim 2 is to perform 5-day chronic recordings to determine whether AC neurons & populations of neurons change how they encode task stimuli during the 5 days of observation, along with an interesting parallel experiment in which, instead of being able to hear actual gerbils performing the task, the test gerbils are exposed to sounds constructed "as if" demonstrator gerbils were performing the task, including specific recorded gerbil vocalizations. Importantly, these will rule out the possibility that the social learning is mediated through other cues that humans cannot detect. These will also allow determining whether improvements in AC representation are correlated with improvements in performance, with presence of a demonstrator, or with presence of an artificial demonstrator. There is a modest dependency between aims in that if Aim 1 shows that learning in the opaque divider condition requires AC activity, that strengthens the argument for performing Aim 2. This aim is somewhat under described in interpretation – it seems that all neurons will be treated as though they were drawn from a single distribution without regard to layer, firing rate, or cell type – but the data is clearly important, nonetheless.

Aim 3 is to perform similar experiments in gerbils which were bilaterally permanently or transiently deafened (P11-P80), to determine whether later social exposure can compensate for the harmful effects of hearing deprivation during early critical or sensitive periods. There is no preliminary data for this aim to indicate whether the answer will be "yes" or "no", but it is a very logical question to ask. This lab is one of the most experienced in the world with these hearing loss models so there is no question whether they will be able to perform the experiment even though there is no preliminary data for this aim. I was not certain about the rationale for performing experiments on permanently deafened gerbils (is there any expectation that they'll be able to learn a purely auditory task once their malleus is removed?), but the rationale for experiments on transiently deafened animals seems strong.

Sex as a biological variable will be considered. Age is explicitly part of the experimental design. In addition to blinding where possible, they will compare results across lab members. Overall, enthusiasm for this application is very high because of the conceptually innovative and very important question, the strong preliminary data justifying the premise, the carefully laid out experiments with clear interpretations, and the outstanding investigator with the ideal expertise, staff, and environment.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all criteria addressed

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:
Acceptable

Authentication of Key Biological and/or Chemical Resources:
Acceptable

Budget and Period of Support:
Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R01 DC020279-01; PI Name: Sanes, Dan Harvey

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

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