

SUMMARY STATEMENT
(Privileged Communication)

Release Date: 03/19/2020
Revised Date:

PROGRAM CONTACT:
[REDACTED]

Application Number: 1 R21 DC017820-01A1

Principal Investigator
MONSON, BRIAN BRUCE

Applicant Organization: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Review Group: CDRC
Communication Disorders Review Committee

Meeting Date: 02/20/2020
Council: MAY 2020
Requested Start: 07/01/2020

RFA/PA: PAR18-487
PCC: HR05

Project Title: Auditory experience during the prenatal and perinatal period

SRG Action: Impact Score:20
Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Age: 1A-Children, Adults, Older Adults, scientifically acceptable

Project Year	Direct Costs Requested	Estimated Total Cost
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]
<hr/> TOTAL	<hr/> [REDACTED]	<hr/> [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.

1R21DC017820-01A1 Monson, Brian

RESUME AND SUMMARY OF DISCUSSION: This resubmitted application for an NIDCD Early Career Research (ECR) Award (R21) (PAR 18-487) seeks three years of support for Dr. Monson to study the effect of premature birth on auditory neurodevelopment and communication behavior. The project proposes to examine the acoustic environment, especially the language environment, of preterm infants exposed to the acoustic input of the neonatal intensive care unit (NICU) versus third trimester in utero infants, and to correlate this with vocalizations and auditory brainstem response. The project is significant and innovative, and has high potential for medical impact for improving therapeutic and prevention strategies in pre-term children who develop auditory processing problems. Strengths of the application include the PI, who has strong publication record and the requisite expertise in electrical engineering and speech-hearing science, as well as experience with preterm infants, a collaborative team which provides additional expertise, and an environment that has sufficient resources and infrastructure for the research activities. The approach is innovative, preliminary data support feasibility and the device (LENA system) provides powerful assessment of auditory and language environments and will be used to record acoustic environments for preterm and term infants. Previous concerns about variabilities of LENA devices due to factors such as heartbeat, mother's voice, interference from respiratory cannulas, and unusual or weak vocalizations have been addressed, and a consultant has been added to help with LENA, vocal and communication development studies. Overall enthusiasm for this project is high, reviewers discussed some less significant issues in the research plan, and note additional consideration should be given for alternate strategies, if the LENA system does not provide sufficient information.

DESCRIPTION (provided by applicant): Within the United States alone, over a half-million infants are born premature each year. While medical advances have dramatically improved survival rates, long-term morbidities related to auditory function are common. The preterm population suffers from a relatively high prevalence of sensorineural hearing loss, auditory neuropathy/dys-synchrony, and central auditory processing disorder. Even preterm infants in whom no specific auditory pathology has been diagnosed exhibit cognitive impairments related to auditory processing, including auditory attention deficits, language processing deficits, and other speech/language communication deficits. Despite these facts, a solid understanding of the impact of premature birth on auditory neurodevelopment is lacking. Possible effects of the acoustic environment are unknown. The long-term objective of this research is to characterize the effect of premature birth on auditory neurodevelopment and communication behavior to aid in improving best medical practices and therapeutic interventions for preterm infants. In this study, we propose to measure the effects of auditory input during the preterm period on neurodevelopmental outcomes. There are three specific aims. In Aim 1 we will recruit a cohort of preterm infants in the neonatal intensive care unit (NICU) to prospectively measure their auditory input during hospital stay. We will quantify detailed auditory experience in the NICU and determine how this differs from intrauterine auditory experience. In Aim 2 we will determine the effect of premature birth on auditory function at 3 months of age. In Aim 3 we will determine the relationship between our measured parameters of perinatal auditory experience and auditory function in infancy. The proposed study will lay the foundation for a longitudinal study aimed to determine the effect of auditory experience in the NICU on long-term auditory and language development. Valuable insight will be gained as to how premature birth and NICU environment might affect auditory neurodevelopment. Results of these studies will ultimately aid in identifying (1) effective interventions to optimize NICU auditory experience and (2) potential early-intervention therapies for NICU infants at greatest risk for auditory and language deficits later in childhood.

PUBLIC HEALTH RELEVANCE: Within the United States alone, over 500,000 infants are born preterm each year, with survivors commonly suffering from cognitive disorders and auditory neurodevelopmental disorders. This research will provide valuable insight as to how premature birth,

medical care, and sounds in the neonatal intensive care unit affect brain development in preterm infants.

CRITIQUE 1

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

Overall Impact: This is a resubmission of a project investigating how the acoustic environment of preterm infants in the NICU compares to that of the third trimester in utero acoustic environment. Experiments investigate how these environmental differences correlate with hearing in premature and full-term infants using auditory brainstem responses (ABR). The project is novel and of high importance, since most studies of the developmental effects of different acoustic environments have been restricted to animal models. The data have the potential to influence early intervention strategies to mitigate auditory and language developmental delays in children born prematurely. The productive PI is well-suited to carry out the proposed research with his broad training and expertise. Institutional commitment is clear, and adequate resources are available to the PI in his own laboratory and department. The resubmitted experimental plan is more focused and well-considered. Previous concerns about using the LENA system in the characterization of the acoustic environment and sources of sounds in utero have mostly been addressed, but there remain some weaknesses in the consideration and analysis of the many factors to be measured. The collaborating team should be able to help troubleshoot any remaining issues. The project, if successful, is likely to produce data that can be used for a competitive R01 application.

1. Significance:

Strengths

- Animal studies have identified numerous deleterious effects of abnormal acoustic experience on auditory development, but it is uncertain how these findings translate to humans. This is not a simple thing to test in humans; therefore, the proposed research represents an important step in understanding how different acoustic experience (prenatally or in the NICU) affects auditory development in humans.
- There is a substantial literature documenting the increased sound levels in NICUs, but our understanding of how exposure to these sounds affects infants' auditory development compared to infants with typical *in utero* acoustic experience is limited. The proposed research takes an important step in understanding this relationship.
- Given the increased prevalence of auditory and language disorders in preterm infants, the research has obvious importance for informing interventions to prevent or ameliorate these disorders.

Weaknesses

- None noted by the reviewer

2. Investigator(s):

Strengths

- The PI has a solid publication record and a record of funding, with several publications that are directly relevant to the proposed research.
- The PI's multidisciplinary training and experience in engineering, speech & hearing, and pediatrics uniquely positions him to perform the proposed research.

- The Co-Is and collaborators enhance the breadth of expertise, including neonatology, clinical auditory physiology, audiology, speech language pathology, and biostatistics.

Weaknesses

- None noted by the reviewer

3. Innovation:

Strengths

- The primary innovation in the proposed research lies mainly in the effort to translate knowledge from studies of the effects of abnormal acoustic exposures on auditory development in animal models. This is not a trivial task, given the logistical difficulties of assessing acoustic experience over time in human infants.
- The experiments will provide important information about the diagnostic potential of using higher frequency tone-burst ABRs in infants.

Weaknesses

- The methodology is not especially novel, other than the more comprehensive assessments to be gleaned relative to other studies. However, this minor weakness does not dampen enthusiasm for the proposed work.

4. Approach:

Strengths

- Measurements in Aim 1 are based on preliminary results that establish feasibility and the existing literature. 24-hr recordings using the LENA device will be compared 3x per week in very preterm infants' incubators and cribs in the NICU or near the abdomen of the mother for full term infants *in utero*. Circadian patterns will be tracked, which is critical since the patterns of acoustic input or silence over time are likely to be important in addition to the overall levels and frequencies of the experienced sounds.
- Diagnostic ABRs (Aim 2) will be performed at later ages to identify auditory pathway developmental delays. Language exposure (Aim 3) will be related to the ABR assessments of auditory pathway status. This is a logical progression of assessments.
- A 'uterine' filter based on mean values reported in the literature will be applied to the *in utero* sound measurements to better approximate what the fetus is exposed to.
- Input from other sensory modalities (somatosensory, visual), medical factors, and maternal demographics will be tracked along with auditory input in NICU patients, which will help determine the contribution of overall abnormal sensory input to auditory development.
- Large sample sizes will ensure adequate statistical power.
- The experiments are considered to be an important starting point for addressing the effects of auditory experience in preterm infants.
- Most of the potential limitations are addressed.

Weaknesses

- Due to the nature of the study, the observed relationships between acoustic experience and auditory development can only be correlational. However, this is a minor weakness at this point in the research program and one that is inherent to this type of human work. Future studies may get at causality, for instance, by randomly assigning participants to different intervention conditions that are developed based on the results of the proposed studies.
- Limitations of the study are considered somewhat, but alternative approaches to using the LENA are not really provided in Experiment 1A. What seems to be missing is validation that the LENA provides an accurate classification of the sounds in the noisy NICU environment (although the possibility of doing this is mentioned in Experiment 1B). This concern is somewhat mitigated by the inclusion of a collaborator with extensive experience with the LENA devices and should be easily addressable.
- Aim 3 does not include plans to look at possible differences in interpeak ABR latencies due to a lack of effect in preliminary data. However, including this additional analysis in the larger sample

might provide information and provide important information about the conduction time along the pathway. It is also unclear how the individual wave latency differences are related to amplitude differences.

- A more developed plan for testing the multiple co-variates that may contribute to the abnormal ABR latencies is needed. Presumably the collaborating biostatistician can assist with this issue.

5. Environment:

Strengths

- The UIUC provides a rich intellectual environment with specialized support for junior faculty. The PI interacts with several other hearing and speech researchers on a routine basis.
- Adequate research and clinical facilities are available to the PI.
- Substantial support services are available.

Weaknesses

- None noted. None noted by the reviewer

Study Timeline: Not Applicable

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

- Risks are minimal and adequate protections are in place.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Since this is a study of infants and pregnant mothers, age and sex distributions are justified.

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Resubmission:

- The application is mostly responsive to previous critiques.

Select Agents: Not Applicable

Resource Sharing Plans: Acceptable

Authentication of Key Biological and/or Chemical Resources: Not Applicable

Budget and Period of Support: Recommend as Requested

CRITIQUE 2

Significance: 2

Investigator(s): 2

Innovation: 2

Approach: 2

Environment: 2

Overall Impact: Preterm infants have high prevalence of hearing loss, auditory neuropathy and central auditory processing disorders. Even without hearing loss, they have higher rates of cognitive and

language disorders. As pointed out by previous reviewers, this is a highly significant and understudied area. This application is well written by a promising investigator to evaluate the level of auditory input of preterm infants in the NICU (Aim1), term pregnancy is used as controls; and assess how auditory development (ABR at 3mo) is affected (Aim2); and compare auditory experience and short-term communication behavior. PI is productive, uniquely trained, and has very high potential working with a strong team with complementary skillsets. Strong pilot data supports feasibility and the applicant has properly addressed previous concerns.

1. Significance:

Strengths

- Over 0.5 million preterm infants born per year, with high rates of hearing loss, auditory neuropathy and central auditory processing disorders
- Sound level and quality of sound exposure to NICU children has not been systematically studied

Weaknesses

- None noted by the reviewer

2. Investigator(s):

Strengths

- Dr. Monson is an Assistant Professor since 2017. Uniquely trained in pediatric newborn medicine and neuroscience.
- Very productive publication record, another one recently added in Jan 2020.
- Dr. Rollo (pediatrician) will help recruit patients. Brown to help with ABRs. Dr. Ambrose is an expert in vocal development. Danielle-Baird to assist with audiologic assessment. Dr. Shen with Statistics.

Weaknesses

- None noted by the reviewer

3. Innovation:

Strengths

- Open question on the level and quality of sounds in preterm infants in comparison to term infants

Weaknesses

- None noted by the reviewer

4. Approach:

Strengths

- NICU sound exposures-both levels and qualities measured
- prelim data showing higher level of sounds and lower exposure to language-related sounds, and periods of silence.
- Aim 1 VPT (very pre-term) will receive 24hr audio recording devices (LENA). Likewise, for pregnant mothers several times per week.
- Aim 2-ABR at 52 weeks for both VPT and FT infants and latency tone bursts will be assessed.
- Aim 3-relationship between auditory exposure and auditory development analyzed
- Excellent power analyses done
- Medical factors considered, including exposure to ototoxic medications

Weaknesses

- Correlation but not causative, but proposed modifying sound exposure

5. Environment:

Strengths

- UIUC has a record of communication research and supportive.
- Equipped with biostatistics support. PI has lab space and office.

- Access to NICU and audiology clinic in Carle Foundation Hospital (<5min)

Weaknesses

- None noted by the reviewer

Study Timeline: Not Applicable

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

- Minimal risks to participants

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion Based on Age: Distribution justified scientifically

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Resubmission:

- Previous concerns about heartbeat and digestive sounds are now considered.
- Another previous concern that LENA will not pick up mother's voice, interference from respiratory cannulas, and unusual or weak vocalizations might not be picked up. So, transfer function is now used to account for attenuation and filtering of sound between the environment outside of the mother and the fetus' ears
- One additional consultant on LENA, infant vocal and communication development

Select Agents: Not Applicable

Resource Sharing Plans: Acceptable

Authentication of Key Biological and/or Chemical Resources: Not Applicable

Budget and Period of Support: Recommend as Requested

CRITIQUE 3

Significance: 2

Investigator(s): 2

Innovation: 2

Approach: 2

Environment: 2

Overall Impact: This is a resubmitted application that addresses many of the critical comments pertaining to the scientific approach, primarily. The topic of science is important and the approach is hypothetically driven. The tools (LENA) and approach are innovative and the results obtained have the potential to impact medical services.

**1. Significance:
Strengths**

- The contribution of noise exposure to infant development is a significant issue that is often overlooked. More research is needed in this area but it is a difficult population to test in a difficult environment. This research proposal is technically sophisticated and well thought out.

Weaknesses

- None noted by the reviewer

2. Investigator(s):

Strengths

- The PI is well trained and well suited for this particular set of experiments. Few people in the world have the background to carry out this type of investigation. They have assembled a strong team of collaborators for additional support as needed.
- The PI is highly productive.

Weaknesses

- None noted by the reviewer

3. Innovation:

Strengths

- This is an important problem with relatively little research being done in this area.

Weaknesses

- None noted by the reviewer

4. Approach:

Strengths

- This is a difficult population to test, housed in a difficult environment. Therefore, the power analysis and acknowledgement of the vulnerable population is a strength, as is the recognition of limitations and preparation for alternative approaches.

Weaknesses

- None noted by the reviewer

5. Environment:

Strengths

- Suitable to conduct this research

Weaknesses

- None noted by the reviewer

Study Timeline: Not Applicable

Protections for Human Subjects: Acceptable Risks and/or Adequate Protections

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion Based on Age: Distribution justified scientifically

Vertebrate Animals: Not Applicable

Biohazards: Not Applicable

Resubmission:

- Previous review concerns addressed appropriately

Select Agents: Not Applicable

Resource Sharing Plans: Acceptable

Authentication of Key Biological and/or Chemical Resources: Not Applicable

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 ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

The protocol features minimal risk to subjects and employs adequate protection against risks.

INCLUSION OF WOMEN PLAN: ACCEPTABLE

The study population is expected to include equal numbers of male and female subjects, which is scientifically acceptable. A Targeted/Planned Enrollment Table is included and reflects this gender breakdown.

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

The study population is expected to include participants from various racial/ethnic groups; this is scientifically acceptable. A Targeted/Planned Enrollment Table is included and reflects this racial/ethnic breakdown.

INCLUSION ACROSS THE LIFESPAN PLAN: ACCEPTABLE

The study is expected to include very pre-term infants (birth less than 32 weeks gestational age), full-term infants, and pregnant women (greater than 18 years of age). A justification is provided, which is scientifically acceptable.

VERTEBRATE ANIMAL: Not Applicable

BIOHAZARDS: Not Applicable

SELECT AGENTS: Not Applicable

RESOURCE SHARING PLANS: ACCEPTABLE

Plan for disseminating research results and sharing any relevant data with the scientific and clinical communities is provided.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: Not Applicable

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested

Footnotes for 1 R21 DC017820-01A1; PI Name: Monson, Brian Bruce

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](http://grants.nih.gov/grants/peer_review_process.htm#scoring).

MEETING ROSTER

Communication Disorders Review Committee
NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS
CDRC
02/20/2020 - 02/21/2020

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html> and NOT-OD-15-106 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html>, including removal of the application from immediate review.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

