SUMMARY STATEMENT

PROGRAM CONTACT: (Privileged Communication) *Release Date:* 06/29/2015

[redacted]

Application Number: 2 R01 DC010813-06A1

Principal Investigator

CARNEY, LAUREL H. PHD

Applicant Organization: [redacted]

Review Group: AUD
Auditory System Study Section

Meeting Date:	06/01/2015	*RFA/PA:*	PA13-302
Council:	OCT 2015	*PCC:*	HR50
Requested Start:	04/01/2016	*Dual PCC:*	3APGRSS
		Dual IC(s):	AG

Project Title: Developing and Testing Models of the Auditory System with and without Hearing Loss
SRG Action: Impact Score: 15 Percentile: 3
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
	[redacted]	[redacted]
TOTAL	[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.

RESUME AND SUMMARY OF DISCUSSION: An exceptional scientist proposes to address an “old problem” (trouble hearing in noisy situations especially for those with hearing loss) with a powerful innovative multidisciplinary approach in animal and human models. Reviewers were unanimous in their excitement about the potential impact this project will have in reshaping our thinking about how the auditory system encodes sounds, a fundamental question of tremendous importance to improving the lives of millions with sensorineural hearing loss. The response to the prior critique was compelling. The investigator is also commended for her willingness to share her work/models with others and for her judicious application of her models to others‟ work. A few minor quibbles did not detract from this terrific proposal.

DESCRIPTION (provided by applicant): This proposal presents plans to develop and test a new model for the processing of acoustic cues in both psychophysical tasks and real-world hearing. Masking paradigms are typically interpreted in the context of two models: The power-spectrum model is based on energy in the responses of one or more band-pass filters that represent peripheral tuning. The envelope-power-spectrum model is based on the responses of a bank of modulation filters. These popular models, however, fail to explain robust performance in a number of psychophysical tasks, especially roving- or equalized-level, and roving- or equalized-envelope-energy tasks. The continued use of these models is largely due to a lack of viable alternatives. Here, we propose a new, alternative model for masked detection and spectral coding that provides a mechanistic explanation for a number of psychophysical results, for listeners with or without hearing loss. Building upon our recent studies of envelope-related cues in masked detection, our proposal focuses on the role of neural-fluctuation cues in the responses of auditory-nerve fibers, and ultimately on how these cues are represented by modulation-tuned neurons in the midbrain. These cues are robust in the healthy ear but, because they are strongly dependent upon peripheral nonlinearities, they are substantially degraded in most common types of hearing loss. We will make detailed measurements on the use of envelope vs. energy cues by individual listeners as a function of frequency and hearing thresholds. These results will provide individualized models that will be used to predict thresholds in specific masking and discrimination tasks. We will use computational, physiological and psychophysical tools to test a diotic model of masked detection, focusing on two classic paradigms: notched-noise and forward-masking tasks. These psychophysical tools have been used extensively to characterize tuning bandwidth, compression, and temporal processing in listeners with and without hearing loss. We will re-examine these tasks with neural fluctuation- based representations. Our preliminary results show that the contrast in fluctuations across peripheral channels establishes a representation of stimulus features at the level of the midbrain that is robust in noise across a wide range of levels, thus addressing the primary challenges of roving-parameter paradigms. These cues are particularly strong near spectral slopes, and thus warrant consideration for other stimulus features with sharp spectral slopes, such as fricative consonants and pinna cues. We therefore also propose to extend our dichotic model based on interaural differences in neural fluctuations to the spectral slopes of pinna cues, which code sound location and externalization. Our preliminary work indicates that neural-fluctuation cues associated with the diotic and dichotic stimuli occur in the modulation frequency range where the majority of midbrain neurons are tuned. Consideration of these tasks and stimuli in the framework of neural-fluctuation cues provides a novel and general understanding for coding stimulus spectra by the normal and impaired ear.

PUBLIC HEALTH RELEVANCE: Hearing loss typically involves difficulty understanding complex sounds such as speech, especially in noise. Knowledge of how the healthy brain copes with difficult listening environments will provide new and important insights for aiding listeners with hearing loss. The Public Health Relevance of this project is to develop a better understanding of the difficulties in noisy situations for listeners with hearing loss. We are developing and testing a computational model for the auditory system of listeners with and without sensorineural hearing loss.

CRITIQUE 1

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

Overall Impact: This proposal examines a new mechanism by which masked sounds and spectral contrasts are encoded in the auditory system. The mechanism has the potential to explain a much larger body of literature than current energy-based models. Moreover, the model can be extended to predict perceptual deficits by listeners with sensorineural hearing loss (SNHL). SNHL is a common affliction that impacts normal communication, yet the precise mechanisms are not understood. Hence, this proposal has potentially high significance as the results will give deeper insight into this problem mechanistically. Additional strengths include the exceptional PI and research team, innovative conceptual advancements (i.e., a new approach to an old problem), a comprehensive approach that includes psychophysics, physiology and modeling and an outstanding environment. The PI was also receptive to the prior critiques and responded appropriately. There were a few negligible weaknesses that did not detract at all from a strong and important proposal.

1. Significance:

Strengths

- Detection of signals in the presence of noise is essential for normal communication; however, this ability is impaired in listeners with sensorineural hearing loss (SNHL). The neural bases for this isn‟t clear, and current models of signal in noise detection fail to explain much of the findings. This proposal focuses on the new idea that fluctuations in neural responses, rather than the total energy at the target frequency, can explain detection in both normal and hearing impaired listeners.
- The proposal is approached from a multidisciplinary perspective including modeling, psychophysics and physiology that together will yield a much deeper and comprehensive understanding of normal and impaired hearing than could be achieved via just one or two of these approaches. Hence, the results will advance knowledge in many different fields.

Weaknesses

- None

2. Investigator(s):

Strengths

- The PI is exceptionally qualified to conduct all aspects of the proposed work. She has a strong history of funding and productivity. She is a leader in the field and the impact of her work has been recently evidenced by her award in 2015 of the William and Christine Hartmann Prize in Auditory Neuroscience by the Acoustical Society of America.
- Progress during the prior grant period was good, with 6 papers in leading journals including JASA, JARO and the Journal of Neuroscience. A non-provisional patent based on the prior work was also submitted.

- Despite being fully capable of leading the proposed work, the PI has assembled a strong team of knowledgeable collaborators to assist in key areas of the proposal.

Weaknesses

- None

3. Innovation:

Strengths

- There are several conceptual innovations of the proposal, the most key being the new approach to the encoding of masked sounds and spectral contrasts by neural fluctuations rather than by rote energy- and neural rate-based models. An interesting aspect of the new model is that the information about neural fluctuations is not found in the acoustic stimuli, but rather it results from peripheral and central processing of the stimuli, including non-linearities. And it is impairments in the neural processing that can be predictive of impaired behavioral performance.
- The particular combination of psychophysics in normal and impaired listeners, physiology and modeling in this proposal is somewhat innovative

Weaknesses

- None

4. Approach:

Strengths

- For the most part, the psychophysical, physiological and modeling methods are fairly routine and there is a fair amount of preliminary data for each proposed experiment. Together, this lends confidence that the project will be completed.
- There are some nice control experiments designed to explicitly separate the proposed models based on performance. For example, roving the level renders energy-based models ineffective but not the neural fluctuation models. Additional stimulus manipulations are designed to produce an effect in „opposite" directions such that there should be little doubt about which model is more correct.
- The physiological experiments are logically designed to test empirically whether the model predictions are valid.

Weaknesses

- None

5. Environment:

Strengths

- The scientific and intellectual environment at Rochester is outstanding.
- The PI and her research team have all of the equipment and facilities required to conduct the proposed work

Weaknesses

- None

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- The proposed use of human subjects is acceptable and necessary for the research. Adequate provisions are in place to protect human subjects from anticipated risks.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 21: Including ages < 21 justified scientifically
- Gender representation is acceptable. Both genders are represented. Both minority and non-minority subjects are included. Gender and minority proportions are generally reflective of the demographics of the population in Monroe County, NY (U.S. Census Bureau, estimates for 2013). Children under 21 are studied, which is acceptable.

Vertebrate Animals:

YES, all five points addressed

- Species, strain, sex, age and numbers of animals needed is adequately indicated. Experiments are well justified. Appropriate care is indicated as are procedures to minimize pain and discomfort. Appropriate methods for euthanasia are indicated.

Biohazards:

Not Applicable (No Biohazard)

Resubmission:

- The PI responded well to the prior critiques

Renewal:

- The PI was adequately productive during the prior grant period

Resource Sharing Plans:

Acceptable

- The PI included a plan to disseminate the models and data that result from the proposed work. The PI has a long history of providing such information to the scientific community.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 2
Investigator(s): 1

Innovation: 2
Approach: 2
Environment: 2

Overall Impact: This project investigates an exciting new way of understanding how the auditory system processes signals in noise. The neural-fluctuation contrast model offers a fundamental alternative to energy-based models of signal detection, and promises to shed new light on how cochlear impairment leads to performance deficits. The project incorporates a unique and powerful blend of computational modeling, animal physiology and human psychophysics. The PI is an exceptional scientist and extremely capable of accomplishing all aspects of the project.

1. Significance:

Strengths

- The power spectrum model of masking has been a mainstay of auditory theory despite inherent inconsistencies (e.g., invariance of performance in the presence of level rove) and the neural fluctuation contrast model tested in this project offers a paradigm shift in the understanding of how signal-in-noise information is extracted in the central auditory system.
- Determining the relative use of energy-related vs. envelope-related cues as a function of hearing loss has important ramifications for understanding perceptual difficulties of hearing-impaired listeners.
- The model captures essential features of cochlear impairment such as changes in filter bandwidth, altered cochlear amplification, and enhanced envelope coding.
- The model will shed light on why simple amplification will not restore high-frequency cues related to spectral slopes/notches.
- The neural fluctuation model will clarify whether frequency selectivity (tuning) measured with forward masking paradigms reflects modulation sensitivity in the upper brainstem rather than „pure‟ cochlear tuning.

Weaknesses

- The significance of Aim 3 is undermined, on the face of it, by the hypothesis that interaural differences in neural fluctuations code elevation. It is not clear how this hypothesis (interaural differences) applies to elevation coding for diotic stimuli.

2. Investigator(s):

Strengths

- The PI (Carney) is a senior investigator with a strong record of rigorous and productive investigation. Her ability to blend human psychophysics, animal physiology, and computational models makes her an exceptionally skilled and comprehensive scientist.
- Clinical expertise will be provided [redacted] This provides confidence in the recruitment success of the listeners with hearing loss.
- The inclusion [redacted] as a consultant in psychophysical studies of masked detection (Aim 2) and [redacted] as a consultant on phonetic issues (Aim 3) strengthens the research team.

Weaknesses

- None

3. Innovation:

Strengths

- The neural-fluctuation contrast model is inherently innovative, and the application of the model to steeply sloping spectra will add new insights related to a range of acoustic situations from speech perception (fricative discrimination) to spatial hearing (pinna cues).
- The project introduces a novel approach to permit differentiation of the types of cues (energy vs. envelope) that an individual listener uses across frequency.

Weaknesses

- Many of the computational and experimental procedures are well established in the PI"s work and, in this sense, are not innovative.

4. Approach:

Strengths

- Examining the relation between simultaneous and non-simultaneous (forward) notched noise masking in the context of the neural-fluctuation contrast model will help resolve controversies over apparent differences in derived filter bandwidths obtained with these two methods.
- The modeling approach will carefully consider the ramifications of rate-level saturations (dynamic ranges) in auditory nerve fibers as a function of the spontaneous firing rate of the fibers.
- The dual approach of testing model predictions against both (human) psychophysical performance and direct physiological recordings is particularly rigorous.
- The use of existing published data from other laboratories against which to test model performance (e.g., Aim 2) heightens the scientific integrity of the approach.
- Testing the neural fluctuation model by creating stimuli with divergent predictions for the model vs. power spectrum models in Aim 2 (e.g., substituting narrow band of noise for tonal signal) is clever.

Weaknesses

- The restriction of dichotic cues here to high frequencies because low-frequency dichotic cues are being tested in a different project begs the question as to how the complete spectral picture will be pulled together from these two distinct investigative efforts. In general, reference to certain aspects of the model being explored in other funded work (DC001641 and STTR) makes it difficult to ascertain the boundaries/overlap of the various projects.
- The Dutch-belted rabbit is put forward as providing physiological data that is applicable to modeling human performance, but the behavioral performance of the rabbit itself is dismissed as not comparable (“they have difficulty with complex detection and discrimination tasks”). This selective use of the type of data deemed acceptable from the animal model is somewhat dissatisfying.
- The upper age limit is 80 years. The inclusion of listeners with hearing loss across the age span will increase the challenge of differentiating age and hearing loss effects, especially as it may prove difficult to find age-matched controls (normal audiometric hearing up to 4 kHz) in the higher age groups. However, the PI clearly has access to a substantial pool of older subjects through the Center for Navigation and Communication Sciences.

- It is not clear how individual measures of audiometric threshold and DPOAEs will be converted to metrics of inner and outer hair cell loss to „individualize" the neural fluctuation model. Because the success of the individualized model (in terms of comparing its predictions to the actual performance of the individual listeners) depends on the accuracy of the initial parameter-tailoring, further details would have been welcome.

5. Environment:

Strengths

- All facilities necessary for the project are available to the PI.
- Given the heavy computational modeling component of the project, the availability of the Center for Research Computing is of particular note.

Weaknesses

- None

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 21: Including ages < 21 justified scientifically
- Children below the age of 18 years will not be included which is appropriate given the duration and difficulty of the psychophysical tasks.

Vertebrate Animals:

YES, all five points addressed

- No concerns

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The PI has carefully considered the comments on the previous submission and has revised the application accordingly.

Renewal:

- The goals of the previous funding cycle appear to have been generally met. Five peer-reviewed papers have been published, with others in various stages of submission.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

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

Overall Impact: This is a strong project from an experienced and productive investigator who proposes to explore new ways of thinking about how signals are detected in noise and discriminated. Among other things, the project aims to solve long-standing mysteries about the resistance of signal detection to roving overall levels. The proposed research considers specifically that energy detection at the output of a filter is not a good model of detection in many cases, and that a model based on mid-brain analysis of modulations in auditory nerve outputs may be more successful. A notable strength of the project is that it combines modeling with both physiology and psychophysics. It also considers the effects of hearing loss, and this will not only assist in the understanding of how different types of auditory pathologies may affect performance on these and other tasks, but will also help inform models of normal processing. The model and research also promises to help us understand how sharp edges in the spectrum are processed to facilitate vertical sound localization and fricative identification. Overall, this is an excellent application that pushes the field forward in significant new ways. One issue is that it‟s not explained whether and how loudness recruitment as a perceptual phenomenon, regardless of what is responsible for it, is expected to affect the ability of a listener to deal with roving level tasks, and whether this will make it difficult to model the effect of hearing loss on the experimental tasks.

1. Significance:

Strengths

- For a long time it has not been possible to understand how even the most basic of tasks, detecting a tone in noise, is carried out by the auditory system. The absence of effects of roving level in many cases cannot easily be explained by traditional models. The proposed research promises to produce a breakthrough with an innovative re-examination of the way in which the auditory nervous system processes temporal modulations and with the strong likelihood based on preliminary data that processing of modulation is a key to explaining the previously unexplainable results.
- The research promises to explain additional puzzling results such as how the processing of edges and notches within the high-frequency spectrum due to pinna effects can take place with broadly tuned high-frequency fibers.
- The research promises to explain how hearing loss affects this type of modulation processing, leading to new insights that will ultimately help understand what amplification can and cannot be expected to improve.

Weaknesses

- None

2. Investigator(s):

Strengths

- Dr. Carney is a world-renowned auditory researcher who has made major contribution in neural modeling and physiology.

Weaknesses

- The P.I. has assembled a team to assist her with various aspects of the project, but as most of the consulting has no time associated with it, it is not clear how much commitment there is.

3. Innovation:

Strengths

- Innovation is high. This is a whole new way of looking at old data that have been difficult to explain.

Weaknesses

- None

4. Approach:

Strengths

- The overall combination of modeling, physiology, and psychophysics is a powerful approach.
- The experimental studies are universally driven by new theories of how modulation processing may be involved in basic auditory tasks.
- The use of subjects with hearing loss will not only reveal new understandings of hearing loss but will also help inform normal models.
- The shift to reproducible masking noises seems well justified.
- Two very interesting auditory puzzles are attacked in the Aim 3 with the same unified theory of fluctuating neural responses.
- The corroboration of modeling efforts with actual measurements from rabbit is a strong approach.

Weaknesses

- The meaning of the term “strategy” for how hearing-impaired subjects might approach these tasks is not easy to understand. How central or intentional is this strategy? The proposal asks whether a listener can change strategies in different frequency regions but it is not clear whether this is taken to mean that they have differing strengths of modulation in neural outputs in different regions or instead can consciously focus on one type of cue over the other. This should be clearer if the research is to interpret the results from hearing-impaired subjects.
- Loudness recruitment in hearing-impaired listeners could make it difficult to deal with roving level, and one would think this would be an important and potentially confounding consideration when evaluating who is affected by roving level and who is not. It was not easy to see that loudness growth functions were going to be regularly measured or accounted for in each subject.

5. Environment:

Strengths

- The environment at the University [redacted] is outstanding, as proven by the success of previous research efforts.

Weaknesses

- None

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- No concerns are noted. Only children over the age of 18 will participate.

Vertebrate Animals:

Acceptable

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The new application appeared to be responsive to previous comments.

Resource Sharing Plans:

Acceptable

- The sharing of the model with the research community is a valuable resource.

Budget and Period of Support:

Recommend as Requested

Additional Comments to Applicant (Optional):

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:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

VERTEBRATE ANIMAL (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.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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