

Specific Aims

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Aim 1: Really cool stuff.

- 1.1. First sub-aim with more details
- 1.2. Second sub-aim with more details.

Aim 2: Really cool stuff.

- 2.1. First sub-aim with more details.
- 2.2. Second sub-aim with more details.

Aim 3: Really cool stuff.

- 3.1. First sub-aim with more details.
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A. Significance

A.1. Instructions. Optional subtitle

Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.

Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.

Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

A.2. Subheading.

Tinnitus, the perception of ringing, buzzing, or hissing in the ears when no external sound is present, is a health condition estimated to affect 10-15% of adults worldwide [henryTinnitusEpidemiologicPerspective2020]. The condition is highly heterogeneous and can range from mild and transient to debilitating and constant. In the U.S., tinnitus affects approximately one in ten Americans, with 7.2% of those rating their tinnitus as severe ([bhattPrevalenceSeverityExposures2016]. Tinnitus can be perceived unilaterally or bilaterally and may differ over time, even within individuals. This heterogeneity in characterization has important implications for research and clinical practice. Identifying patterns in how tinnitus sounds and its relationship to hearing may aid in identifying different forms of tinnitus and revealing their underlying mechanisms. However, the subjective nature of characterizing tinnitus makes it difficult to reliably define and measure [vajsakovicPrinciplesMethodsPsychoacoustic2021].

Current methods to determine cognitive representations of tinnitus are inefficient and introduce bias, resulting in a lack of standardization in tinnitus assessment [henryTinnitusEpidemiologicPerspective2020]. Alternate forced-choice (AFC) paradigm tasks ask the patient to determine which of two sounds is closer to their tinnitus percept [henryComparisonTwoComputerautomated2001, henryComputerautomatedTinnitusAssessment2004, henryComputerautomatedTinnitusAssessment2013, korthOneStepCloser2020]. Recent computer and methodological advances have made the test more portable and efficient, but the AFC paradigm still relies on assumptions about the subject's tinnitus percept. Tinnitus percepts are too heterogeneous to be represented by pure tones or small-envelope waveforms. Adequately sampling the psychoacoustic space of possible tinnitus percepts via an AFC task is unfeasible. Other approaches have attempted to capture the richness of tinnitus percepts using likeness measures, in which the subject rates whether a presented stimulus is part of their tinnitus percept or not [norenaPsychoacousticCharacterizationTinnitus2002]. While this method is able to capture more features of cognitive representations of tinnitus, it is time-consuming and limited by the aural skills of the subject [vajsakovicPrinciplesMethodsPsychoacoustic2021]. Both these approaches involve the subject comparing an external stimulus to their cognitive representation of the tinnitus percept, however AFC tasks introduce biases by artificially limiting the stimulus space and likeness measures are time-consuming.

We believe that a novel reverse correlation-based approach will produce efficient and unbiased cognitive representations of tinnitus percepts [gosselinSuperstitiousPerceptionsReveal2003]. Reverse correlation allows for unconstrained and unbiased characterization of latent representations directly from stimulus-response data by eliciting responses to richly varying stimuli, such as white noise (Marmarelis & Marmarelis, 1978; Nishimoto et al., 2006). Rich stimuli, by virtue of the fact that they are inherently vague, force the top-down process to exert a clearly measurable influence on responses. Latent representations that drive the top-down process can then be estimated by regressing observed responses against the stimuli over many trials (Mineault et al., 2009). Reverse correlation, as a method, is powerful enough to characterize any aspect of neurological, cognitive or psychological function that can be modeled as a transductive process (Ringach, 2004). It has become a primary method used to characterize the latent representations encapsulated in neural tuning (e.g., receptive fields; Ringach, 2004), and is closely related to the widely-used "white noise approach" to characterizing physiological (Marmarelis & Marmarelis, 1978) and engineering (Ljung, 1999) systems.

Reverse correlation, in addition to its prominence as an important tool relative to lower-level neural mechanisms, has been increasingly used for inferring higher-level cognitive representations, including psychophysical kernels that drive the top-down processes of perception (Ahumada & Lovell, 1971; Gosselin & Schyns, 2003; Neri

& Levi, 2006; Smith et al., 2012), and even abstract psychological categories (e.g., “male” vs. “female” faces; Brinkman et al., 2017; Mangini & Biederman, 2004; Ponsot et al., 2018). Recent work in vision (e.g., Gosselin & Schyns, 2003; Liu et al., 2014) has demonstrated that reverse correlation can effectively characterize cognitive representations underlying letter and face recognition (Fig 2A). One speech study has also estimated steady-state representations of vowels the /a/ and /i/ using a closely-related paradigm to the one proposed here (Fig 2B; Brimijoin et al., 2013). Our proposed use of reverse correlation in the domain of speech expands on classic efforts to understand top-down processing in speech with the presentation of rich, vague stimuli to elicit responses from listeners (Warren & Warren, 1970; Vokey & Read 1985). These studies provide clear evidence that rich stimuli, such as white noise, are sufficient to engage the top-down process, even if they do not attempt to characterize the latent representations.

Incomplete characterizations of cognitive representations impoverish our scientific understanding of tinnitus, weak causal explanations for its etiology, and hinder progress towards effective treatments. Reverse correlation shows promise to provide a more complete characterization of cognitive representations of tinnitus and is applicable to other psychophysical domains as well. Directly characterizing complex representations of tinnitus can enable more effective, targeted treatments, reveal insights about subtypes of the condition, and pave the way for new tinnitus-masking assistive devices. Fully characterizing a high-dimensional representation of tinnitus will improve causal explanations for currently unexplained variability in tinnitus experience both between subjects and within single subjects over time.

A.3. Rigor of the Prior Research

The premise of the proposed work is that reverse correlation will deliver unbiased estimates of cognitive representations of tinnitus. Furthermore, that compressive sensing will dramatically increase the efficiency of experiments, resulting in convergent cognitive representations in a fraction of the samples.

The evidence for this premise is first based on well-established studies using reverse correlation to derive cognitive representations of sounds and symbols. Reverse correlation has been applied to infer cognitive representations from letters [gosselinSuperstitiousPerceptionsReveal2003], vowel sounds [brimijoinInternalRepresentationVowel2013], and faces [brinkmanVisualisingMentalRepresentations2017, smithMeasuringInternalRepresentations2012]. More broadly, it has been applied to infer the shape of receptive fields in linear transducers and spiking neurons [ringachReverseCorrelationNeurophysiology2004]. The reverse correlation paradigm makes minimal assumptions about the derived cognitive representation since the subject is presented with high-dimensional random input. A large number of stimulus-response samples are typically required for accurate reconstruction of cognitive representations using conventional techniques. To address this inefficiency, studies often limit the richness of stimuli, or impose strict constraints on the reconstructions, leading to estimates that are biased or incomplete. However, recent advances in signal processing, most notably a techniques known as compressive sensing, are leading to dramatic improvements the efficiency of traditional sampling.

We propose to develop an advanced signal processing pipeline that will enable us to overcome the inefficiencies of existing reverse correlation methods through the use of compressive sensing, a recent advance in signal processing which has led to dramatic improvements the efficiency of traditional sampling and signal estimation methods (Baraniuk, 2007). Compressive sensing has recently gained wide recognition in domains such as medical imaging (Graff & Sidky, 2015; Lustig et al., 2008), where considerations of efficiency and bias reduction are critical. Compressive sensing holds promise to similarly improve the efficiency of reverse correlation, without the drawback of biasing estimates. By dramatically decreasing the number of trials needed for signal reconstruction, this technique will extend the range of perceptual mechanisms that can be estimated. Moreover, compressive sensing can be directly substituted for conventional, regression-based estimation, with no other required changes to existing experimental protocols. Our ultimate objective is to develop and validate a compressive sensing data processing pipeline - culminating in an open-source software tool – that will allow for efficient and accurate reconstruction of latent representations using data obtained via the reverse correlation method.

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Table 1: Example Table

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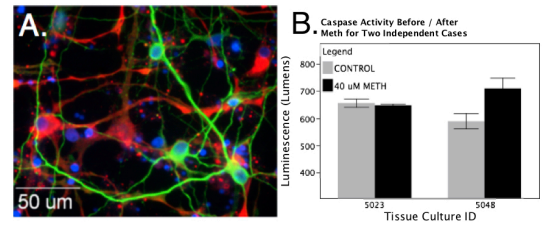


Figure 1: Example wrapped figure. (A) Impressive microscopy image. (B) Impressive data.

A.3. Another subheading: optional subtitle.

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B.1. Instructions.

Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.

Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

C.1. Instructions.



Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in Item 15 (Resource Sharing Plan), include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.

Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.

Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised. A full discussion on the use of Select Agents should appear in Item 11, below.

As applicable, also include the following information as part of the Research Strategy, keeping within the three sections listed above: Significance, Innovation, and Approach.

C.2. Preliminary Studies for New Applications

Preliminary Studies for New Applications: For new applications, include information on Preliminary Studies. Discuss the PD/PI's preliminary studies, data, and or experience pertinent to this application. Except for Exploratory/Developmental Grants (R21/R33), Small Research Grants (R03), and Academic Research Enhancement Award (AREA) Grants (R15), preliminary data can be an essential part of a research grant application and help to establish the likelihood of success of the proposed project. Early Stage Investigators should include preliminary data (however, for R01 applications, reviewers will be instructed to place less emphasis on the preliminary data in application from Early Stage Investigators than on the preliminary data in applications from more established investigators).

5. Progress Report Publication List (Renewal Applications Only)

List the titles and complete references to all appropriate publications, manuscripts accepted for publication, patents, and other printed materials that have resulted from the project since it was last reviewed competitively. When citing articles that fall under the Public Access Policy, were authored or co-authored by the applicant and arose from NIH support, provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the Pubmed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the Journal submits articles directly to PMC on behalf of their authors, indicate "PMC Journal – In Process." A list of these journals is posted at: http://publicaccess.nih.gov/submit_process_journals.htm.

Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PMCID numbers along with the full reference (note that copies of these publications are not accepted as appendix material, see Part I Section 5.5.15 for more information).

6. Protection of Human Subjects

Refer to Part II, Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan.

This section is required for applicants answering "yes" to the question "Are human subjects involved?" on the R&R Other Project Information form. If the answer is "No" to the question but the proposed research involves human specimens and/or data from subjects applicants must provide a justification in this section for the claim that no human subjects are involved.

Do not use the protection of human subjects section to circumvent the page limits of the Research Strategy.

7. Inclusion of Women and Minorities

Refer to Part II, Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan. This section is required for applicants answering "yes" to the question "Are human subjects involved?" on the R&R Other Project Information form and the research does not fall under Exemption 4.

9. Inclusion of Children

Refer to Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan, Sections 4.4 and 5.7. For applicants answering "Yes" to the question "Are human subjects involved" on the R&R Other Project Information Form and the research does not fall under Section 4, this section is required.

10. Vertebrate Animals

If Vertebrate Animals are involved in the project, address each of the five points below. This section should be a concise, complete description of the animals and proposed procedures. While additional details may be included in the Research Strategy, the responses to the five required points below must be cohesive and include sufficient detail to allow evaluation by peer reviewers and NIH staff. If all or part of the proposed research involving vertebrate animals will take place at alternate sites (such as project/performance or collaborating site(s)), identify those sites and describe the activities at those locations. Although no specific page limitation applies to this section of the application, be succinct. Failure to address the following five points will result in the application being designated as incomplete and will be grounds for the PHS to defer the application from the peer review round. Alternatively, the application's impact/priority score may be negatively affected.

If the involvement of animals is indefinite, provide an explanation and indicate when it is anticipated that animals will be used. If an award is made, prior to the involvement of animals the grantee must submit to the NIH awarding office detailed information as required in points 1-5 above and verification of IACUC approval. If the grantee does not have an Animal Welfare Assurance then an appropriate Assurance will be required (See Part III, Section 2.2 Vertebrate Animals for more information). The five points are as follows:

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Strategy section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines on Euthanasia. If not, include a scientific justification for not following the recommendations.

Do not use the vertebrate animal section to circumvent the page limits of the Research Strategy.

11. Select Agent Research

Select Agents are hazardous biological agents and toxins that have been identified by DHHS or USDA as having the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal and plant products. CDC maintains a list of these agents. See <http://www.cdc.gov/od/sap/docs/salist.pdf>.

12. Multiple PD/PI Leadership Plan

For applications designating multiple PD/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PD/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PD/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Grant Award.

13. Consortium/Contractual Arrangements

Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee. The signature of the Authorized Organization Representative on the SF424 (R&R) cover component (Item 17) signifies that the applicant and all proposed consortium participants understand and agree to the following statement:

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

15. Resource Sharing

NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. See Part III, 1.5 Sharing Research Resources.

1. **Data Sharing Plan:** Investigators seeking \$500,000 or more in direct costs (exclusive of consortium F&A) in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible. Specific Funding Opportunity Announcements may require that all applications include this information regardless of the dollar level. Applicants are encouraged to read the specific opportunity carefully and discuss their data-sharing plan with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application. See Data-Sharing Policy or <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.
2. **Sharing Model Organisms:** Regardless of the amount requested, all applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state why such sharing is restricted or not possible. See Sharing Model Organisms Policy, and NIH Guide NOT-OD-04-042.
3. **Genome Wide Association Studies (GWAS):** Applicants seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088, and <http://grants.nih.gov/grants/gwas/>.