SUMMARY STATEMENT

PROGRAM CONTACT: [redacted]

(Privileged Communication)

Release Date: **06/17/2019**
Revised Date: **06/18/2019**

Application Number: **2 R01 DC013580-06A1**

Principal Investigator

CRANE, BENJAMIN T

Applicant Organization: [redacted]

Review Group: **SMI**
Sensorimotor Integration Study Section

Meeting Date: **06/06/2019**
Council: **OCT 2019**
Requested Start: **12/01/2019**

RFA/PA: **PA18-334**
PCC: **BV01**

Project Title: **Multi-modal vestibular perception**

SRG Action: **Impact Score:17 Percentile:2**
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			
6	[redacted]	[redacted]	[redacted]
7			
8			
9			
10			

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.
REVISION NOTE

RESUME AND SUMMARY OF DISCUSSION: This application describes a highly clinically relevant research project to study perception of self-motion in a multisensory context in human subjects. The reviewers agreed that the project is likely to generate crucial insights into vestibular perception and multisensory processing in patients suffering from unilateral vestibular loss. The response to the prior review was excellent, effectively addressing the major concerns of the prior reviewers and providing additional preliminary data. The rigor of the prior research was judged strong, based on preliminary data and literature references, and the level of experimental rigor in the proposed project is appropriate and bolstered by inclusion of more quantitative methods. Sex as a biological variable was adequately addressed, the PI, his colleagues and the research environment were judged outstanding and progress during the prior grant cycle was excellent. There were, however, a few concerns raised by Reviewer 3, primarily that the project does not include the role of intended movement and it was also noted that tactile cues are not properly controlled. These concerns had little influence on the generally very strong enthusiasm for the proposed project.

DESCRIPTION (provided by applicant): Dizziness, vertigo, motion sickness, and simulator sickness are common clinical problems rooted in abnormal perception of movement. Clinical testing of the vestibular system and understanding of vestibular physiology has historically focused on reflex function and perception of isolated vestibular stimuli. However, vestibular reflex function is poorly correlated with perceptual symptoms. Perception of self-motion is at the root of understanding navigation, dizziness, motion sickness, and simulator sickness. Self-motion perception is also multi-sensory and primarily involves the vestibular and visual systems, although auditory and proprioception also may play a role in some situations. In many common clinical disorders, perceptual testing is the first line of clinical investigation. For instance an evaluation of vision usually begins with having the patient report what they are able to see and evaluation of hearing begins with testing what the patient is able to hear. However, understanding of self-motion perception is not yet at a state where perceptual testing is clinically meaningful. Most of the previous work on vestibular perception has focused on unimodal stimuli of perceptual thresholds and tests of visual vertical which do not address the more complex multisensory situations in which self-motion is usually experienced. The current proposal aims to advance understanding of human motion perception into a clinically and physiologically relevant arena by examining this perception in an appropriate, multisensory context. The project will measure visual-vestibular integration and define the conditions where it occurs. Visual motion can be ambiguously interpreted as self-motion through a fixed environment, environmental motion relative to a fixed observer, or inaccurate sensory calibration. The project will examine all of these possibilities but determining the factors involved in determining common causation which is essential for knowing if visual motion is a result of self-motion and can be integrated with vestibular cues or is the result of external motion and should be segregated. The project will also look at mechanism adaptation in two contexts – exposure to consistently offset visual and inertial stimuli and exposure to a rotating environment. This will be examined in normal controls but also individuals with unilateral loss of vestibular function. Developing a method of adaptation that is effective in vestibular pathology will be helpful in developing tools that are potential methods of future vestibular rehabilitation.

PUBLIC HEALTH RELEVANCE: Heading perception is determined from visual and vestibular cues which must be integrated to determine self-motion within an environment. This is this proposal seeks to better understand these phenomena which are likely factors in dizziness and motion sickness.

CRITIQUE 1:

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

Overall Impact: This proposal is a revised application of an outstanding proposal from an accomplished investigative team. The project will address an important enigma regarding how motion perception is generated through causal inference of visual and vestibular cues. Although multisensory integration of motion cues at the perceptual and neural level have begun to be examined in both NHP and human models, the use of causal inference for inertial and visual cues remains lacking. In fact, there is a long-standing puzzle of why people continue to suffer from dizziness and other spatial dysfunctions, long after vestibular reflexes have compensated. Understanding how motion perception is generated will be key to solving real problems associated with vestibular disorders such as illusions, motion sickness, and optical and balance problems. Further, the role of causal inference in vestibular disease is totally unexplored. Understanding these interactions and computations by the brain could also provide insightful novel treatments for patients following vestibular insult or disease, where current methodologies have proven inadequate. A key component of the proposal will tackle this issue and may lead to better treatment outcomes. The work outlined in this continuation proposal is insightful, significant, detailed, and presented with a clear rationale. High enthusiasm is generated in the careful design and proposed experimental paradigms. Innovation is high and potential benefits toward advancing basic understanding of motion perception in both health and disease is promising. The proposal is slated as a clinical trial, since patient populations will be used to evaluate novel therapeutic rehabilitation paradigms to determine effectiveness toward alleviating symptoms present in vestibular dysfunction.

Scientific Premise: The premise is that the brain uses causal inference to perceive motion with predictions obtained from combinations of visual and inertial motion cues. These can be directly tested using quantitative perceptual methods in normal and vestibular compromised patients.

Rigor and Transparency: The methods are sound, with appropriate repetitions, more than adequate subject numbers, and significant comparisons between normal and patient populations.

Sex as a Biological Variable: Adequately addressed with equal populations of male and female subjects represented.

1. Significance:

Strengths

- High significance in the novel nature of the application of psychophysical methods to address computational processing of inertial motion perception.
- Causal inference is rapidly being understood as a significant mechanism used by the brain to solve ambiguities and perform cognitive decisions.
- Significance will be high in advancing our understanding of multisensory integration of visual and vestibular cues for motion perception.
- Significance is high in a potential development of more effective therapies for patients experiencing perceptual illusions, motion sickness, visual instability, and other symptoms currently present in compensated vestibular deficits.
- The potential to further develop prosthetic devices and VR techniques will significantly aid in technology development.

Weaknesses

- None noted:

2. Investigator(s):

Strengths

- The PI, Dr. Ben Crane, is an outstanding clinician scientist with an international reputation and well established laboratory. He has a clinical practice in Otolaryngology specializing in vestibular disorders [redacted] Dr. Crane has protected research time in the department, a rich history of impactful research, and is a leader in the field.

Weaknesses

- None noted:

3. Innovation:

Strengths

- The proposed work is highly innovative in that preliminary data suggest that visual – inertial integration of self versus external motion cues will be explored computationally.
- Innovation is present in comparing normal subjects to compensated patients with unilateral vestibular loss that are still experience motion perceptual deficits.
- The proposed studies will open the door to new approaches in our understanding of how the brain processes inertial motion perception.

Weaknesses

- None noted.

4. Approach:

Strengths

- A revised proposal that considered comments from previous review.
- A carefully designed set of integrated experiments is proposed to examine inertial motion perception in normal and vestibular unilateral loss patients.
- Computational methods will be utilized to examine causal inference mechanisms that could underlie visual-inertial motion perception.
- The work naturally has been developed with considerable insight gained from the previously funded grant period. Findings from that effort significantly provided rationale and derived informative methodologies to deepen the impact of the effort.
- The question of how the brain determines self from external motion, or combinations of both during natural behaviors is interesting, timely, and could only be examined in a few labs with sophisticated equipment and experienced approaches.
- The work promises to reveal new data that will be basic to our knowledge of general brain processing mechanisms using cue weighting and causal inference.
- Significant number of observations in an advanced number of subjects will be obtained for rigor.

Weaknesses

- A minor point: specifics on how stimulus acceleration and duration will be varied was not given.

5. Environment:

Strengths

- The environment [redacted] is outstanding for both basic and clinical research on vestibular related projects. Sophisticated multisensory motion equipment is in place, the clinics provide

access to a large pool of patients and normal subjects for experiments, and the support from science colleagues familiar with the research field are excellent.

- The PI has protected research time that is crucial to the success of the research.
- Has the administrative, coordination ability, and subject depth for the clinical trial.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Minimal risk study, appropriate protections in place

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- Acceptable risks, adverse events, if encountered, will be reported. All subjects will provide informed consent. All subject data will be encrypted for privacy.

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion Based on Age: Distribution justified scientifically
- Appropriate inclusion of normal subjects and patients will be recruited from the natural population at the U. Rochester and available through the clinics.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The resubmission included address points to the major concerns of the previous review, including patients with differing lesion source compensation, use of more quantitative power analyses, visual stimulus field size, and presentation of preliminary data.
- Revised proposal is much improved.

Renewal:

- The application represents a continuation of five years support from a previous grant. There was significant progress and scientific achievement during that funding period. The PI and team were very productive with 9 publications related to the SAs, 6 publications generated from similar work, 2 book chapters and a number of abstracts presented. In addition, from the results obtained, new questions were generated and preliminary data obtained supporting the present application.

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): 1
Innovation: 1
Approach: 1
Environment: 1

Overall Impact: This revised clinical trial application is a renewal of a currently funded project that will attempt to parse out the perception of visual and vestibular signals for the estimation of heading direction in humans. The investigators propose the novel mechanism of causal inference to explain how visual and inertial cues could conflict and still be used to differentiate self-motion from motion through an environment or environmental motion or both. Understanding how motion perception is generated during self, external, and combinations of both conditions can lead to illusions, motion sickness, and more severe optical and balance problems. Results of these studies may provide novel interventions for patients following vestibular insult or disease which is highly significant as current interventions are often inadequate. The hypothesis that vestibular instability and dizziness are generated by conflict or mismatch in visual and inertial inputs has become predominant recently, and this is a timely and focused application designed to examine how inertial vestibular and visual cues are integrated to generate a percept of self-motion in normal humans, and in patients with unilateral vestibular loss. There is high enthusiasm for this multifactorial approach to motion perception and the identification for weaknesses in the scientific premise of prior studies that concentrate mostly on reflex behavior. Scientific premise for these studies is clearly stated and supported by the preliminary data. Data generated by the current funding is strong and has guided the aims in this renewal. The experiments are well designed to test the hypotheses with adequate subject numbers supported by power analyses and comparisons between healthy and patient populations. Sex as a biological variable has been considered. Concerns of prior reviewers have been adequately addressed by the PI.

1. Significance:

Strengths

- Application of psychophysical methods to address computational processing of inertial motion perception.
- Causal inference as the mechanism used by the brain to solve ambiguities and perform cognitive decisions applied to multisensory conflict.
- Most of the previous work on vestibular perception has focused on unimodal stimuli of perceptual thresholds and tests of visual vertical which do not address the more complex

multisensory situations in which self-motion is usually experienced. Will examine perception in a multisensory context.

- Results will advance our understanding of multisensory integration of visual and vestibular cues for motion perception through revealing cue weighting and causal inference.
- How motion perception is generated using visual and vestibular cues through causal inference determining common causation which is essential for knowing if visual motion is a result of self-motion and can be integrated with vestibular cues or is the result of external motion and should be segregated.
- Current treatments for dizziness and postural instability rely on adaptation of VOR even though vestibular reflex function is poorly correlated with perceptual symptoms. High potential for development of more effective therapies.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The PI, Dr. Crane, is an outstanding clinician scientist with an international reputation and well-established laboratory. He was very productive in the current grant period with 10 publications related to the specific aims, 6 publications generated from similar work, 2 book chapters and a number of abstracts presented.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Exploration of common causation for adaptation to visual and inertial signals during motion perception.
- Distinguishing between visual (efferent copy) and inertial (closed loop) adaptation in heading.
- Method of offsetting visual and inertial motion stimuli in order to parse out perception of signals in a multisensory task.

Weaknesses

- None noted.

4. Approach:

Strengths

- Concerns of prior reviewers have been adequately addressed including adding a power analysis based on preliminary data for Aim 3 and analyzing the unilateral deficit and gentamycin treated populations separately in the analyses for Aim 3.
- Computational methods to tease out causal inference mechanisms that could underlie visual-inertial motion perception.
- Findings from previous grant period have provided rationale and methodologies for proposed studies.
- Prior reviewers raised concerns about the ecological validity of the task. The HMP apparatus has a visual display that covers 98 deg. The human visual field is approximately 150 deg.

Peripheral vision is important for perception of vection and the reviewer rightly states that if subjects can see borders of the visual display, the effects of visual motion will be diminished making the results apparatus dependent. This is correct but the room will be dark so that borders are unlikely to interfere and studies with HMD and small visual field size have shown immersive and vection behaviors. The weighting of the inertial and visual cues may not be the same as in a natural environment, but these studies will still answer the questions posed here about causal inference and weighting in this controlled environment. Future studies of walking in natural environments are planned and will be more meaningful once the controlled parameters are identified.

- Potential influential variables such as visual field size, peripheral flow, stimulus duration, and acceleration will now be examined.
- The concern that it is not clear how the proposed research will affect the incidence of falls or motion sickness seems premature given that the primary focus of this application is to understand the mechanisms for vestibular symptoms and the PI does suggest that once we obtain these results further determination of interventions can be made.
- Fig. 5 has been strengthened and supports a conclusion that head adaptation appears in all subjects.
- The question of bias will be adequately addressed in Aim 3 by sequentially measuring directional bias and perceptual thresholds of yaw rotation, sway, and heading in individuals with acute loss of vestibular function.
- Forced choice measures of perception are scientifically justified.
- Gender will be treated as a biological variable with equal numbers of each sex.

Weaknesses

- None noted.

5. Environment:

Strengths

- [redacted] is an outstanding environment for both basic and clinical research on vestibular related projects. Sophisticated multisensory motion equipment is in place.
- Clinics provide access to a large pool of patients and normal subjects for experiments.
- PI has protected research time.

Weaknesses

- None noted.

Study Timeline:

Strengths

- Timeline is realistic and progressive – builds on results from prior actions.
- Publications will be generated as results are obtained.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Minimal risks.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- Motion sickness will be monitored.

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion Based on Age: Distribution justified scientifically

- 150 patients over a 5 year period is feasible and plans for drop-outs.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- Excellent response to the prior review.

Renewal:

- The application represents a continuation of five years support from a previous grant. There was significant progress and scientific achievement during that funding period.

Resource Sharing Plans:

Acceptable

- Publications and presentation.

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 2
Investigator(s): 2
Innovation: 4
Approach: 4

Environment: 2

Overall Impact: This is a strong revised proposal that was responsive to the first review. As a competitive renewal, it shows only adequate productivity.

As to Scientific Premise, there seems to be a strong disconnect between the claims to novelty and motivation of the study and its hypotheses vs. and the design of the experiments. The fundamental premise is that "During everyday activities we move through complex environments that can include fixed or moving objects. We also make gaze shifts which dissociate the visual and inertial coordinates." And "Perception of self-motion is at the root of understanding navigation, dizziness, motion sickness, and simulator sickness." Understanding navigation requires understanding how the brain combines or disambiguates visual and inertial (vestibular) signals to behave appropriately in the world. Yet all experiments are founded on passive movements applied to the subject without the subjects having made any volitional action for self-motion. Such intended physical motion to inform sensory processing (i.e., active sensing) is the root belief of the individual that sets the Bayesian conditionals to process sensory stimuli, and thus likely at the root of causal inference. As the project stands, it is a very good perceptual study of thresholds on various shades sensory conflict/agreement. But by lacking the critical element of intended movement, the proposal lacks innovation and does not really address the role of active sensing in clearing up and grounding multisensory ambiguities. This is also problematic when it comes to the interpretation of the results because the asymmetric adaptation visual vs. inertially biased conditions is attributed to distinct perceptual integration mechanisms, rather than the alternative possibility that subjects are allowed to use volitional control of gaze to inform their visual-vestibular integration. Similarly, tactile cues from chair and helmets that respond to chair movement should be mentioned and considered as confounds.

Rigor of the prior research, plans to address any weaknesses in the rigor of the prior research and Transparency: The extant literature is well understood and the work is done as to the standards of perceptual studies. However, there is lack of rigor when it comes to the active sensing literature.

Sex and age as a Biological Variable: Acceptable as to sex, but did not mention the new requirements for justification of exclusion of older adults.

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: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION ACROSS THE LIFESPAN PLAN: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

REVISION NOTE: Administrative correction to Inclusion Across the Lifespan heading

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Footnotes for 2 R01 DC013580-06A1; PI Name: Crane, Benjamin T

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.

[redacted]