PI: **Crane, Benjamin T**	Title: Multi-modal vestibular perception	
Received: 03/20/2019	Opportunity: PA-18-334 Clinical Trial:Required	Council: 10/2019
Competition ID: FORMS-E	FOA Title: NIDCD Clinical Trials in Communication Disorders (R01-Clinical Trial Required)	
2R01DC013580-06A1	Dual:	Accession Number: 4287463
IPF: 7047101	Organization: [redacted]	
Former Number:	Department:	
IRG/SRG: SMI	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) [redacted]	Animals: N Humans: Y Clinical Trial: Y Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Benjamin Crane M.D.	[redacted]	PD/PI

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
DC013580

b. Agency Routing Number

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: [redacted]
Department:
Division:
Street1*: [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted] UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Jennifer Middle Name: Last Name*: Carlson Suffix:
Position/Title:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number* [redacted] Fax [redacted] Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1160743209A1

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Multi-modal vestibular perception

12. PROPOSED PROJECT
Start Date* Ending Date*
12/01/2019 11/30/2024

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Benjamin Middle Name: T Last Name*: Crane Suffix: M.D.
Position/Title: Associate Professor
Organization Name*: [redacted]
Department:
Division:
Street1*: [redacted]
[redacted]
[redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number* [redacted] Fax Number: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]
[redacted]
[redacted]
[redacted]

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Jennifer Middle Name: Last Name*: Carlson Suffix:
Position/Title*: Research Administrator
Organization Name*: [redacted]
Department: ORPA
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
[redacted]
[redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number* [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*
Jennifer Carlson

Date Signed*
03/20/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter_A1.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

○ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: [redacted]

[redacted]

USA: UNITED STATES

Zip / Postal Code*: [redacted]

Project/Performance Site Congressional District*: [redacted]

Additional Location(s) File Name:

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ○ **Yes** ● **No**

IRB Approval Date: 10-25-2017

Human Subject Assurance Number 0000009386

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Crane_project_summary.pdf
8. Project Narrative*	Crane_project_narative.pdf
9. Bibliography & References Cited	Crane_References_cited.pdf
10.Facilities & Other Resources	Crane_Facilities_and_other_resources2.pdf
11.Equipment	Crane_Major_equipment.pdf

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

Project Summary

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.

Project Narrative

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.

Facilities and Other Resources

Laboratory: Three laboratory spaces are available for this project. Dr. Crane has his own laboratory space which includes a control room and a hexapod motion platform (HMP) which is currently available for human motion experiments. The room contains all the necessary computer and safety equipment. This laboratory is 250 sq. ft. A second HMP is available in a similarly sized space at the clinic where it is more accessible by patients. There is a third laboratory with a multiple axis sled/rotator (MASR) in a nearby laboratory [redacted] which Dr. Crane has access. In addition, there is ample office space both for primary investigator, technicians, and students.

Clinical: There are ample clinical facilities available for this project. Subjects with unilateral lesions will be recruited from Dr. Crane's clinic as well as the other 3 neurotologists at University [redacted] These neurotologists see a significant number of patients with balance disorders, as well as vestibular related disorders such as vestibular schwannomas. Standard VNG (video neurography) testing equipment is available as well as vestibular evoked myopotentials (VEMP), rotatory chair testing, video head impulse testing, and posturography.

The institution has a database of approximately 300 individuals who have previously participated in vestibular research and would be willing to participate in future projects. About 70 of these subjects would be appropriate controls who are currently available for research studies. There is IRB approval to recruit additional 150 human subjects if needed.

Computer: Each laboratory is equipment with state-of-the-art computers equipment with data acquisition cards and software. There is additional office area that includes computers that can be used for data analysis and preparation of manuscripts. The project also has access to web servers and computer support. There are also appropriate software licenses for Matlab, Prism, Mathematica, Kaleidagraph, Microsoft office as well as other software appropriate for data acquisition, analysis, and manuscript preparation.

Institutional Resources: The department guarantees Dr. Crane's salary, and currently provides a minimum of 50% protected time for research activities. The department of otolaryngology provides all faculty members an allowance to pay for travel to meetings, courses, society membership fees, medical license fees, etc. The University [redacted] offers a wide range of courses and collaborators in ethics, statistics, experimental design, and data analysis that are potentially available to Dr. Crane and other members of the laboratory. There is a rich scientific environment at the author's institution with several active investigators in the vestibular field [redacted] as well as in visual motion perception [redacted] Because of this rich group there are frequent journal clubs to discuss interesting new reports in the visual and vestibular fields, and opportunities for informal faculty interaction. These faculty have attracted top graduate students and postdoctoral fellows who are interested in these areas. There are also well-known investigators in these areas at other institutions who are frequently invited to visit the University [redacted] The department employs a research coordinator [redacted] who assists with institutional review board approval, subject recruitment, and statistical analysis.

Other: A fully equipped machine shop including lathe, mill, band saw, and drill press is available for use. There are resources for management of human subjects including recruitment, clinical testing, assistance with IRB approval, and staff training.

Major Equipment

1) Two Hexapod motion platforms (HMP, Moog model 6DOF2000E). These systems are capable of moving a human subject in any of the 3 angular axes and 3 translation directions in any combination. The system also has a visual display which covers 98° of the visual field in azimuth which can be synchronize with the platform motion. Appropriate software for running the experiments has and analyzing the data been developed. The systems are identical and can be used simultaneously.

2) Multi-axis sled/rotator (MASR, Contraves USA/JA Design). The apparatus consists of a linear sled sandwiched between two rotational axes (chair and base). This system can translate and rotate a human subject in the horizontal plane. Although the degrees of freedom are more limited than the Moog system, the amount of angular rotation is unlimited making this system ideal for studying low frequency rotations near the threshold of rotation. It also has greater translation in the horizontal plane than the HMP systems which may facilitate heading discrimination at low frequencies.

3) Flux gate magnetometer (Ascension Technology, trakSTAR). This system can be used to track head and body movement independently during platform motion as well as during ambulation. It is available on both HMPs.

4) Two binocular video eye tracking systems are available and can be used with the HMP. They acquire data 60 Hz using infrared head mounted system (ETD-300HD, IScan Inc, Woburn, MA).

5) Two WorldViz Vizard Development systems using HTC Vive headset, Dell workstation, and handsets.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Benjamin Middle Name T Last Name*: Crane Suffix: M.D.

Position/Title*: Associate Professor
Organization Name*: [redacted]
Department:
Division:
Street1*: [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: 585-275-1210 Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: biosketch_BTC_Mar2019.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12818994 Funding Opportunity Number: PA-18-334 . Received Date: 2019-03-20T17:01:10.000-04:00

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Crane. Benjamin Thomas

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Associate Professor of Otolaryngology, Bioengineering, and Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, San Diego	B.S.	1990-1994	Bioengineering
University of California, Los Angeles	M.D., Ph.D.	1994-2000	Medicine, Neuroscience
University of California, Los Angeles	Internship	2000-2001	General Surgery
University of California, Los Angeles	Residency	2001-2006	Otolaryngology
University of California, Los Angeles	N/A	2006-2007	Postdoctoral scholar
American Board of Otolaryngology	Certification	2007-	Otolaryngology
Johns Hopkins University School of Medicine	Fellowship	2007-2009	Neurotology
American Board of Otolaryngology	Certification	2010-	Neurotology

A. Personal Statement

I am a clinician-scientist in the field of neurotology, balance and motion perception disorders. As a clinician I see a lot of patients with dizziness, vertigo, and disorders such as vestibular migraine that are probably rooted in the abnormal multisensory integration. Currently available clinical tests are limited in their ability to diagnose these patients due to the underlying pathology, as well as neurophysiology in healthy individuals being poorly understood. My research career has been motivated by gaining better understanding in these areas which I hope will lead us to better diagnosis and treatment of this patient population. I have a strong research background and was previously the principal investigator of the K23 grant: “Visual and vestibular percepts of motion” (K23 DC011298). I also completed research grants from private foundations including the Triological Society Clinician-scientist award, the American Otological Society clinician-scientist grant, and the Giannini Family Foundation Fellowship. I am the current principal investigator of the R01 grant: “Multimodal vestibular perception” (R01 DC013580). My immediate goal is to renew this grant to allow my lab to continue our research in this area. Recent work has uncovered several areas worthy of further study including visual-vestibular heading estimation as a model of multisensory integration, the potential for adaptation of heading perception, and pathology in heading perception in subjects with unilateral lesions. Better understanding of this area is not only important for the neuroscience community but is likely the key to rehabilitating a patient population that currently has limited treatment options.

B. Positions and Honors

Positions and Employment

7/1994 – 6/2000 MD/PhD student, Medical Scientist Training Program, University of California, Los Angeles
6/2000 – 6/2002 General Surgery Intern/resident, Department of Surgery, University of California, Los Angeles
7/2002 – 6/2006 Otolaryngology Resident, Department of Surgery, University of California, Los Angeles
7/2006 – 6/2007 Postdoctoral Scholar, Jules Stein Eye Institute, University of California, Los Angeles
7/2006 – 6/2007 Otolaryngology Attending, Harbor-UCLA Medical Center, Los Angeles, CA

7/2006 – 5/2007 Otolaryngology Attending, UCLA (Arthur Ashe) Student Health Center, Los Angeles, CA
7/2006 – 6/2007 Otolaryngology Attending, West-LA VA Medical Center, Los Angeles, CA
7/2007 – 6/2009 Neurotology Fellow, Johns Hopkins School of Medicine, Baltimore, MD
7/2009 – 6/2012 Assistant Professor, University of Rochester, Rochester, NY
7/2012 – 8/2017 Associate Professor, University of Rochester, Rochester, NY
9/2017 – Associate Professor with tenure, University of Rochester, Rochester, NY

Other Experience and Professional Memberships

1994 – 1998 Class Treasurer, UCLA School of Medicine Class of 1998
1995 – 1996 UCLA School of Medicine Admissions Committee
1995 – Society for Neuroscience
1996 – 2000 Interviewer for UCLA Medical Scientist Training Program Admissions.
1997 – 1998 Neuroscience Ph.D. program curriculum committee
1998 Chair, Neuroscience Ph.D. program annual retreat planning committee
2005 UCLA division of otolaryngology resident selection committee
2006 – Association for Research in Otolaryngology
2008 Johns Hopkins department of otolaryngology neurotology fellowship selection committee
2009 – 2017 University of Rochester department of otolaryngology resident selection committee
2009 – American Neurotology Society
2011 – 2016 Assistant Editor, *Otology and Neurotology*
2011 NIDCD study section ZDC1 SRB-R35
2012 NIDCD study sections ZDC1 SRB-L44 and ZDC1 SRB-L47
2012 – Fellow, American College of Surgeons
2013 NIDCD study sections CDRC, ZDC1 SRB-L42, ZDC1 SRB-L48
2013 – Fellow, American Neurotology Society
2014 NIDCD study sections ZDC1 SRB-L46
2014 DoD Military Training Injuries, Hearing, Balance, and Ears (MTI-HBE)
2014 DoD Clinical and rehabilitative medicine hearing and balance study section
2015 – 2017 Association for Research in Otolaryngology Travel Awards Committee
2015 DoD Clinical and rehabilitative medicine research program balance disorders study section
2016 – Associate Editor, *Otology and Neurotology*
2016 interim Editor-in-chief, *Otology and Neurotology*
2016 Ad Hoc promotion committee for Marc T. Swogger
2016 NIDCD study sections ZRG1 IFCN-J, ZRG1 ETTN-12
2016 University of Rochester CTSI phase I pilot grant reviewer
2016 – 2019 American Neurotology Society (ANS) Research Committee
2017 University of Rochester Phase II reviewer for CTSI pilot studies
2017 NIDCD study sections ZRG1 ETTN-G12B, ZRG1 IFCN-B2M, ZDC1 SRB-Y59
2017 – Fellow, Triological Society
2017 – 2020 American Neurotology Society (ANS) Scientific Program committee
2018 – 2020 Association for Research in Otolaryngology Publications Committee
2018 – 2019 Triological Society Career development grant review committee.
2018 NIDCD study sections ETTN-12, ZRG1 ETTN-G12

Honors

1990 – 1994 Gannet Scholarship
1992 – 1994 Regents Scholarship
1994 Golden Key
1997 Optical Society of America student travel award
1998 Neural Control of Movement student travel award
2002 Barany Society travel award.
2005 Resident Research Award, UCLA division of otolaryngology
2006 Association for Research in Otolaryngology, Resident Travel Award
2006 UCLA Paul Ward Society chief resident teaching award
2008 American Neurotology Society Fellows Award
2015 Nicolas Torok Vestibular Award

C. Contributions to Science

1. Characterization of the human vestibulo-ocular reflex (VOR) during combined translation and rotation. This work formed the basis of my PhD dissertation as well as subsequent research in Joseph Demer's laboratory. Prior to this work there had been a long history of scholarship on the VOR but relatively little was known about how translation (as sensed by the otoliths) interacted with rotation (as sensed by the semicircular canals) to produced a compensatory eye movement. Major advances in this area occurred by building a device which allowed human subjects to undergo highly reproducible yet still high acceleration whole body rotation while controlling the location of the rotation axis. This allowed not only better understanding the VOR in healthy humans but to also understand its function after vestibular and cerebellar lesions. This work helped build some basic understanding of the semicircular canal and otolith system which I now hope to extend into perception.

Crane BT and Demer JL Human gaze stabilization during natural activities: translation, rotation, magnification, and target distance effects. *Journal of Neurophysiology*, (1997) 78(4):2129-44. PMID: 9325380

Crane BT and Demer JL Human horizontal vestibulo-ocular reflex initiation: effects of angular acceleration, linear acceleration, stimulus intensity, target distance, and unilateral deafferentation. *Journal of Neurophysiology*, (1998) 80(3):1151-66. PMID: 9744929

Crane BT and Demer JL Effect of adaptation to telescopic spectacles on the initial human horizontal vestibulo-ocular reflex. *Journal of Neurophysiology*, (2000) 83:38-49. PMID: 10634851

Crane BT, Tian JR, and Demer JL Initial vestibulo-ocular reflex during transient angular and linear acceleration in human cerebellar dysfunction. *Experimental Brain Research*, (2000) 130:486-96. PMID: 10717790

2. Better understanding and treatment of clinical neurotology disorders. During my fellowship at Johns Hopkins I had the opportunity to focus on some clinical research projects. There was a large population of patients with superior canal dehiscence syndrome there. Some of these contributions focused on this population including documenting for the first time quality of life improvement after superior canal plugging as measured using the dizziness handicap inventory. Also, autophony (being bothered by the sound of one's own voice) is a major cause of decreased quality of life in some patients with superior canal dehiscence syndrome. I played a key role in development and validation of the first instrument for assessing autophony symptoms. This 'autophony index' demonstrated significant improvement after superior canal plugging. Finally, patients with cochlear implants have historically been limited from getting magnetic resonance imaging (MRI) without removing and subsequently replacing the magnet in their cochlear implant which required two surgical procedures. I played a key role in developing and testing a procedure by which the cochlear implant could be bound without removing the magnet. These techniques have now become standard in the field.

Crane BT, Minor LB, and Carey JP Superior Canal Dehiscence Plugging Reduces Dizziness Handicap. *Laryngoscope.* (2008) Oct; 118(10):1809-13. PMID: 18622314

Crane BT, Lin FR, Minor LB, and Carey JP Improvement in autophony symptoms after superior canal dehiscence repair. *Otology & Neurotology.* (2010) Jan;31(1):140-6. PMID: 20050268

Crane BT, Gottschalk B, Kraut M, Aygun N, Niparko JK Magnetic resonance imaging at 1.5 Tesla after cochlear implantation. *Otology & Neurotology.* (2010) Oct;31(8):1215-20. PMID: 20729783

Kushner B, and Crane BT, Frequency and demographics of gentamicin use. *Otology & Neurotology*. (2016) Feb:37(2):190-5. PMID: 26719956

3. Vestibular aftereffects. After starting my laboratory at the University of Rochester, I decided to focus on the uncrowded field of suprathreshold vestibular perception. When comparing two suprathreshold stimuli an initially unexpected finding was that the initial stimulus was often perceived larger than an equal second stimulus. Subsequently, it was found that after an initial movement, perception of subsequent motion is biased in the opposite direction. Similar phenomena in other sensory systems have been described as aftereffects, but such effects had not previously been described for the vestibular system. These effects have a frequency dependence and time course not seen with other sensory aftereffects. They likely play a key role in identifying unexpected movements that might indicate risk of an impending fall.

Roditi RE and Crane BT, Supra-threshold Asymmetries in Human Motion Perception. *Experimental Brain Research.* (2012) Jun;219(3):369-79. PMID: 22562587
Crane BT, Fore-aft Translation Aftereffects. *Experimental Brain Research.* (2012) Jun;219(4):477-87. PMID: 22562589
Crane BT, Roll Aftereffects: Influence of tilt and inter-stimulus interval. *Experimental Brain Research.* (2012) Nov;223(1):89-98. PMID: 22945611
Coniglio AJ, and Crane BT, Human yaw rotation aftereffects with brief duration rotations are inconsistent with velocity storage. *JARO*, (2014) Apr;15(2):305-17. PMID 24408345

4. Description of biases in human heading perception. Population vector decoder (PVD) models have proven to be useful for describing how neuronal activity influences behavior. It has previously been shown the majority of neurons have sensitivities to visual and vestibular headings such that they best discriminate left/right of straight ahead. Based on this, a PVD would predicts the later aspect of headings would be overestimated relative to straight ahead. I was able to demonstrate that this actually occurs for both visual and vestibular headings. For recent work has looked at this in the vertical planes which has shown utility in predicting the relative numbers of otolith and saccule units. Current projects in the lab involve using this to look at coordinates of heading perception, further manuscripts in this area are currently in process.

Crane BT, Direction specific biases in human visual and vestibular heading perception. *PLoS One* (2012) Dec:7(12):e51383. PMID 23236490
Crane BT, Human visual and vestibular heading perception in the vertical planes. *JARO* (2014) Feb;15(1):87-102. PMID 24249574
Crane BT, Coordinates of human visual and inertial heading perception. *PLoS One* (2015) Aug 12;10(8):e0135539. PMID 26267865
Crane BT, Perception of combined translation and rotation in the horizontal plane in humans. *Journal of Neurophysiology* (2016) Sept:116(3):1275-85 PMID 27334952

5. Multisensory motion integration. Traditionally, vestibular perception has been studied in response to simple stimuli in isolation. However, this is not how they are experienced during common daily activities such as ambulation where translation and rotation occur simultaneously, and visual stimuli are also present. In this area I have been able to demonstrate that motion perception takes into account the pattern of movement seen during ambulation. An addition visual stimuli influence motion perception including visual motion illusions and effects of vection. Clinical disorders such as migraine have an influence on the transfer of visual motion to perceived inertial motion.

Miller MA, O'Leary CJ, Allen PD, and Crane BT, Human vection perception using inertial nulling and certainty estimation. *PLoS One* (2015) Aug 17;10(8):e0135335. PMID: 26280172
Crane BT, Effect of eye position during human visual-vestibular integration of heading perception. *Journal of Neurophysiology*, (2017) Sept 1;118(3):1609-21 PMID: 28615328
Rodriguez R and Crane BT. Effect of vibration during visual-inertial integration on human heading perception during eccentric gaze. *PLoS One*, (2018) Jun 14;13(6):e0199097 PMID: 29902253
Rodriguez R and Crane BT. Effect of range of heading differences on human visual-inertial heading estimation. Exp Brain Res. (2019). Epub ahead of print PMID: 30847539

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/benjamin.crane.1/bibliography/44555558/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support
R01 DC013580 Crane (PI) 12/1/2014 – 11/30/2019
Multi-modal vestibular perception
The goal of this study was to study human perception of simultaneous vestibular stimuli and the effects of visual stimuli on motion perception.
Role: PI

Completed Research Support

K23 DC011298 Crane (PI) 12/1/2010 – 11/30/2016
Visual and Vestibular Perceptions of Motion
The goal of this study is to measure vestibular thresholds in normal controls and individuals with vestibular lesions. The study also seeks to define visual-vestibular interaction and develop new vestibular rehabilitation strategies.
Role: PI

Triological Society Clinician-scientist award Crane (PI) 9/1/2011 – 8/31/2015
Visual and vestibular perceptions of motion.
This is a supplement to the K23 award to measure vestibular thresholds and visual-vestibular interaction.
Role: PI

American Otological Society Clinician-scientist grant Crane (PI) 7/1/2010 – 11/30/2010
Vestibular motion perception
The goal of the proposal was to define vestibular thresholds in individuals with vestibular lesions and a relevant control population. This mechanism was a bridge to an NIH grant and ended when K23 funding began.
Role :PI

Giannini Family Foundation Fellowship Crane (fellowship) 7/1/2006 – 6/30/2007
Human vestibular control of eye movement. This was funding for a post-doctoral year in Joseph L. Demer's lab at UCLA/Jules Stein Eye Institute.
Role: Post-doc

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

Tracking Number: GRANT12818994 Funding Opportunity Number: PA-18-334 . Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Budget Period: 1

Start Date: 12/01/2019 End Date: 11/30/2020

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC	[redacted]	[redacted]	[redacted]
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, [redacted]

Indirect (F&A) Rate Agreement Date: 04/24/2018

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

Budget Period: 2

Start Date: 12/01/2020 End Date: 11/30/2021

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC			
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, [redacted]

Indirect (F&A) Rate Agreement Date: 04/24/2018

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B) Funds Requested ($): [redacted]

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

Budget Period: 3
Start Date: 12/01/2021 End Date: 11/30/2022

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
Consortium Indirect (F&A)	
Total Direct Costs*	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC			
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, [redacted]

Indirect (F&A) Rate Agreement Date: 04/24/2018

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

Budget Period: 4

Start Date: 12/01/2022 End Date: 11/30/2023

A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium Indirect (F&A)* [redacted]

Consortium Indirect (F&A)

Total Direct Costs* [redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC			
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, [redacted]

Indirect (F&A) Rate Agreement Date 04/24/2018

Total Indirect (F&A) Costs [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($) [redacted]

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

Budget Period: 5

Start Date: 12/01/2023 End Date: 11/30/2024

A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium Indirect (F&A)* [redacted]

Consortium Indirect (F&A)

Total Direct Costs* [redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	MTDC			
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, [redacted]

Indirect (F&A) Rate Agreement Date 04/24/2018

Total Indirect (F&A) Costs [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($) [redacted]

Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium Indirect (F&A) for Entire Project Period ($) [redacted]

[redacted]

2. Budget Justifications

Personnel Justification	Crane_personnel_justification.pdf
Consortium Justification	
Additional Narrative Justification	

Tracking Number: GRANT12818994
Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

Personnel Justification

Personnel
Benjamin Crane, MD, PhD, Principal Investigator effort will be 6 calendar months per year or 50% effort. Dr. Crane will be ultimately responsible for all aspects of the project including directing the research, overseeing recruitment and testing of human subjects, interpreting the data, and drafting the final manuscripts.

[redacted] Technician, 12 calendar months. [redacted] is responsible for recruiting subjects, conducting experiments involving human subjects, maintaining equipment, and performing data analysis. He also is effectively the lab manager.

[redacted] Mechanical Technician, 1.8 calendar months. [redacted] is responsible for fabricating, fixing, and replacing equipment.

Clinical Technician, 6 calendar months (50% effort). Testing of patients will be conducted in our clinic using a HMP similar to the one in the laboratory. This will be done using the same technician that currently does clinical balance testing.

Grad Student (currently [redacted]). 12 calendar months (100% effort) during years 1-2. Another grad student may join the lab in subsequent years of funding.

TBD, Undergraduate students, 6 calendar months each. The laboratory currently employs two undergraduate engineering students. These students work 3 months during the summer full time and part time during the school year. They are currently paid an hourly rate of $11/hour. These students are usually recruited from students that do well in a Matlab course that is taken in the 2nd year of the bioengineering curriculum. These students are often involved in small programming tasks such modifying experiments and are involve in collecting preliminary data.

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	Crane_Response_to_critique_A1.pdf
Research Plan Section	
2. Specific Aims	Crane_Specific_Aims_A1.pdf
3. Research Strategy*	Crane_R01_A1_Research_Plan2.pdf
4. Progress Report Publication List	Crane_Progress_report_publication_list_A1.pdf
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	Crane_Letter_Support_Anson.pdf
10. Resource Sharing Plan(s)	Resource_Sharing_Plan.pdf
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Tracking Number: GRANT12818994
Funding Opportunity Number: PA-18-334. Received Date: 2019-03-20T17:01:10.000-04:00

Introduction to Revised Application, 2 R01 DC013580-06 (Crane PI)

We thank the reviewers for their thoughtful critique of this project. Overall reviewers were enthusiastic and "agreed that the clinical significance is high, likely to generate insights relevant for motion sickness and balance problems." The project was agreed we have "an outstanding research environment, rigorous experimental design is evident and the feasibility of the experiments is supported by preliminary data." Specific concerns were minor and are fully addressed in the revised proposal. We also collected additional preliminary data, updated figures from the initial submission, and have an additional publication from the lab(114) which further motivates the proposed experiments. Areas of major change are marked with a line in the margin.

Reviewer #1: "Compensation in gentamicin patients will have a different time constant"
Reply: We agree that unilateral vestibular lesions due to gentamicin (and vestibular neuritis) are different and less complete that those due to surgical labyrinthectomy. There will also be similarities between these populations, and it is difficult to study uniform lesions across a human population. Because gentamicin has become a popular treatment for Meniere's, we would like to include these patients but will analyze them separately and consider that they may have different perceptual deficits.

Reviewer #2: "The laboratory environment may not reproduce adequately real-world conditions (e.g., active translation during walking in a natural visual environment)"
Reviewer #3: "Considering that peripheral vision is particularly important for perception of vection, if subjects can see borders of the visual display, that will diminish the effects of visual motion…"
Reply: We agree that real-world situations like walking are of interest but also have confounding factors (proprioception, many degrees of freedom, motor effects) which make it difficult to do adequately controlled experiments. Although outside the scope of this application, we plan parallel investigation in this area. We are collaborating with Eric Anson who has applied for a grant focused on ambulation, some subjects in these experiments will also be involved with his gait experiments. The lab has also ordered a 3-D treadmill which will allow unique capabilities in this area. Dr. Anson has provided a letter of support that is new to this submission.

Although the role of peripheral vision is important for vection, the role in heading perception is less clear. A study that looked for potential effects of visual field size on heading perception failed to find an effect(122); however it could have an effect on common causation perception. This is mentioned as a potential pitfall in IA. We added changing the visual field size to experiment IB. Our laboratory is currently limited to 110° with our VR headset and 98° with the screen on our motion platform. Virtual reality equipment with up to 200° field of view is coming which could be used in conjunction with our motion platform, making experiments with a large field of view potentially feasible during the period of funding. Smaller visual fields will also be considered.

Reviewer #1: "How does difference in stimulus duration and acceleration affect the findings."
Reply: This is an excellent question which we plan to explore. These factors will be varied within the limits of the available equipment and also by the ability to comfortably delivery stimuli to a human subject. This has been added as part of experiment IB.

Reviewer #3: "The evidence cited regarding VR simulator sickness is not recent"
Reply: Despite technological advances, simulator sickness remains a major issue. References are updated.

Reviewer #3: "Power analysis is qualitative and not supported by actual effect sizes which is possible given all the previous data collected." Reviewer #2 raised a similar concern.
Reply: Quantitative power analysis calculations have been performed using G*Power and are presented.

Reviewer #3: "It is not clear how the research proposed will affect the incidence of falls or motion sickness."
Reply: Some motion sickness and falls are likely rooted in errors in multisensory integration. This proposal aims to improve understanding in this area and develop tools for adapting this. It is hoped that this will lead to improved clinical outcomes in the future, but this is beyond the current proposal.

Reviewer #2: "Adaptation experiments should define the timing of post-adaptation testing."; "How many trials will be used for adaptation and how was this determined?"
Reply: It is now clarified that testing will occur immediately after adaptation and 80 stimulus presentations will be used. This number was chosen because it yielded a robust effect without an undue burden on subjects.

Reviewer #3: "does not seem that heading deviation was canceled in all 3 subjects, as the PI states."
Reply: Although the previous description of the initial session was correct, the prior Fig. 5A was confusing. Some subjects maintained correction of the heading deviation into later sessions leaving little room for further correction. The figure has been revised for clarity and includes 2 additional subjects.

A. Specific Aims

As we move through natural environments, we experience both visual and inertial stimuli. These can be integrated into a unified perception of self-motion (i.e. **common causation**) or segregated so that inertial or vestibular stimuli represents self-motion and visual represents external motion. There has been very little work on how **causal inference (CI)** or determination of common causation occurs for visual and inertial stimuli. Yet this is an important factor in fall risk, motion sickness, simulator sickness, concussion, dementia, and migraine. This proposal aims to develop and establish methods for studying CI in visual and inertial heading perception. This will be used to define the relevant variables in CI for these sensory systems. Common causation is likely a plastic process that occurs when stimuli occur simultaneously. The proposal will also examine this hypothesis by adapting heading perception, which may form the basis for a novel vestibular rehabilitation method.

Aim I: Causal inference (CI) for visual and inertial headings. During natural movements visual and inertial cues occur together. Inertial cues always represent self-motion, visual cues are ambiguous as they can represent motion through a fixed environment, environmental motion relative to the observer, or a combination of both. **IA.** Techniques for measuring CI for visual and inertial stimuli are not well established. We have developed a technique to measure CI by presenting offset visual and inertial headings simultaneously using a full range of possible directions within the horizontal plane. Subjects report the perceived direction of the visual and inertial stimuli independently and whether or not they share common causation. These trial blocks can be repeated to determine reproducibility. **IB.** Parameters that influence perception of CI will be varied to determine their relative influences. These parameters will include stimulus timing, duration, acceleration, and visual field size. It is hypothesized that full-field visual stimuli that are most consistent with the inertial stimulus will be perceived as having common causation. **IC.** Subjects with unilateral vestibular lesions will be tested using the techniques in IA. These individuals may have increased reliance on visual cues as well as decrease reliability and biases in inertial heading perception. As such, this may cause inertial headings to be more influenced by vision and result in a greater range of common causation.

Aim II: Visual-inertial heading adaptation. Plasticity in vestibular perception has received minimal attention, despite perception being the primary issue in common disorders such as vertigo, motion, and simulator sickness. Better understanding of how adaptation occurs could form the basis for improved therapeutic options as well as better tolerated virtual environments and simulations. **IIA.** Exposure to visual and inertial headings with similar characteristics, that are systematically offset, will be studied. It is hypothesized that exposure to this situation will influence subsequent visual and inertial heading perception as well as their common causation. These factors will also be measured before and after adaptation. The limits of what types of offsets can induce adaptation, and the range of headings that can be adapted will be explored. **IIB.** Preliminary data demonstrate that heading adaptation can also be induced by exposure to a virtual environment with an angular velocity offset in the visual stimulus. This method of adaptation will also be studied with regard to its influence on perception of rotation, visual and inertial headings and common causation of these headings. As with IIA, the potential limitations of the method will be explored.

Aim III: Heading adaptation after vestibular loss. Errors in heading perception are a clinically significant problem. Abnormal perception of rotation often quickly normalizes after vestibular lesions, but preliminary data indicate heading perception remains deviated for years afterwards. This could be due to asymmetry in the otolith system which current vestibular rehabilitation methods do not address. Abnormal heading perception may be a significant factor in other disorders including vestibular migraine, dementia, and concussion. Understanding long-term adaptation is potentially important in these populations. **IIIA.** Time course and etiology of perceptual pathology after acute vestibular lesions is unclear. This will be investigated by sequentially measuring bias and perceptual thresholds of yaw rotation, sway, and heading in individuals with acute loss of vestibular function. Initially subjects have a rotation bias towards the intact side which normalizes over time. The heading bias may correlate with rotational bias or may be related to otolith dysfunction, as measured with sway translation perception, or may occur as a result of adapting to the rotatory vertigo. **IIIB.** Study of long-term heading adaptation in subjects with chronic unilateral vestibular hypofunction (e.g. those who have had vestibular schwannomas removed, gentamicin ablative therapy for Meniere's disease). Since these subjects often have biased heading perception at baseline, they may be able to exhibit long term adaptation. Heading perception as well as visual-inertial common causation will be measured using the techniques described in Aim IC. Ability to adapt these patients to heading offsets will be measured using the methods established in normal controls (Aim II) but the adaptation will always be in a consistent direction to attempt to normalize baseline deviation in heading perception. It will be determined if durable long-term heading adaptation can be achieved. **The proposal aims to understand how visual and inertial cues inform motion perception and how adaptation has the potential to improve pathological perception.**

B. Significance

B1. Self-motion perception is a clinically significant but poorly understood problem. Abnormal motion perception or dizziness affects more than 20% of the working age population(1). Bedside tests suggest vestibular disorders in 35% of those age >40(2), and >60% of the elderly(3). Using a stricter vertigo definition, a prevalence of 7.4% was suggested, 80% of whom seek medical consultation(4). Vestibular migraine produces dizziness symptoms in 3.2% of the population(5). Of those who consult a physician for these symptoms, only 20% are correctly diagnosed(6) and fewer are appropriately treated. Falls are also a major clinical problem that can result from abnormal movement perception with a third of individuals over age 65 suffering a fall each year (7, 8) and 10% of these resulting in serious injury(9). Individuals with vestibular impairment have difficulty with navigation(10), driving(11, 12), a higher chance of vehicle accidents(13), higher chance of cognitive impairment(14), and lower quality of life(15). Better understanding of how complex multi-sensory motion is perceived during daily activity is crucial to address these clinically relevant problems.

Motion sickness is a common problem in healthy people. One common situation where this occurs is when visual and vestibular motion are decoupled(16-19). This is a common situation that occurs when moving through a crowd, viewing external motion, or viewing the internal environment when traveling by vehicle. There are individual differences in motion sickness susceptibility based on gender(20), age, migraineurs, and peripheral vestibular disease(21). Virtual reality (VR) is quickly gaining importance in our society as technology has now made these systems inexpensive and powerful. Virtual reality systems are now extending well beyond the realm of entertainment into use for medical therapy, diagnosis, job training, and will be an important part of some occupations. Unfortunately, 80% of VR users experience simulator sickness or cybersickness, and in half of users this limits their use of these systems(22-25). Methods of dealing with cybersickness include adding noise(26), limiting exposure(23), and changing some of the stimulus parameters(27, 28). Efficacy of these methods is limited, and development of such strategies requires better understanding of visual-vestibular integration. Although the vestibular organs are the primary sense of inertial motion(29), factors such as proprioception and somatosensation also play a subordinate role. In this proposal, inertial perception is used to refer to combined vestibular, somatosensory, and proprioceptive components.

B2. There is little knowledge on how multisensory stimuli are integrated to inform self-motion perception. Current understanding of self-motion perception has been focused on the vestibular reflexes, and perception of isolated stimuli. The most studied reflexes are the vestibulo-ocular reflex (VOR) and vestibular evoked myopotentials (VEMP). Vestibular reflex tests correlate poorly with symptoms(30). This is not surprising given vestibular perception pathways are fundamentally different than reflexes(31, 32) and symptoms correlate with perception(30). Research on vestibular perception has mostly focused on thresholds of isolated movements(29, 33-36) or comparison of supra-threshold motion stimuli(37-39).

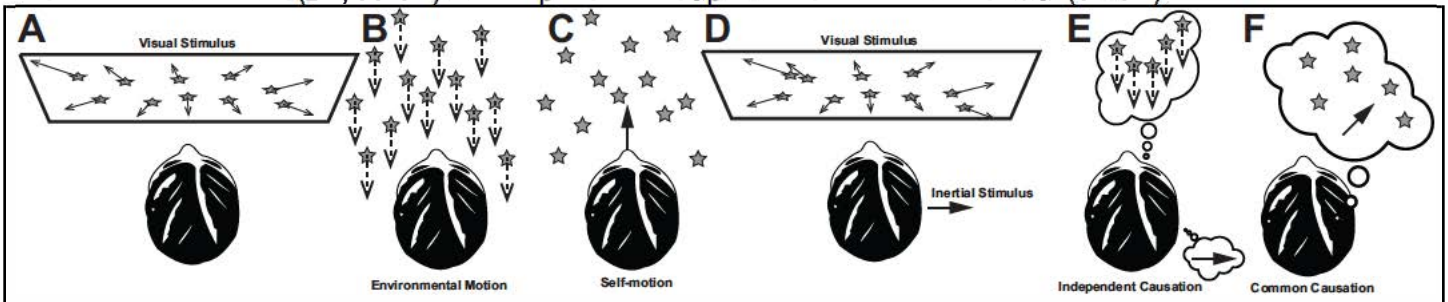


Figure 1. Conceptualization of motion perception. During constant velocity translation vestibular cues may be absent. If only a visual stimulus is present (**A**) the stimulus ambiguously represents environmental motion (**B**) or self-motion through a fixed environment (**C**). In the multisensory example both visual and inertial motion are present **(D)**, but the direction of the stimuli is offset such that the inertial motion is to the right while the visual motion is consistent with forward. Causal inference (CI) determines if these stimuli have independent causation (**E**) or a common causation (**F**). Theory predicts that independent perception will occur if the stimuli are felt to be unrelated (**E**) but this may not always be the case. With common causation (**F**) the stimuli should be integrated into a common perception.

Perceptual testing forms the mainstay of diagnosis in most sensory systems and also guides investigations into the underlying physiology. Current clinical evaluation of motion perception disorders including dizziness, vertigo, and balance problems focuses on vestibular reflexes. We have not developed the tools to investigate important related issues such as the role of vision and central integration. To make an analogy to communication, auditory thresholds give us some information about hearing but not about sound localization, speech perception, the ability to use visual cues, and context. Our understanding of self-motion perception is based largely on studies of isolated stimuli. In our daily experience, self-motion is rarely perceived with only a single sensory system. Visual and vestibular stimuli must both be considered and appropriately integrated to make optimal use of available information. Thus, it is not surprising that current clinical vestibular tests are a

poor predictor of falls(40) which occur in the context of pathology in self-motion perception. Current tests are also poor at identifying common motion perception disorders like vestibular migraine(41, 42), mal de debarquement(43), and are weakly correlated with motion sickness(44) and traumatic brain injury(45). These disorders are due to pathology in motion perception and visual-vestibular integration, not pathologic reflexes.

B3. Significance for Aim I, Causal inference (CI) for visual-inertial headings: During daily activities we simultaneously experience inertial and visual stimuli which both provide self-motion cues. Visual-inertial integration has been shown to be near optimal based on the relative reliability of these cues or Bayesian(46-53). These previous studies have used discrepancies in visual and inertial headings which are assumed to be within the threshold of common causation, although the limits of this integration are unknown. Visual motion is ambiguous and can represent motion of fixed objects relative to a moving observer, or object motion – for instance a crowd of people moving down a street, blowing snow, vehicles passing, etc. External and self-motion often occur simultaneously (Fig. 1). This raises issue of how the brain determines if visual and inertial headings have common causation (e.g. they both are caused by self-motion) and should be integrated or have separate causation (e.g. there is environmental motion) and should have segregated perceptions(54). An analogous problem which has been much more extensively studied is visual-auditory integration in the form of visual capture or the ventriloquist effect – which refers to the perception that speech is coming from a direction displaced from its true direction by a visual stimulus from an apparent speaker(55-57). Techniques have now been established to study CI (i.e. if two sensory cues are perceived to have arisen from a single event) in multisensory perception. This is an important issue as most real-world event perception is multisensory(58). Prior work in this area has focused on visual-auditory(59-61) and visual-haptic(62-66) integration. In these areas, stimuli need to be perceived as having a common causation for multisensory integration to occur, but this hypothesis has not been fully tested for visual-inertial stimulus integration. Furthermore, preliminary data suggest that common causation is unnecessary for visual-inertial heading integration. The area of visual-inertial heading integration has only recently been examined. It has been demonstrated that artificially displaced visual and inertial headings are usually integrated(53, 67), although all these studies used relatively small displacements (≤20°) between visual and inertial and focused on headings near straight ahead. A recent study used larger offsets between visual and inertial headings but only asked subjects for a single combined direction perception making it difficult to know if subjects really perceived them as the same(68). Another study looked at offsets up to 40° and asked subjects to report if the visual and inertial headings had common causation and in other trials the direction of the inertial heading relative to straight ahead(52). However even with the largest offsets of 40° where visual and vestibular headings would have been in opposite directions relative to midline, subjects still reported visual and inertial directions were the same in about a quarter of trials suggesting the limits of common causation were not explored. Furthermore, the direction of the visual stimulus was not independently reported making it difficult to know how it was influenced by the inertial heading.

Several areas of visual-inertial heading integration deserve further investigation. First, it seems that integration can occur even with very large offsets in visual and inertial headings(47, 52, 68, 69). The limits of this have yet to be determined, due to prior studies focusing on small offsets and headings near straight ahead. Second, there seems to be significant variation between individual subjects in terms of the strategy used in heading integration(47, 67, 69, 70), but many models are based on population averages(52, 53). Current models cannot account for the potential that individuals may not all use the same strategy. Understanding the variation in healthy normal responses is needed before studying clinical populations.

Several factors influence the integration of visual and inertial stimuli. Differences in motion profiles(71) and stimulus duration(68) influence heading integration. Temporal dynamics of otolith afferents and downstream cortical circuits(72) suggest a mechanism. Many other factors also likely play a role including timing, reliability, visual field size, and degree of vestibular function. To quantify the relative roles of these factors, visual-inertial heading needs to be studied using standardized techniques in which the perceived direction of each modality is assessed as well as the perception of common causation. This knowledge would provide the framework needed for understanding normal physiology as well as disorders involving abnormal visual-vestibular integration such as motion sickness, concussion, and vestibular migraine.

B4. Significance for Aim II, Visual-inertial heading adaptation: Adaptation of the vestibulo-ocular reflex (VOR) has formed the basis for successful rehabilitation of unilateral peripheral vestibular disorders(73-76) in which the VOR is known to be deficient(77, 78). However, asymmetries in vestibular perception exist after reflex recovery(79), and these adaptation methods are even less effective for patients with conditions like migraine(80) when there is no VOR deficit(42). This could be expected given vestibular perception is fundamentally different from vestibular reflexes(31, 32). Although we have a good understanding of how to

adapt the VOR using mismatch of visual and vestibular cues(81-86), perceptual asymmetries persist after the VOR is adapted(87) suggesting that even for rotation perception the mechanism is different.

Visual-inertial heading integration is an important model for multisensory integration(46-51). When visual headings are offset, such as using prisms while walking, subjects follow a curved path(88-90). Previous work at adaptation to visual offset has focused on tasks such as walking or throwing(90, 91), and when adaptation occurs with feedback it is unclear if this is a cognitive or perceptual effect. Neurons sensing sensory conflict are found at the first stage of central otolith processing(92, 93), suggesting a mechanism for heading adaptation. However, even when visual and inertial headings are similar, their perceived direction is different during eccentric gaze(47, 94) and eccentric gaze causes a trajectory deviation when driving(95). This is due to visual headings being biased towards retina coordinates(96-98) and inertial headings in body coordinates(48, 99). Thus, adaptation during eccentric gaze may be limited. How and when visual-inertial heading perception adapts is potentially important and a novel mechanism worthy of study.

B5. Significance for Aim III, Adaptation of heading perception after vestibular loss: Disorders of visual and inertial integration are clinically relevant. In vestibular migraine, abnormal tilt perception is present(100, 101), suggesting a disorder of direction perception. Unilateral vestibular midbrain lesions present with disorders of the head direction cells(102), rather than rotatory vertigo. Furthermore, vestibular and balance symptoms persist long after feelings of rotation have resolved and remain the primary factor determining quality of life after vestibular schwannoma surgery(103). Heading perception(104) and navigation(10) are impacted after unilateral vestibular lesions. Self-motion perception is correlated with dizziness in individuals with chronic unilateral vestibular loss, while reflex tests are not(87). The ability to discriminate visual and inertial headings decreases with age and this may increase fall risk(53). The potential for adapting heading perception as a mechanism of vestibular rehabilitation has not been explored but has potential to improve symptoms and decrease morbidity in populations of patients who receive minimal benefit from currently available methods. Long-term adaptation needs to be studied in individuals with a baseline heading deviation. Adaptation of the vestibulo-ocular reflex is possible in healthy individuals, but quickly returns to baseline in the presence of everyday experience(81, 105). Conversely, with vestibular lesions, adaptation techniques can lead to long term compensation(106-108). Understanding long-term adaptation of heading perception would be more appropriate in subjects with unilateral vestibular loss.

C. Progress Report

During the previous grant period we completed all the proposed experiments in addition to collecting the preliminary data for the current proposal. Ten peer reviewed papers were accepted or published supporting the proposed aims, as well as six papers outside the specific aims. Two book chapters are in press. There were 18 abstracts which were associated with presentations at major international meetings including the Society for Neuroscience, Association for Research in Otolaryngology, and American Academy of Otolaryngology. Additional publications and presentations are expected during the final year of support.

Aim I: Perception of multiple vestibular stimuli. The first part of this aim was to develop psychometric techniques for study of vestibular perception; these results were the foundation for subsequent work in the previous grant as well as the foundation of current proposal. This aim also examined effects of motion context similar to vestibular after effects(109-111) but for stimuli involving a rotation and translation component. This was reported for tilt-translation(112). When yaw rotation and sway were combined similar to how they occur during ambulation their perception was minimized(113). The current proposal builds on this work by examining effects of experience in rotating environments on subsequent translation perception.

Aim II: Coordinates of motion perception. It was found that visual heading perception was in retinal coordinates, and inertial perception was in body coordinates(94). This result raised the question of how visual-inertial headings were integrated. It was demonstrated that they were integrated close to their relative reliability with a higher than Bayesian predicted weight on the inertial cue(47). The greater weight of the inertial cue persisted even when the reliability of the inertial stimulus was degraded(69). This work raised the issue of the range of visual-inertial headings that can be perceived as having common causation and how they are integrated or perceived independently. A recently accepted paper demonstrates large ranges of separation can be integrated(114). This is a major theme of the current proposal.

Aim III: Visually induced motion perception (vection) in controls and vestibular migraine. We described how vection can be quantified by nulling with inertial motion in the horizontal plane(115), in roll(116) and compared it with static perception(117). We also examined how static visual images can induce vection(118). A limitation of this line of research was that not everyone perceived vection as equivalent to inertial motion

which limited participants and generalizability of the findings. This result motivated the proposed experiments in which heading direction will be used to judge perception and integration of visual and inertial motion.

D. Scientific Premise

1. Methods have been developed for delivering combined inertial and visual stimuli, collecting responses that inform perception, and analyzing these psychometric responses.
2. Our preliminary data suggest visual-vestibular heading integration is significantly different from other types of multisensory integration. What has been learned from other fields (e.g. visual-auditory) cannot be directly applied, although many of the techniques developed in these areas are applicable.
3. Testable models of visual-vestibular heading integration have already been developed(52, 119, 120).
4. Adaptation is a standard method of vestibular rehabilitation to treat loss of semicircular canal function and rotatory vertigo. Analogous methods could be used for translation and heading perception.

E. Innovation

This highly innovative proposal represents a paradigm shift in the understanding of self-motion perception by defining effects of self vs. external motion. Most current multisensory integration models are based on other sensory systems (e.g. visual-auditory) and assume common causation is necessary for integration. Preliminary data suggests visual-inertial integration occurs over a wider range of stimulus disparity than in other sensory systems and can occur in the absence of common causation perception (e.g. visual stimuli can influence heading perception even when they are known to be inconsistent with inertial motion). This suggests that visual-inertial integration has a novel mechanism. Prior work in this area has been limited to a narrow range of headings and has not looked at the potential for adaptation. **Aim I** applies CI principles developed in other multisensory contexts to understand perception of self-motion vs. external motion in the common and relevant experience of combined visual and inertial motion. We have developed a novel method by which subjects can report both forced choice (e.g. visual and inertial directions the same or different) and direction in response to a single stimulus presentation using the full range of headings within the horizontal plane. Such techniques have not previously been applied to visual-vestibular integration. This technique will then be applied to determine the effect of timing, duration, and visual field size on the perception of visual-inertial common causation. This is important for understanding common clinical disorders rooted in abnormal visual-inertial heading integration such as migraine, motion sickness, dementia, and simulator sickness. **Aim II** examines the effect of previous experience on visual-inertial heading perception. Visual-inertial heading integration is a dynamic process with plasticity. This area has not previously been studied but preliminary data suggests at least two methods are possible. First separating visual-inertial headings by a constant amount and retesting subjects after some experience with this. Second, adaptation by having the subject experience a virtual reality environment with a constant velocity rotation. This has implications for virtual reality experience as well as for rehabilitation. **Aim III** examines the time course of heading perception after vestibular lesions and the potential for long-term perceptual adaptation. Although offsets in heading perception have been documented with vestibular pathology, there has been no previous work on why these headings offsets develop or the feasibility of long-term adaptation. This has the potential to establish a novel vestibular rehabilitation technique.

F. Approach

This study has primarily basic science goals but is a clinical trial by National Institute of Heath criteria. As such human subjects, power analysis, statistical design, and timeline are presented in detail in separate attachments. All of the experiments will share the same pool of human subjects, experimental apparatus, data collection, and analysis methods. The key elements of these are presented after the experiments.

F1. Aim I: Causal Inference (CI) for visual and inertial headings. 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(47, 69, 94). Although we now have significant knowledge of how visual and inertial headings are integrated using statistically optimal methods(46-51), relatively little is known about how it is determined if visual and inertial motion should be interpreted as having common causation and integrated or perceived as separate and segregated. Early data suggest that integration can occur with large differences between visual and inertial headings(68, 121). Our preliminary data demonstrate there is a wide range where visual and inertial headings influence each other such that the perceived offset between them is smaller than the actual offset(114). There is a smaller range where they are actually perceived as similar.

Experiment IA: Determination of CI using high reliability synchronized stimuli. **Rationale:** Very little is published on CI using visual and inertial stimuli. Previous work in this area has used only limited ranges of

headings(52, 68, 121), has only asked about combined perception or just one sensory modality, and doesn't always ask subjects if they perceive stimuli as the same or different. The initial experiment will determine normal responses. **Hypothesis:** There will be a narrow range where visual and inertial headings are perceived as similar; however, over a much wider range they will influence each other. **Stimuli and Task**: Subjects will experience a paired visual and inertial translation such that they move 15 cm in 2s. The direction of the visual and inertial translation will be randomized such that there are 12 possible directions of each (the full 360° range in 30° increments), and each combination of visual and inertial stimulus directions will be presented in a trial block (144 total stimuli). After each stimulus combination subjects will be asked if the two stimuli are the same (e.g. consistent with visual motion through a fixed environment) or not. They will also be asked to use a dial to report the perceived direction of one of the stimulus modalities (visual or inertial). In alternate trial blocks they will be asked to report the other stimulus modality (Fig. 2A). These two trial blocks will be repeated three times each so that multiple estimates of heading direction and precision can be determined. This will result in 6 reports of stimuli agreement and 3 reports each for visual and inertial heading estimates per subject for each of the 144 combinations. **Outcomes and Interpretation**: Preliminary data has been collected in 4 subjects to demonstrate feasibility. Each subject repeated the trial block 6 times: In 3 blocks they reported inertial heading and in 3 they reported visual heading. In every trial they reported if visual and inertial were the same or different. With 0° offset subjects reported 95% headings were when aligned with a cardinal direction but only 55% for other directions, the fraction decrease for larger offsets and was <4% for offsets ≥90° (Fig. 2B). In every subject perception of inertial heading was biased towards the visual heading with offsets of 30-120° (Fig. 2C, T-test < 0.01), with the inertial heading being strongly influenced when it was in non-cardinal directions. Thus, visual motion influences inertial heading perception even when headings are offset beyond the range in which they are perceived to have common causation. Visual headings were minimally influenced by inertial directions(data not shown). These preliminary data strongly suggest that, visual stimuli influence inertial perception even when common causation is absent and the influence is also dependent on absolute direction, making heading perception different from other forms of multisensory integration. **Power Analysis:** A significant result was shown with the 4 subjects tested, although we recognize there maybe be individual variation and more subtle effects that will require more subjects to define. If a conservative mean bias of 10° is assumed with a large standard deviation (SD) of 15°, a power of 0.80 and type I error rate of 5% then a sample size of 18 is needed. We anticipate focusing on about 20 subjects. This should allow us to determine normal responses for the population as well as determining if the sample has significant outliers. **Potential Pitfalls:** By choosing to cover the full 360° range of headings uniformly the gaps between headings tested are large (30°). The preliminary data indicates this is an appropriate spacing, but it is possible some subjects will have relatively narrow tuning that won't adequately sample headings close to each other. It is also possible the chosen spacings influence subject's responses so they could deduce that relatively few headings are similar. Our visual display covers about 98°, which is less than the full visual field, but a previous study found that varying the visual field over 51 to 112° had no effect on heading estimation(122). However, it is possible that the visual field size influences common causation perception. We plan additional experiments in which the full range of inertial headings is tested at 30° increments but visual headings close to those aligned with the inertial heading are more tightly sampled while still covering the full range.

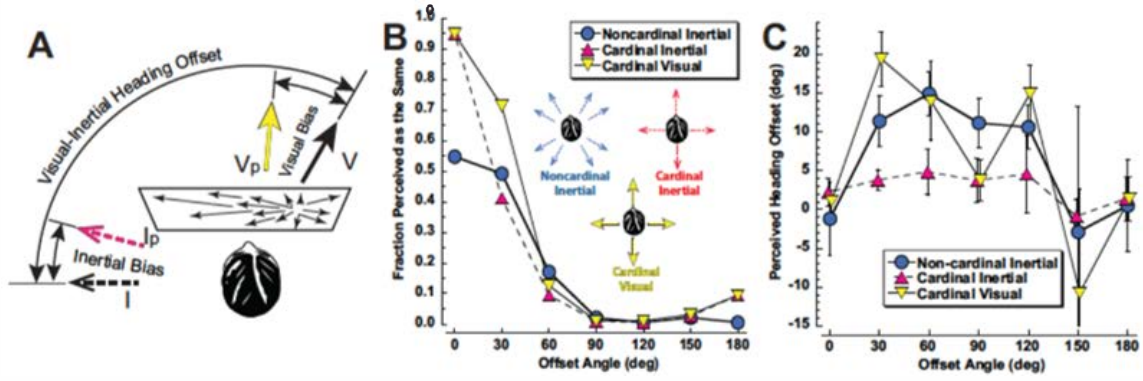


Figure 2. Preliminary unpublished data from 4 subjects who experienced visual and inertial headings. Visual headings are represented by solid lines and inertial or vestibular headings by dashed lines. **A**: Diagram of experimental setup. Subjects viewed a visual screen while also experiencing platform motion. After each stimulus the perceived visual (Ve, outlined solid) or inertial (Ie, outlined dashed) motion direction and if these stimuli were in the same direction or not. In the example shown they are separated by 120°. Visual and inertial biases were defined as positive if they were towards the other stimulus. In the case of 0 and 180° offsets, positive was towards the right. **B**: Fraction of stimulus presentations with headings reported the same by offset. Aligned headings were much more likely to be perceived as similar if they were aligned in a cardinal direction. **C**: Inertial heading bias by offset. Offsets in opposite directions have been combined, error bars represent standard error.

Experiment IB: Effects of stimulus parameters on CI. **Rationale:** In addition to being in compatible directions, CI likely requires that visual and inertial stimuli have compatible timing and motion characteristics. The size of the visual stimulus plays a role as motion in the peripheral vision is usually interpreted as self-motion(123-126). It has previously been shown that stimuli of different motion profiles can be integrated(71) although only a small range of headings were tested and the limits of integration remain unclear. Duration of stimuli also has some effect, with more reliance on vision for longer duration stimuli(68). Determining the parameters at which stimuli are similar enough to be perceived as common causation is important for understanding simulator sickness and motion sickness. **Hypothesis:** Visual and inertial headings have to be closely timed and visual stimuli have to involve peripheral vision to be perceived as having common causation, with longer duration stimuli larger differences may be acceptable. **Stimuli and Task:** As with experiment IA, subjects will experience visual and inertial stimuli in trial blocks containing combinations of both. Starting parameters will be 15 cm of translation over 2s. Timing between the stimuli will initially be tested in 50 ms offset increments up to 200 ms and the effects of the visual stimulus being first or second explored. Preliminary data (not shown) indicate a high degree of sensory segregation at 200 ms, but the limits and effects of smaller offsets are unknown. We also plan to do the experiment with the total duration and acceleration of the stimuli varied. The visual field will be tested at 98°(exp 1A), 45°, and 20°. Equipment which may be available soon may allow larger visual field sizes up to 200°. These angles may be adjusted based on the findings. The protocol for these experiments will be similar to experiment IA, which will essentially serve as the control condition for these experiments. **Outcomes and Interpretation:** There are two related outcome measures that will be determined – if subjects consider the stimuli the same or different and how far apart they are perceived. **Power Analysis:** If we assume that conditions which show influence have a mean difference of 10° with the SD also 10°, a power 0.80 to detect a type I error rate of 0.05 then the needed sample size is 8. We anticipate focusing on about ten subjects which should allow us to determine normal for the population as well as to determine whether there are significant outliers. Individual variation is expected and has been noticed in previous studies of visual-inertial heading perception when individual results are reported(47, 69, 121, 127). **Potential Pitfalls:** How stimuli are perceived depends on previous experience and subject expectations (i.e. Bayesian priors). Part of the reason the full range of stimuli will be used is so that subjects won't have expectations that stimuli are limited to one direction. Continued experience with a stimulus condition (e.g. a temporal offset of 200 ms) might cause subjects to perceive these stimuli to be associated over time. We plan to bring in naïve subjects with each series of experiments to test for this and also vary the order conditions are tested within the series. **Future Directions:** There are many other potential variables that will determine if headings are associated including prior experience, gaze direction, and binocular disparity. Developing a standard way to measure this will be valuable, and also form a framework for experiments on multisensory integration and common causation.

Experiment IC: Effects of vestibular lesions on CI. **Rationale:** It is known that unilateral loss of vestibular function influences heading perception(104). Furthermore, visual stimulus reliability influences multisensory integration(46-51). Attempts to modify the inertial stimulus reliability using vibration has demonstrated the vestibular cue can be weighed greater than Bayesian predictions based on relative reliability(69). It is unclear that adding vibration is more than just a distractor, and a unilateral lesion is a physiologically and clinically relevant mechanism of decreased vestibular reliability. Studying visual-inertial integration in subjects with chronic unilateral lesions will give valuable insight in this area. **Hypothesis:** Inertial heading perception will be more deviated towards visual headings with a greater difference in heading direction being perceived as having common causation. **Stimuli and Task:** Will be similar to experiments IA and IB to facilitate direct comparison with results in normal controls. The subjects will be recruited from the otolaryngology clinics at the University of Rochester. Subjects with unilateral lesions due to labyrinthectomy for removal of benign tumors such as acoustic neuromas will be included. Some of these subjects are already involved in experiments in the lab, and more will be recruited during the study period. **Outcomes and Interpretation:** As with experiments IA and IB we will determine if stimuli are perceived as having common causation and how far apart they are perceived. Unlike control subjects we anticipate that this behavior might change as these subjects recover. We will also consider that performance may be predicted by standard clinical tests such as vestibulo-ocular reflex function as measured with the video head impulse test and clinical measures such as the dizziness handicap inventory (DHI)(128). **Power Analysis:** We anticipate these subjects will have more variation due to clinical factors related to the underlying nature of human unilateral lesions. However, for a human disease population, those with unilateral vestibular lesions are relatively homogeneous. The power calculation would be similar to IB and ten subjects will likely be sufficient to demonstrate the differences relative to a control population. **Potential Pitfalls:** These subjects could be more difficult to recruit which means the experiments will need to

be done over a longer period. The nature of human vestibular lesions (e.g. slow growing tumors) can make it difficult to know the effective duration of the lesion but use of chronic lesions will decrease this effect. The method of compensation and effects on heading integration may not be uniform across subjects which itself would be an interesting finding. The etiology of the lesion (e.g. gentamicin, vestibular neuritis, trauma) may also have an influence which will be considered in the analysis. **Future Directions:** Some subjects will also be involved in aim III. Examining how adaptation influences integration and common causation is also important. This can be accomplished by testing these subjects before and after adaptation. Another investigator at our institution (Eric Anson) plans to do gait experiments involving the same subject pool and correlations between experimental outcomes may be found.

F2. Aim II: Adaptation of heading perception. An important feature of neural systems is plasticity, and this is especially important for visual motion perception(129-132) and the VOR(81-86). It is unclear how plasticity in vestibular heading perception occurs, although some studies focused on rotation(87, 133) heading adaptation has been limited to demonstrating feasibility as a method of calibration(134). **Rationale:** Although adaptation has been studied in many neural systems, heading perception has some interesting qualities which make it potentially unique. One interesting finding is that gaze shifts bias visual heading perception but not inertial heading perception(47, 94). Gaze shifts occur regularly during daily behavior in multiple directions, which may be the reason this does not lead to adaptation. Furthermore, misalignment of visual-inertial motion is a factor in motion sickness(16-19) and simulator sickness(22-25). Understanding which conditions adapt visual or inertial heading perception has clinical and scientific relevance.

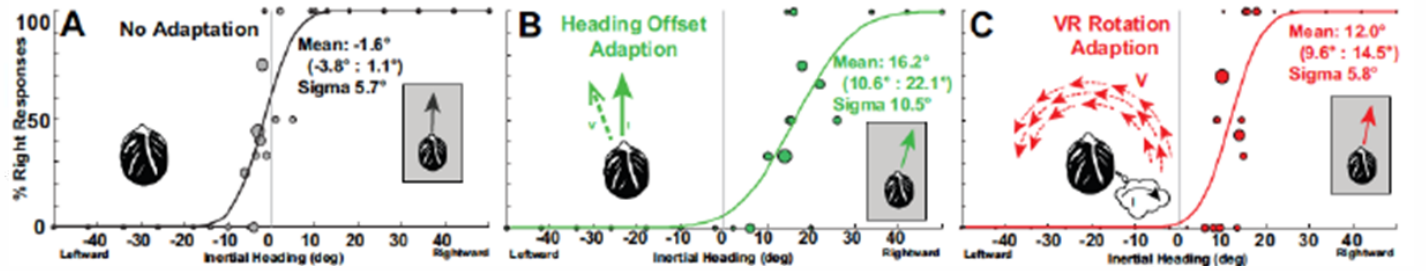


Figure 3: Adaptation of inertial heading perception in an individual subject. The subject completed a forced choice task in which they reported if an inertial stimulus without a visual component is left or right of midline. Initially headings were presented at ±50° in randomly interleaved staircases with subsequent headings adjusted in the opposite direction but no feedback was given. Small data points represent a single stimulus presentation and larger points represent multiple stimuli, with the number of stimuli in proportion to the diameter of the circle. In each panel the mean of the Gaussian cumulative distribution function (CDF) that is the best to the data is show as well as the 95% confidence interval based on random resampling of the responses(135). The mean is also the point of subjective equality (PSE) at which the subject would be equally likely to respond left or right. **A**: Baseline performance prior to adaptation. The subject's is equally likely to respond to the left or right when a heading is straight ahead. **B**: The same subject after exposure to a series of stimulus presentations in which 100 heading stimuli were presented with the visual offset 20°to the left of the inertial stimulus. This type of adaptation led to perception of subsequent stimuli being deviated to the left, such that a 16.2° deviation to the right was needed to reach the PSE. **C**: Performance after adaptation in a virtual reality environment which was rotating to the left at 40°/s for 10 minutes while the subject made voluntary head movements to search for visible targets in the virtual environment. After this a 0° heading would be reliably perceived as leftward, a 12°deviation to the right would be needed to reach the PSE.

Experiment IIA: Heading perception adaptation using offset visual and inertial motion stimuli (Fig. 3B). **Hypothesis:** Exposure to visual and inertial headings that are systematically offset from each other will adapt inertial heading perception and perception of common causation. **Stimuli and Task:** Adaptation will occur while subjects do a task in which they report whether headings are right or left of straight ahead. During this task, visual and inertial headings will be offset from each other such that subjects are not cognizant of the offset (e.g. visual will be 20° to the right of the inertial stimulus). Although the subject will be asked to report heading, this is used mainly to encourage attention. In the preliminary investigations 40, 80, and 120 trials of adaptation were examined. Adaptation was seen with all of these, but 80 offset stimulus presentations was chosen as it was comfortable for subjects to maintain attention (20-25 minutes) while yielding a robust adaptation. Data will be analyzed to compare baseline perception (measured prior to adaptation) with performance on a task afterwards to measure the effect of adaptation. Multiple variations on this experiment are planned with regard to which sensory modality is measured after adaptation (visual or inertial), direction of adaptation (left or right), and range of stimuli used during adaptation and testing (e.g. does adaptation induced over a narrow range of stimuli extend to a wider range of stimuli tested afterwards). Multiple methods of measuring adaptation will be tested: Using a forced choice task (e.g. left or right of midline) will be the primary method of assessing adaptation. Additionally, an estimation task (e.g. point in the direction of perceived motion) will be used in a subset of experiments to test the range of adaptation beyond straight ahead. We will also have subjects report if the visual and inertial stimuli have common causation and the direction of one

modality (similar to exp. I). **Outcomes and Interpretation:** There are two related outcome measures – how visual and inertial heading perception are influenced, and how common causation is influenced. Using some variations on the experiment we hope to define the range of headings in which adaptation occurs as related to the range of angles that are adapted (e.g. does adapting angles near straight ahead influence the full range of headings). **Power Analysis:** We see an adaptation effect of 16° in Fig. 3A. Conservatively assuming the mean and SD of the population are 8° ± 10°, power of 0.80, and type I error rate of 0.05 then the sample size needed is 13. We anticipate focusing on 15 normal subjects, and plan to use subjects who can participate for a long period so performance across sessions can be explored. **Potential Pitfalls:** There will be individual variation. Some situations that induce adaptation in some subjects may not in others. Adaptation may be limited to the range of headings adapted, which will be tested, and the method can be modified to use as wide of heading range as needed. **Future Directions:** Previous work suggests that subjects do not adapt to gaze shifts and perceive visual and inertial headings as offset during these conditions(47). This suggests limits to heading adaptation. Other strategies may be important such as aligning eye and head position during gaze changes. Determining the effects of adaptation on common causation (e.g. repeating exp. I after adaptation) could be insightful. Adaptation may also have relevance for virtual reality systems in limited space(136).

Experiment IIB: Heading adaptation using rotational velocity offset in virtual reality environment (Fig. 3C). **Hypothesis:** Exposure to a rotating environment will shift heading perception towards the direction of implied inertial rotation. **Stimuli and Task:** Subjects will be exposed to a virtual environment consisting of a rotating star field with decreased coherence (i.e. stars disappear and are regenerated at a random new location) to decrease use of landmarks. Subjects will be encouraged to look for objects (e.g. aliens) in the virtual environment to encourage head rotation and attention. We have found that after a minute or two, rotations of 40°/s are not perceived by subjects and this type of stimulus induces robust adaptation of inertial heading perception (Fig. 3C). Afterwards subjects will have visual and inertial heading perception tested using methods similar to exp. IIA. In addition, we plan to measure thresholds of potential biases in inertial rotation perception before and after adaptation. Methods for doing this have previously been described in the current laboratory(36, 37, 137). **Outcomes and Interpretation:** Similar to IIA, outcome measures that will be determined – how visual heading perception is influenced, how inertial perception is influenced, and the range of headings that are adapted. In addition, we will look at potential effects of rotation perception before and after testing. **Power Analysis:** Similar to IIA, we plan to focus on 15 subjects and will use some of the same subjects included in IIA. **Potential Pitfalls:** Rotation may be more likely induce motion sickness symptoms in some subjects than translation protocols, although this has not been a major issue in the preliminary data. Adaptation may also depend to some degree on how much subjects move during the trial and their attention. Techniques could be used to standardize the adaptation experience such as requiring a minimum amount of motion (or minimum velocity) before the search object appears. **Future Directions:** These experiments will focus on heading perception within the horizontal plane. Rotation in the vertical planes (pitch and yaw) is also of interest and more complicated due to the potential otolith role due to the change in the gravity vector relative to the head. Testing CI (exp. I) after adaptation could also provide insight as to the mechanism.

F3. Aim III: Long term heading adaptation. There is growing evidence that errors of heading perception are clinically significant. Vestibular and balance symptoms are the primary factor determining quality of life in vestibular schwannoma patients(103). Heading perception(104) and navigation(10) are known to be impacted by unilateral vestibular lesions as well as central vestibular lesions(102). After an acute vestibular lesion, it is common to have a perception of rotation towards the intact side(30, 138). This perception normalizes quickly even though asymmetry in the VOR persists(79) presumably due to central compensation.

Experiment IIIA: Characterization of heading bias in subjects with unilateral lesions. **Rationale:** After unilateral vestibular lesions, patients often perceive rotatory vertigo towards the intact side (Fig. 4A)(79, 87) which, unlike vestibulo-ocular reflex asymmetries, resolves after compensation. However, even after rotation is no longer perceived, heading bias is common and is such that straight forward motion is perceived to be towards the side of the lesion (Fig. 4B-C). Unlike rotatory vertigo, this heading bias does not appear to recover spontaneously with time or with conventional vestibular rehabilitation. Initially this bias is masked by a compelling sensation of rotation, and it is not clear how it develops or how stable it is. It is also unclear if it is related to unilateral loss of otolith function or if it is induced by a prolonged sense of rotation and may be a pathological adaptation to this experience. **Hypothesis:** Heading bias occurs once rotatory vertigo subsides. This may be related to asymmetric otolith function vs. central rotation compensation (Fig 4D). **Stimuli and Task:** Subjects with unilateral vestibular hypofunction will be recruited, preference will be to recruit acute patients (e.g. after surgery, vestibular neuritis (VN), and Meniere's disease recently treated with gentamicin). It is recognized that VN and gentamicin may produce incomplete lesions so subjects will be analyzed separately

by etiology. Subjects will undergo psychometric testing to measure heading bias (similar to healthy controls, Fig. 3A), and measure the bias and thresholds of yaw rotation and sway translation as previously done in the current laboratory(36, 118). These responses will be measured weekly for the first month, then once per month for six months, at nine months, and at one year. These measures will also be correlated with video head impulse testing, calorics, and VEMP which are routine clinical tests in these individuals as well as symptoms measured using the DHI(128). **Outcomes and Interpretation:** Bias and thresholds will be measured using established curve fitting. After acute loss subjects perceive spinning towards their intact ear. Preliminary results indicate the heading is acutely deviated towards the intact side (Fig. 4A) due to perceived rotation. Likewise, the yaw rotation perception will be strongly biased while sway translation may be more balanced. Pathological rotation perception and vertigo will diminish with natural adaptation. Observing the pattern of biases during recovery will be helpful in determining the origin of the heading deviation after chronic lesions. If this is due to otolith asymmetry it should be manifest with a bias or asymmetric threshold in perception of sway translation. If it is due to exposure and adaptation to rotatory vertigo, sway translation asymmetry should be minimal. Preliminary data (not shown) suggests a bias in sway translation develops in a delayed fashion after vestibular loss. We will also examine the stability of these asymmetries over time.

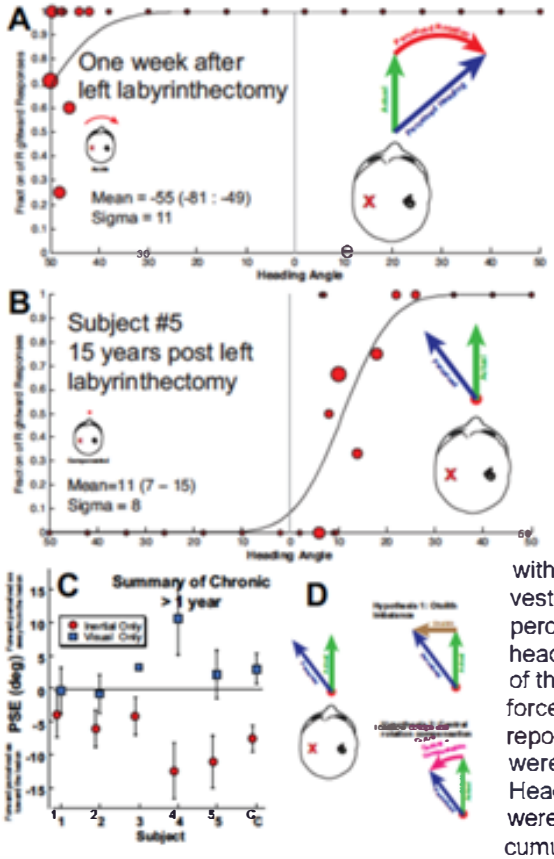


Figure 4: Heading deviation in subjects with unilateral vestibular loss. In these experiments subjects experienced a heading which they identified as left or right of midline. Subsequent headings were adjusted based on responses so that stimuli near the end of the trial block were near the point that subjects were equally likely to choose either direction. Panel **A:** After a unilateral lesion (subject shown is a week post left labyrinthectomy for Meniere's) subjects perceive they are rotating towards the intact side which results in a strong heading deviation. In this case the deviation was more than the 50° range tested. Panel **B:** Subject with 15 year history of unilateral vestibular hypofunction no longer perceived rotatory vertigo but headings as deviated towards the side of the lesion. Subjects completed a forced choice task in which they reported if visual or inertial headings were to the left or right of midline. Headings near straight ahead (0°) were reported as leftward. A cumulative distribution function fit to the data demonstrated a deviation of 11°. Panel **C:** Summary of findings in 5 subjects with chronic unilateral vestibular hypofunction. Visual headings (blue squares) were not systematically deviated while inertial headings (red circle) were deviated towards the lesioned side. Panel **D:** Hypotheses on why heading may be deviated: otolith effect or overcompensation of central vertigo.

Power Analysis: We anticipate there will be variation between subjects due to the nature of human lesions, the lesion may not have occurred at a single time point (e.g. with a growing tumor that is eventually removed), subject's experience outside the laboratory will be varied, there will be effects of age, and other factors which may contribute to individual variation. However, in the preliminary data all subjects with a unilateral lesion developed heading deviation although the cause and time course of this may not always be the same. Previous studies of this type have looked at 30 subjects(87) with unilateral lesions. The preliminary data in Fig. 4C demonstrates a mean deviation of 7.5 ± 3.4° in 5 subjects and is already significantly different from zero. If we assume the normal population averages 0 ± 7 and SD of the UVD population is similar, a power of 0.80 and type I error rate of 0.05 requires a sample size of 16. **Potential Pitfalls:** Patients with unilateral lesions can come from a long distance which can make serial testing difficult. Some that enroll may miss visits or may be lost over time. The dropout rate is anticipated to be similar to established clinical trials at about 50%. **Future Directions:** This will establish the time course of patient symptoms and perception. Understanding how perception changes after vestibular lesions will form the foundation for a successful intervention strategy. Causal inference could be examined during the acute period, which could correlate with intervention potential.

Experiment IIIB: Using adaptation to remove heading bias in subjects with stable unilateral vestibular lesions. **Rationale:** Heading adaptation is possible (Fig. 3), but in normal subjects is likely to be transient due to experience with aligned visual and inertial stimuli during ordinary activities outside the adaptation sessions. Longer term adaptation may be possible in subjects who have an asymmetry in the otolith system due to vestibular loss and could form the basis of a rehabilitation tool. **Hypothesis:** Heading bias is common in

individuals with unilateral vestibular hypofunction. Long term correction of this heading bias maybe possible. **Stimuli and Task:** Subjects with unilateral vestibular hypofunction will be recruited (e.g. those with transtympanic gentamicin treatment of Meniere's disease or those with vestibular schwannomas). Only individuals who have had a unilateral lesion for at least a year will be included; these will include some subjects who completed exp. IIIA. Subjects will undergo standard clinical testing to establish the nature of their lesion including calorics, VEMP, video head impulse testing and DHI(128) to measure symptom severity. Each testing session will include a heading perception task based on forced choices (left vs. right of midline) using a staircase to focus stimuli near the point of subjective equality. This will be fit with a cumulative distribution function to determine the bias in their heading perception. A similar task will be used to determine biases in rotation and sway translation perception during the same visit. As a safety factor, these subjects will also complete the dizziness handicap inventory (DHI)(128) at each visit to gauge their symptoms and ensure that the experimental intervention is not associated with worsening symptoms. Both heading offset adaptation (exp. IIA) and rotational adaptation (exp. IIB) tasks proposed in aim II will be used in the same individuals, not simultaneously, so both tasks can be assessed independently. The utilized adaptation task will depend on the time of enrollment with early subjects doing the rotation task first and later subjects doing the heading offset task first; both tasks have potential advantages. The rotation task does not require a hexapod motion platform (HMP) so it would be more practical as a clinical intervention. However, rotation may cause discomfort in this population. Heading adaptation using offsets in visual inertial headings is more equipment intensive as it uses the HMP in the current proposal but could potentially be adapted to virtual reality headsets. Subjects will always be adapted in the direction that will eliminate their heading bias. Adaptation sessions will occur once per week with baseline measurements of both visual and inertial heading perception before each session. Preliminary data demonstrated 5 subjects had adaptation during the first session to nearly eliminate or overcorrect their bias (Fig. 5). The residual bias was reduced at the start of the session a week later in 4 of 5 subjects. These subjects had a baseline DHI of 23 ± 14 (range 2-38). After adaption DHI change was minimal: -0.8 (range -4 to 2)The number of sessions may vary across subjects based on tolerance and degree of adaptation. If a subject no longer has an inertial bias or reversed bias, further adaptation will not be performed but the subject will continue with subsequent sessions to assess the stability of their heading perception.

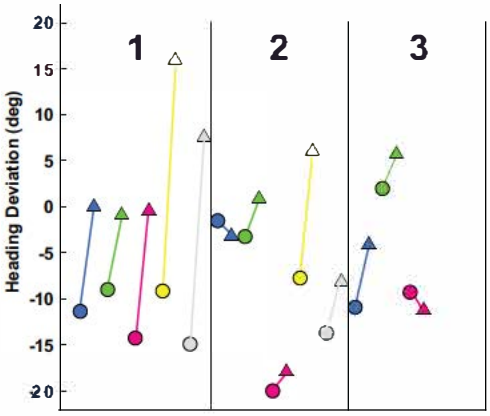


Figure 5: Heading adaptation in 5 subjects with chronic (>4 years) UVL. Subjects underwent 2-3 sessions of rotational adaptation about a week apart. Negative values indicate a bias towards the lesioned side. Pre-adaptation for each day is represented by a circle and post adaptat1on by a triangle. Each subject Is shown as a separate color. Heading deviation was 7-15° prior to adaptation (negative towards the lesion). In the first session robust adaptation was seen in all subjects. Some subjects retained some adaptation in subsequent sessions.

Outcomes and Interpretation: These experiments will determine if durable adaptation of heading can occur using two methods. Although the main goal is to adapt inertial perception it is possible that visual heading perception may be impacted, therefore this will be monitored. We will also assess if this adaptation can be performed safely, without causing increased dizziness symptoms, as measured with the DHI. **Power Analysis:** We anticipate being able to enroll about one new subject with chronic unilateral vestibular loss per month, in addition to testing ten patients known to us and willing to participate. The effect is likely to be most robust in subjects with heading deviations >10°, making these the preferred individuals. Assuming an initial mean deviation of 10° and post adaptation deviation of 2° with both having a SD of 8°, then a sample size of 8 would be needed to reduced the type I error rate to 0.05 with a power of 0.80. A total sample size of 20 or larger will likely be obtained to allow independent examination of different lesion etiologies (e.g. gentamicin, surgical lesions). **Potential Pitfalls:** The nature of the lesion will be unclear in some because of clinical attempts to preserve vestibular function and in some other structures may not be completely normal. It is probable the adaptation may worsen symptoms and make it less feasible, but parameters could be adjusted (e.g. duration, speed of visual rotation) to improve feasibility. **Future Directions:** Issues with heading perception may also be important in other clinical disorders such as traumatic brain injury, blast trauma, migraine, Alzheimer's disease, and concussion. Unilateral vestibular lesions are a reasonable place to start because the pathology is relatively uniform and well understood in these patients. It is hoped that if long term adaptation is possible, this data could be useful for the design of a randomized controlled clinical trial of heading adaptation to improve patient symptoms and potentially decrease the risk of morbidity such as falls.

Future clinical trials could include a range of conditions that involve abnormal motion perception. The laboratory has experience developing web based rehabilitation tools(73) which could be applied to heading adaptation methods to make them easily accessible to patients if they are found to be helpful.

F4. Human Subjects. This study is classified as a clinical trial with separate human subject documents. Dr. Crane is a primary investigator of an institutional review board (IRB) approved protocol with access to a database of ~500 screened individuals in the University [redacted] human subject core. Standard screening includes visual acuity, vestibular testing, audiometry, medical history, any medications, prior dizziness or balance symptoms, and migraine history(139-141). Additional clinical vestibular tests include rotatory chair, posturography, and vestibular evoked myopotentials (VEMP)(142). There are a large population of normal controls who regularly participate in our laboratory. Subjects represent a cross section of the [redacted] population with both sexes, ages 13 – 89, and all races and ethnicities. We will look for potential effects of age and sex as a biological variable in our analysis. A wide age range is relevant to vestibular pathology. Our IRB approval excludes non-English speakers, children <13, and elderly >89. We do not plan to enroll children <13 because vertigo is rare in this population. Individuals >89 are excluded because multiple medical comorbidities may confound results. Existing IRB approval allows 150 additional subjects, which could be expanded.

We currently have about 20 individuals with unilateral vestibular function of various etiologies (e.g. surgical lesions, and Meniere's disease treated with gentamicin(143)) who are willing to participate. About 30 patients per year have vestibular lesions related to acoustic neuromas and their treatment, vestibular neuritis, or treatment of Meniere's disease at the University of Rochester. Historically about half are willing to participate in research. For patients with peripheral vestibular hypofunction, the lesion will be confirmed with ice-water caloric irrigation, VEMP, and video head impulse testing(77).

Risks to subjects are minimal. Subjects who choose to participate will do so only after informed consent. Subjects will be paid $15/hr plus expenses related to their participation such as parking and travel. This has been adequate to recruit subjects, but future payments can be amended upward if necessary.

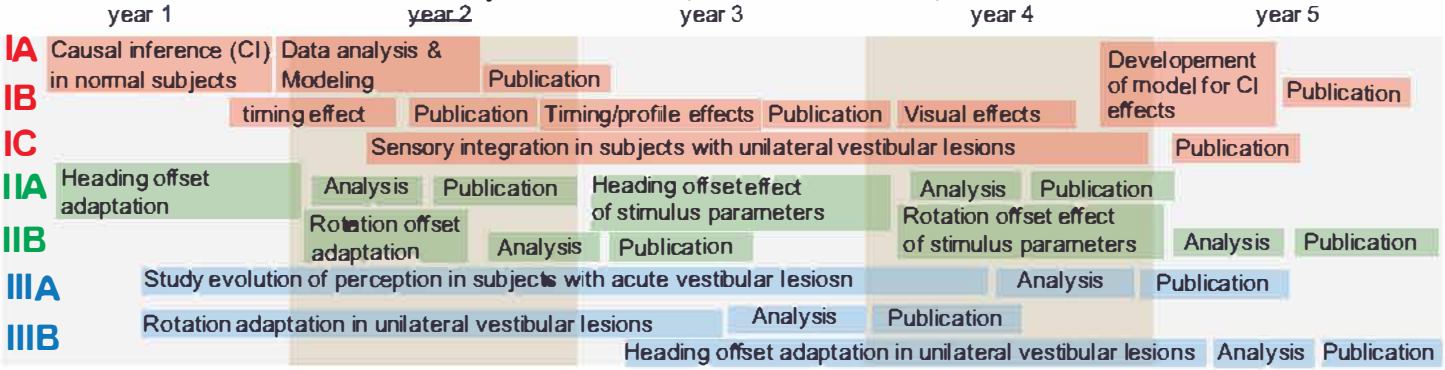
F5. Subject Training. Naïve subjects recruited from the community will be used; often subjects have participated in previous studies. Prior to each experiment, the task and range of responses will be explained in layman's terms, using the same language for each subject. To test the apparatus for comfort and to ensure the task is clear, large, unambiguous stimuli similar to those in the experiment will be delivered prior to any data collection. Feedback will not be given during or after the experiment.

F6. Experimental Apparatus. The nucleus of the laboratory is a **hexapod motion platform (HMP)** (Moog, model 6DOF2000E, East Aurora, NY) which is set up for human subjects (36, 37, 47, 69, 94, 110, 111, 113, 144) similar to that used by others(29, 35, 145). The motion profile typically used is a sine wave in acceleration which is now standard in the field(29, 35, 36, 146). The HMP is coupled with a visual display covering 98° in azimuth which can provide visual stimuli synchronized with inertial motion(144). It can also be used with a virtual reality (VR) headset that has 110°, and it is anticipated that upcoming VR technology will expand on this range. The HMP includes accelerometers, angular rate gyros, and a flux-gate magnetometer position tracking. During the experiments the subject is seated in a padded racing style seat; the head can be coupled to the platform using customized football helmets in a range of sizes(36). A second identical HMP is available in the clinic to facilitate testing of additional subjects, allow easier access for patients, and allow multiple experimental configurations simultaneously. There is also a custom-built **multi-axis sled/rotator (MASR)** consisting of a linear sled between two vertical rotational axes(147, 148). The MASR allows an unlimited range of yaw rotation and a greater range of translation in the horizontal plane compared with the HMP. The MASR may be used for test conditions requiring low frequency and/or long duration stimuli where the range of the HMP could be limiting. The laboratory has a fulltime technician who is familiar with the equipment and can conduct experiments. We also have two programmable **virtual reality (VR) systems** from WorldViz (Santa Barbara, CA) with Vizard development software. Each system allows head tracking and an immersive display with binocular disparity. These systems can be used with the subject standing/freely moving or while seated on our HMP or MASR. We also have independent methods of measuring eye, head and body position which can be used with the HMP, MASR, or in free standing conditions. These methods include infrared head mounted video eye tracking (ETD-300HD, IScan Inc, Woburn, MA), and a fluxgate magnetometer to monitor 6-degree of freedom motion (trakSTAR, Ascension Technologies, Burlington, VT).

F7. Data Collection. The laboratory is set up to use multiple methods to investigate the relationship between stimuli and perception. **F7.1 Forced choice methods:** The current laboratory is set up to use a number of psychometric techniques including N-down/1-up staircase with a fixed step size(36), the method of constant stimuli, and variable step size procedures(110, 111, 144). When feasible, trial blocks that use a staircase include multiple interleaved staircases to limit the potential for subjects to make predictions based on

prior experience. This will be primarily used in Aims II & III to report perception as left or right of straight ahead. **F7.2 Heading estimation methods:** Although forced choice methods are adequate for measuring discrimination (e.g. left vs. right), they do not allow measurement of estimates. For heading estimation, a method has been previously published in the current laboratory in which subjects orient a mechanical dial towards the perceived heading(149, 150). Because the dial can rotate continuously without limits it avoids many of the issues of magnitude estimation techniques(151). It is still subject to potential haptic and cognitive influences, but previously published control experiments suggest such influences are secondary(149, 150). Results using this method were similar to heading estimates measured by others using an independent technique(152). Additionally, we are able to use a technique in which subjects use a dial similar to what has been previous described for determining integration vs. segregation of visual and auditory stimuli(59) to report if two stimuli have a perception of unity (i.e. if the visual and inertial stimuli are consistent with motion through a fixed environment) and the direction of one of these stimuli. It was confusing and problematic for subjects to report both visual and inertial heading direction in the same trial block, but we found it effective to have them report visual and inertial direction in separate trial blocks.

F8. Data Analysis. Perception will be determined in two ways: Collecting a forced choice response (e.g. right vs. left) or using continuous data such as the angle of a perceived heading reported using a dial. In some experiments, both methods will be used. **F8.1 Discrete responses:** Forced choice data will be analyzed by fitting a cumulative Gaussian function to these data using a Monte Carlo maximum-likelihood criterion. This allows confidence intervals to be determined and has been described (135, 153) and used by others (70, 145), as well as in our laboratory (36, 37, 110, 111, 144). This technique can also be used to determine if the sets of responses from different test conditions are significantly different. Using this method (108, 109, 139), it has previously been demonstrated in the current laboratory that $p \leq 0.01$ is a conservative criterion for significance. This technique has the advantage that it can be used to determine significance in individual subjects (as needed for a clinical test) as well as from data combined across subjects. **F8.2 Dial responses:** Heading estimates will be collected as an angle reported using a dial. The laboratory has developed analysis techniques that allow precision to be determined even when directions are presented once(149). Continuous responses can be analyzed using established methods such as ANOVA and T-test. We will repeat the same trial block at least 3 times in each subject so that the precision of the responses can be assessed.



F9. Schedule: Year 1 of funding will focus on developing the CI methods in normal subjects (IA). The heading offset adaptation will begin in parallel to this, with an initial focus on determining the offset most ideal for adaptation. We will also start studying perception in subjects with acute unilateral vestibular loss (IIIA) and adaptation in subjects with chronic unilateral lesions (IIIB). **Year 2** will use the CI techniques developed in the first year and take them into other areas such as timing. Experiments using rotational velocity to offset heading (IIB) will be performed. Studying sensory integration and CI in some subjects with unilateral lesions will start (IC) and continue as these subjects are available. Initial experiments will be prepared for publication. **Year 3** Stimulus parameter influences on CI will be studied (IB) as well as the influence of these parameters on adaptation (IIA). Adaptation of unilateral lesion subjects will continue. **Year 4** Effects of stimulus duration on CI will be examined as well as effects of stimulus parameters on rotation offsets. Analysis and publication of previous work. Completion and analysis of heading offset in unilateral vestibular lesion subjects will refine the technique. **Year 5** Combining of CI effects into a unified model publication and analysis of effects of stimulus parameters and vestibular function (IABC). Complete previous work with analysis and publication of results (IIAB, IIIA). Further studies as suggested by previous data. Analysis of unilateral of heading adaptation (IIIB).

F10. Summary: The current proposal aims to open new avenues of investigation by developing methods for understanding how visual and inertial headings are determined to be the same or different, and how the central nervous system is able to adapt to these changes. Pathology in heading perception due to vestibular lesions will be studied as well as potential for long-term adaptation.

Publications resulting from previous funding (R01 DC013580 2014-2019)

1. Crane BT, The influence of head and body tilt on human fore-aft translation perception. *Experimental Brain Research*, (2014) Dec;232(12):3897-905. [PMID 25160866].

2. Crane BT, Coordinates of human visual and inertial heading perception. *PLoS One*, (2015) Aug 12;10(8):e0135539. [PMID 26267865]

3. Miller MA, O'Leary CJ, Allen PD, and Crane BT, Human vection perception using inertial nulling and certainty estimation: The effect of migraine history. *PLoS One*, (2015) Aug 17;10(8):e0135335. [PMID 26280172]

4. Rosenblatt SD, and Crane BT, Influence of visual motion, suggestion, and illusory motion on self-motion perception in the horizontal plane. *PLoS One*, (2015) Nov 4;10(11):e0142109. [PMID 26536235]

5. Crane BT, Perception of combined translation and rotation in the horizontal plane in humans. *Journal of Neurophysiology*, (2016) Sept:116(3):1275-85 [PMID 27334952]

6. Miller MA, Crane BT, Static and dynamic visual vertical perception in subjects with migraine and vestibular migraine *World Journal of Otorhinolaryngology-Head and Neck Surgery*, (2016) 2(3):175-80 [PMID 28782063]

7. Miller MA, Crane BT, Roll vection in migraine patients and controls using inertial nulling and certainty estimation *PLoS One*, (2017) Feb 13;12(2):e0171332 [PMID 28192443]

8. Crane BT, Effect of eye position during human visual-vestibular integration of heading perception. *Journal of Neurophysiology*, (2017) Sept 1;118(3):1609-21 [PMID 28615328]

9. Rodriguez R and Crane BT. Effect of vibration during visual-inertial integration on human heading perception during eccentric gaze. *PLoS One*, (2018) Jun 14;13(6):e0199097 [PMID 29902253]

10. Rodriguez R and Crane BT. Effect of range of heading differences on human visual-inertial heading estimation. *Experimental Brain Research*, (2019) Mar 7 Epub ahead of print [PMID 30847539]

Additional publications during the funded period outside the specific aims

10. Kushner B, Allen PD, and Crane BT, Frequency and demographics of gentamicin use. *Otology & Neurotology*, (2016) Feb:37(2):190-5. [PMID 26719956]

11. Miller MA, Kesarwani P, and Crane BT, Autophony in a patient with giant cell tumor of the temporal bone. *Otology and Neurotology*, (2016) Aug;37(7):e238-9 [PMID 25973842].

12. Lin EP, Crane BT, Management and imaging of vestibular schwannomas. *AJNR*, (2017) Nov;38(11):2034-43 [PMID 28546250]

13. Crane BT and Schubert MC, An adaptive vestibular rehabilitation technique. *The Laryngoscope*, (2018) Mar;128(3):713-18 [PMID 28543062]

14. Lambert PA and Crane BT, Metastatic renal cell carcinoma presenting as cerebellopontine angle and internal auditory canal mass. *Otology & Neurotology*, (2018) Apr;39(4):e294-6 [PMID 29498963]

15. Andrzejewski KL, Ma S, Owens A, Bull MT, Biglan KM, Kanchana S, Mink JW, McDermott MP, Crane BT and Barbano R. Alterations in vestibular function in individuals with cervical dystonia and the effects of botulinum toxin treatment. *Basal Ganglia*, (2018) In press

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Multi modal vestibular perception	Yes

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Multi modal vestibular perception

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	○ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	○ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	○ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Unilateral vestibular hypofunction
- Normal perception

2.2. Eligibility Criteria

Normal controls will be human subjects age 13-89 who do not have a history of prior dizziness, balance symptoms, or migraine history. Additional some subjects will be recruited with a history of unilateral (one sided) vestibular lesions. These patients will be similar with the exception that they can and likely will have a prior history of dizziness and balance symptoms.

2.3. Age Limits	Min Age: 13 Years	Max Age: 89 Years
2.4. Inclusion of Women, Minorities, and Children	Inclusion_of_Women_and_Minorities.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_retention_plan.pdf	
2.6. Recruitment Status	Recruiting	
2.7. Study Timeline	Study_Time_Line.pdf	
2.8. Enrollment of First Subject	12/02/2019	Anticipated

Inclusion of Women and Minorities

Subjects will not be excluded from participation based on gender, racial, or ethnic group. We anticipate that women will comprise about half the study population. In both the groups with unilateral vestibular loss and controls we anticipate that the gender distribution will be similar to the population of the [redacted] area as these conditions are relatively uniformly distributed across race, ethnicities and genders.

We do not anticipate an outreach program will be needed to recruit an appropriate mix of gender and racial/ethnic groups. If we find that the some groups are not adequately represented, this will be remedied by inviting appropriate subjects from our database of normal controls to participate or by asking different patient groups to participate. It is anticipated that more patients will be encountered in clinic that will be appropriate candidates than will be needed. If it is found that one gender or group is becoming over represented, care will be taken to balance the study population by preferentially asking patients of other genders or races if they wish to participate.

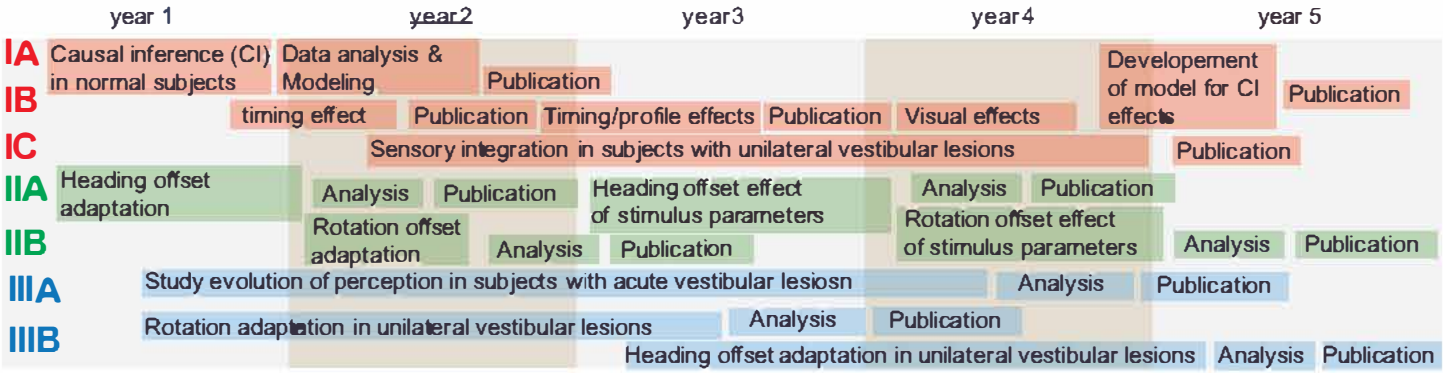
Recruitment and Retention Plan

The University [redacted] maintains a human subjects core as part of the sensorimotor integration in spatial orientation protocol. Dr. Crane is a primary investigator of an institutional review board (IRB) approved protocol with access to these individuals. The database contains ~500 previously screened individuals, many of which are actively participating in other studies within the institution. Standard screening includes visual acuity, caloric testing, audiometry, and health related information such as the Jacobsen dizziness handicap inventory, medical history, any medications, prior dizziness or balance symptoms, migraine history, and screening for vestibular migraine. There are typically about 30 normal controls who regularly participate in our laboratory. We plan to recruit normal new or additional subjects as needed which can be done through word of mouth from existing subjects and lab personnel, fliers posted on the University [redacted] campus as well as fliers posted at nearby facilities such as grocery stores. We have found that fliers posted at the nearby Jewish Community Center has been a good source of interested healthy older subjects.

Recruitment of subjects with unilateral vestibular hypofunction will be primarily through Dr. Crane's clinic and other otolaryngologists at the University [redacted]. Additionally, a few subjects have been identified from screening subjects who respond to fliers and from organizations such as the Acoustic Neuroma Society.

Subject's will be paid $15/hr plus expenses related to their participation such as parking and travel costs. We have had several subjects who have participated for several years so we anticipate that retention will not be an issue. Subject's with unilateral vestibular hypofunction can be more difficult to retain, often because they come from a greater distance. We have found that retention of these subjects is greater when experiments can be scheduled in conjunction with medical visits and the laboratory apparatus both in our clinic and in the hospital makes this easy to facilitate this. We have also been able to do experiments on weekends and evenings to facilitate participation.

Study Time Line



Year 1 of funding will focus on developing the causal inference (CI) methods in normal subjects (Aim IA). The heading offset adaptation will begin in parallel to this, with an initial focus on determining the offset most ideal for adaptation. We will also start studying perception in subjects with acute unilateral vestibular loss (Aim IIIA) and adaptation in subjects with chronic unilateral lesions (Aim IIIB). **Year 2** will take the CI techniques developed in the first year and take them into other areas such as timing. Experiments using rotational velocity to offset heading (Aim IIB) will be performed. Studying sensory integration and CI in some subjects with unilateral lesions will start (Aim IC) and continue as these subjects are available. Initial experiments will be prepared for publication. **Year 3** Motion profile influences on CI will be studied (Aim IA). Influence of stimulus parameters on heading adaptation will be examined (Aim IIA). Adaptation of unilateral lesion subjects will continue. **Year 4** effects of stimulus duration on CI will be examined as well as effects of stimulus parameters on rotation offsets. Analysis and publication of previous work. Completion and analysis of heading offset in unilateral vestibular lesion subjects will refine the technique. **Year 5** combining of CI effects into a unified model publication and analysis of effects of stimulus parameters and vestibular function (Aim IABC). Complete previous work with analysis and publication of results (Aim IIAB, IIIA). Further studies as suggested by previous data. Analysis of unilateral of heading adaptation (Aim IIIB).

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	University of Rochester

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ○ Yes ● No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): University of Rochester

Comments: Ethnic and Racial Categories calculated from Monroe County 2015 Demographics http://www.census.gov/quickfacts/table/PST045215/36055

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	3	3	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	12	12	0	0	24
White	54	54	6	6	120
More than One Race	0	0	0	0	0
Total	70	69	6	6	151

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Crane_protection_human_subjects.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	Crane_Data_Safety_and_monitoring_plan.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	Structure_of_the_Study_Team.pdf

Protection of Human Subjects

The proposed project involves human subjects. The use of human subjects is justified because vertigo and dizziness are common clinical complaints and there are no good animal models of these conditions. Also, much of the data collected will be perceptual responses which are difficult to collect in non-human subjects. The research does not involve any invasive testing and poses only minimal risk to those involved. In the majority of proposed experiments, human involvement will be limited to give perceptual responses by pushing buttons or orienting objects. In is anticipated that in some experiments eye movements will be recorded using video oculography, or head and body movement will be measured with non-invasive techniques.

The population of subjects to be recruited for these studies include normal controls and individuals with peripheral vestibulopathy.

Vertigo and dizziness are conditions which can occur in people of any age, but these conditions are rare in children and incidence of these conditions increases with advancing age. We anticipate that over the 5 year period approximately 120 normal controls will participate. When possible, we will involve the same individuals in multiple experiments so that correlations between conditions can be made more easily. There are currently about 100 normal individuals in our database of human subjects who have a recent history of participating in vestibular and motor control experiments at our institution and are available for future experiments. These individuals have already been screened using appropriate questionnaires, clinical tests (caloric testing, audiometry, visual acuity testing, etc.), and physical examination. These individuals cover a range of ages from 18 to 89. We do not plan to recruit subjects older than 89 because subjects in this age range frequently have medical co-morbidities which make their participation difficult. We do not anticipate subjects who participate in this study will be younger than age 18. Vertigo symptoms and vestibular loss are rare in the pediatric population. However, we do have institutional review board approval to include subjects as young as 13. Because we are in a university environment, we have found it is easy to recruit subjects who are between the ages of 21 and 30. We will use normal subjects in this range, but will make attempts to include older subjects who are in the age range so that we can collect data from the population in which vestibular symptoms are more likely to occur. If new normal subjects need to be recruited this will be done through the institutional review board (IRB) approved protocol which includes filers.

The proposed project also requires us to recruit subjects with vestibulopathy. Patients with peripheral vestibulopathy will be recruited primarily from clinic of Dr. Crane, although a small number of individuals may originate from other specialists at the University [redacted] who see patients with dizziness symptoms. Usually these patients will be recruited directly from clinic, but they many occasionally be recruited using letters and phone calls. We anticipate about 30 subjects over the course of the study will be recruited.

Subjects who participate in research will be paid $15 per hour for the time they spend on site. Transportation costs, and parking expenses are be reimbursed.

We do not plan to involve most vulnerable populations including fetuses, neonates, pregnant women, prisoners, or institutionalized individuals. In is possible that a small number of individuals between the age of 13 and 17 will be involved in the proposed research although we do not plan to specifically target this group for recruitment. In this age group, we will obtain informed consent from both the patient and their parent or guardian. We have a special IRB approved assent form to use in this population which uses age appropriate language.

This proposal includes no collaborating sites.

Data from human subjects collected during these studies will be stored separate from identifiers in a HIPPA compliant manner. Only the PI (Benjamin Crane) and technician [redacted] will have access to individually identifiable private information.

Prior to participation all subjects will be required to read, understand, and sign an informed consent form. Informed consent will be obtained by the PI (Benjamin Crane) or one of the laboratory personal who have completed the appropriate training. In most cases the informed consent will occur several days prior to participation in any experiments, when the subject is recruited. Participation in these studies will not preclude any future or alternative treatment. We anticipate the risks of participating are minimal and may include motion sickness symptoms in some individuals. Subjects are informed that they may end their participation at any time. In the case of adaptation studies, subjects will be monitored with a questionnaire (the dizziness handicap inventory) to ensure that any symptoms are not worsening with participation in the study.

It is unlikely, that the proposed research will have a direct benefit to any of the participants. The research may have a benefit to future patients with vestibular disorders by providing better understanding of these disorders including better diagnostic and treatment strategy. Because the risks of participation in this study are minimal, we believe the knowledge gained from this proposal would outweigh any risks.

The protocol outlined above has been approved by the University [redacted] Institutional Review Board (RSRB 39535), and all personnel involved in recruiting and testing human subjects have had appropriate coursework and certifications.

Data and Safety Monitoring Plan

NIH Study Number: R01 DC0135580

Title: Multimodal vestibular perception

Principal Investigator: Benjamin T. Crane, M.D., Ph.D.

I. Overview

A. This is a single center, prospective, observational, minimal risk basic science study performed with adult human subjects: 1) Most of the subjects will be healthy controls. We plan to measure heading perception using visual and inertial stimuli delivered by a motion platform. The nature of the stimuli presented will generally be motion along a linear path and visual motion with a star field 2) In some experiments adaptation will occur by separating visual and inertial headings in a systematic way (e.g. have visual and inertial headings offset 15° from each other) or exposure to a rotating virtual reality environment. 3) Subjects with unilateral vestibular loss will also be studied to see how their perception of visual-inertial heading integration may differ from controls. In addition, those subjects with an offset in inertial heading will be studied to see if long term adaptation is possible.

B. Adherence statement. The Data and Safety Monitoring Plan (DSMP) outlined below for this study will adhere to the protocol approved by the University [redacted] Research Subjects Review Board (RSRB).

II. Adverse Events

A. Adverse event assessment
   a. This is a minimal risk study and there is a risk of loss of privacy and of motion sickness due to exposure to visual and inertial motion.
   b. In subjects with existing dizziness symptoms, symptoms will be monitored at each visit with the dizziness handicap inventory (DHI).

B. Adverse event reporting
   a. Every adverse event that is reported to either the PI or study staff by the subject or other medical staff caring for the subject and which meets the above criteria, or which otherwise merit documentation in the judgement of the PI, will be documented with a description of the event along with a determination by the PI of severity and relatedness to study participation.
   b. Adverse events will be reported annually to the RSRB as part of their Continuing Review of the study.

III. Safety Review Plan and Monitoring

A. Justification of sample size

Previous work in the laboratory has been able to show significant effects with these types of psychophysics experiments using about 10 subjects. However, there is also likely to be variation between subjects which is of interest. Consequently, we propose using 10-20 individuals in each series of experiments. Over the course of the 5-year proposal we anticipate 120 normal subjects will be included as well as 30 with unilateral vestibular loss. This is a relatively large number of subjects, but we anticipate it may be needed due to some attrition of subjects over the 5-year period and the need for naïve subjects for some experiments.

B. Safety and study progress reviews

The principal investigator will review adverse events as they occur and annually will review and report to the RSRB on study progress including recruitment and protocol adherence. This annual report will include a list and summary of adverse events, a statement of whether adverse event rates are consistent with pre-study assumptions, a summary of recruitment, and reason for withdrawals.

IV. Informed Consent

Eligible subjects may be approached during a clinical encounter with information about the study or via telephone, or an online questionnaire especially if they have responded to a flyer. The risks and potential benefits of the study will be explained at the first visit. Interested subjects will be given the opportunity to take the consent form home for study, although most opt to sign the consent at the first visit. The study member obtaining consent will review the inclusion and exclusion criteria with the subject prior to consent (on the phone or in person). If they are eligible then consent may proceed. If eligibility was determined via telephone or online, the study visit will be scheduled, and consent will be obtained at the start of the first study visit. Permission/Consent forms will be stored in the office of the Otolaryngology Research Coordinator.

V. Data Quality and Management

A. Data collection forms will be completed during the study visit and transcribed to the REDCap database within a week of the study visit. Psychometric data will be associated with an alpha numeric code that will be stored in the REDCap database. The PI will review all data collection forms and REDCap on a monthly basis.

B. The psychometric data will be collected in the labs system in a way that there is no protected health information (PHI) to individually identify the subject. The only link between the PHI and the experimental data will be a code stored in the REDCap data.

C. The REDCap database and psychometric data is cloud based and backed up by the University [redacted] It logs data entry and modification and so provides an audit trail if necessary. It also allows compliance of data types during data entry and has other quality control tools to allow the PI to assess the completeness and accuracy of data entry.

VI. Confidentiality

Subject data will be identified in the research data set using a unique alpha numeric identifier. Subject identifiers such as name and address will be collected (primarily for scheduling) and we will protect against disclosure of those identifiers by using REDCap for storage of all PHI and utilizing its build-in features for protection of PHI.

Research data will be only tagged with the alpha numeric identifier and will not be associated with any PHI. During the study it will be stored in an encrypted password protected research-dedicated computer.

Overall Structure of the Study Team

The primary investigator (Crane) will oversee the experiments and laboratory personnel. The head technician [redacted] will recruit subjects, conduct experiments, and will consent most subjects. He will also do data analysis and help with day to day functions in the lab. Additionally, the lab includes a graduate student [redacted] who is involved in data analysis and works with the primary investigator in design of the experiments and publishing of the results. Technical projects in the lab will often be undertaken by undergraduate students under the supervision of the technician or primary investigator. Additionally there are periodically otolaryngology residents and medical students who do projects in the lab under the direction of the primary investigator.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

On the initial visit subjects will be explained the risks and benefits of participation and have any questions about their participation answered by an authorized member of the laboratory (The primary investigator, technician, or student who has completed the appropriate training). If they are agreeable to participating they will sign a consent form. They will then be explained their task in the experiment (e.g. orient a dial towards their perceived direction, report on if a visual and inertial stimulus are in the same direction). They will also be told that they should tell his if they feel uncomfortable at any point and the experiment can be halted at any time. New subjects will undergo some orientation to the equipment, which may include a practice task to make sure they understand the instructions. When possible, sessions will be limited to one hour per day to maintain alertness although there will be some longer sessions with paid breaks. Many of the proposed experiments will take place over multiple sessions with the order of session randomized between subjects when appropriate. The primary end point of the study will be to determine what the subject perceives with regard to direction of visual and inertial stimuli and if these are perceived to share a common causation. Several manipulations will be done which may influence perception including the characteristics of the stimuli and previous experience (e.g. adaptation). A secondary end point will be to measure the stability of any dizziness symptoms using the dizziness handicap inventory in subjects with vestibular pathology.

4.2. Study Design

4.2.a. Narrative Study Description

Human Subjects: Dr. Crane is a primary investigator of an institutional review board (IRB) approved protocol with access to a database of about 500 screened individuals in the University of Rochester human subject core. Standard screening includes visual acuity, vestibular testing, audiometry, medical history, any medications, prior dizziness or balance symptoms, and migraine history. Additional clinical vestibular tests include rotatory chair, posturography, and vestibular evoked myopotentials (VEMP). There are about 30 normal controls who regularly participate in our laboratory. Subjects represent a cross section of the [redacted] population with both genders, ages 13 to 89, and all races and ethnicities. We will look for potential effects of age and gender in our analysis. A wide age range of subjects is relevant to vestibular pathology. Our IRB approval excludes non-English speakers, children <13, and elderly >89. We do not plan to enroll children <13 because vertigo is rare in young children. Individuals >89 are excluded because multiple medical comorbidities have potential to confound results. The IRB approval allows recruitment of 150 additional subjects, which could be expanded if needed.

Patients with relevant conditions are available to participate. We currently have about 20 patients with unilateral vestibular function of various etiologies (e.g. surgical lesions, and Meniere's disease treated with gentamicin) who are willing to participate. In addition, about 30 patients per year have vestibular lesions related to acoustic neuromas and their treatment, vestibular neuritis, or treatment of Meniere's disease at the University of Rochester. Historically half these patients are willing to participate in research. Patients with relevant clinical pathology have been recruited from Dr. Crane's clinic and additional patients will be recruited on an ongoing basis during the project. For patients with peripheral vestibular hypofunction the lesion will be confirmed with ice-water caloric irrigation, VEMP, and video head impulse testing.

Risks to subjects are minimal. Subjects who choose to participate will do so only after informed consent. Subjects will be paid $15/hr plus expenses related to their participation such as parking and travel. This has been adequate to recruit subjects, but future payments can be amended upward if necessary.

Subject Training. Naive subjects recruited from the community will be used although often subjects will have participated in prior studies. Prior to each experiment, the task and range of responses will be explained in layman's terms using the same language for each subject. Large, unambiguous stimuli similar to those in the experiment will be delivered prior to any data collection to test the apparatus for comfort and ensure the task is clear. Feedback will not be given during or after the experiment.

Data Collection. The laboratory is set up to use multiple methods to investigate the relationship between stimuli and perception.

Forced choice methods: The current laboratory is set up to use a number of psychometric techniques including N-down/1-up staircase with a fixed step size, the method of constant stimuli, and variable step size procedures. When feasible, trial blocks that use a staircase include multiple interleaved staircases to limit the potential for subjects to make predictions based on prior experience. This will be primarily used in Aims II and III to report perception as left or right of straight ahead.

Heading estimation methods: Although forced choice methods are adequate for measuring discrimination (e.g. left vs. right) they do not allow measurement of estimates. For heading estimation, a method has been previously published in the current laboratory in which subjects orient a mechanical dial towards the perceived heading. Because the dial can rotate continuously without limits it avoids many of the issues of magnitude estimation techniques. It is still subject to potential haptic and cognitive influences, but previously published control experiments suggest such influences are secondary. Results using this method yielded results similar to heading estimates measured by others using an

independent technique. Additionally, we are able to use a technique in which subjects report the if two stimuli have a perception of unity (i.e. if the visual and inertial stimuli are consistent with motion through a fixed environment) and the direction of one of these stimuli using a dial similar to what has been previous described for determining integration vs. segregation of visual and auditory stimuli. We found it was confusing and problematic for subjects to report both visual and inertial heading direction in the same trial block but have done well having them report visual and inertial direction in separate trial blocks.

Aim I: Causal Inference (CI) for visual and inertial headings. 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. Although we now have significant knowledge of how visual and inertial headings are integrated using statistically optimal methods, relatively little is known about how it is determined if visual and inertial motion should be interpreted as having common causation and integrated or perceived as separate and segregated. Early data suggests that integration can occur with large differences between visual and inertial headings. Preliminary data suggests there is a wide range where visual and inertial headings influence each other such that the perceived offset between them is smaller than the actual offset. There is a smaller range where they are actually perceived as being the same.

Experiment IA: Determination of CI using high reliability synchronized stimuli. Rationale: Very little is published on CI using visual and inertial stimuli. Previous work in this area has used only limited ranges of headings, has only asked about combined perception or just one sensory modality, and not always asked subjects if they perceive stimuli as the same or different. The initial experiment will determine normal responses. Hypothesis: There will be a narrow range where visual and inertial headings are perceived as similar, over a much wider range they will influence each other. Stimuli and Task: Subjects will experience a paired translation visual and inertial translation such that they move 15 cm in 2s or the visual equivalent of this. The direction of the visual and inertial translation will be randomized such that there are 12 possible directions of each (the full 360 deg range in 30 deg increments), and each combination of visual and inertial stimulus directions will be presented in a trial block (144 total stimuli). After each stimulus delivery subjects will be asked if the two stimuli are the same (e.g. consistent with visual motion through a fixed environment) or not. They will also be asked to use a dial to report the perceived direction of one of the stimulus modalities (visual or inertial). In alternate trial blocks they will be asked to report the other stimulus modality. These two trial blocks will be repeated three times each so that multiple estimates of heading direction and precision can be determined. This will result in 6 reports of stimuli agreement and 3 reports each for visual and inertial heading estimates per subject for each of the 144 combinations. Outcomes and Interpretation: Preliminary data has been collected in 3 subjects to demonstrate the feasibility of the technique. Each subject repeated the trial block 6 times: In half the blocks they reported inertial heading and in the other half they reported visual heading. In every trial they reported if visual and inertial were the same or different. With 0 deg offset subjects reported headings were similar in 64% of trials, this fell to 46% with a 30 deg offset, 14% and a 60° offset, and <4% for larger offsets . In all subjects inertial headings were biased towards the visual heading with offsets of 30-120 deg. Thus, visual motion influences inertial heading perception even when headings are displaced beyond the range in which they are perceived to have common causation. In one subject visual heading was biased towards inertial over a similar range. This preliminary data strongly suggests that for this task, stimuli can influence the perception of each other even when common causation is absent, making heading perception different from other forms of multisensory integration. Power Analysis: A significant result was shown with the 3 subjects tested, although we recognize there maybe be individual variation and more subtle effects that will require more subjects to define. We anticipate focusing on about 10 subjects this a similar population size to other studies of this type and should allow us to determine normal responses for the population as well as determining if the sample has significant outliers. Potential Pitfalls: By choosing to cover the full 360 deg range of headings uniformly the gaps between headings tested are large (30 deg). The preliminary data indicates this is likely to be an appropriate spacing but it is possible some subjects will have relatively narrow tuning that won't adequately sample headings close to each other. It is also possible the chosen spacings influence subject's responses so they could deduce that relatively few headings are similar. We plan additional experiments in which the full range of inertial headings is tested at 30 deg increments but visual headings close to those aligned with the inertial heading are more tightly sampled while still covering the full range (e.g. relative offsets of 180, 90, 45, 22, 11, 6, and 0). The parameters of these experiments could be changed depending on what is found.

Experiment IB: Effects of stimulus parameters on CI. Rationale: In addition to being in a compatible direction, CI likely requires that visual and inertial stimuli have compatible timing and motion profiles. The size of the visual stimulus also likely plays a role as motion in the peripheral vision is more likely to be interpreted as self-motion. It has previously been shown that stimuli of different motion profiles can be integrated although only a small range of headings was tested and the limits of integration are unclear. Duration of stimuli also likely has some effect, with more reliance on vision for longer duration stimuli. Determining the parameters at which stimuli are similar enough to be perceived as common causation is import understanding simulator sickness and motion sickness. Hypothesis: Visual and inertial headings will have to be closely timed and have a similar profile, and visual stimuli will have to involve peripheral vision to be perceived as having common causation, with longer duration stimuli larger differences may be acceptable. Stimuli and Task: As with experiment IA, subjects will experience visual and inertial stimuli in trial blocks containing combinations of both. Starting parameters will be to look at 15 cm of translation over 2s. Timing between the stimuli will initially be tested in 50 ms offset increments up to 200 ms with the effects of the visual stimulus being first or second explored. Preliminary data (not shown) indicate a high degree of sensory segregation at 200 ms, but the limits and effects of smaller offsets are unknown. We also plan to do the experiment with a constant velocity visual

stimulus as well as modifying the peak velocity of the visual stimulus so it is inconsistent with the inertial stimulus. The visual field will be tested at 90 deg (exp 1A), 45 deg, and 20 deg. These angles may be adjusted based on the findings. The protocol for these experiments will be similar to experiment IA, which will essentially serve as the control condition for these experiments. Outcomes and Interpretation: There are two related outcome measures that will be determined - if subjects consider the stimuli the same or different and how far apart they are perceived. Power Analysis: We anticipate focusing on about 10 subjects this a similar population size to other studies of this type and should allow us to determine normal for the population as well as get a feeling if there are significant outliers. Individual variation is expected and has been noticed in previous studies of visual-inertial heading perception when individual results are reported. Potential Pitfalls: How stimuli are perceived, likely depends on the previous experience and subject expectations (i.e. Bayesian priors). Part of the reason the full range of stimuli will be used is so that subjects won't have expectations that stimuli are limited to one direction. Continued experience with a stimulus condition (e.g. a temporal offset of 200 ms) might cause subjects to perceive these stimuli to be associated over time. We plan to bring in naïve subjects with each series of experiments to test for this and also vary the order conditions are tested within the series.

Experiment IC: Effects of vestibular lesions on CI. Rationale: It is known that unilateral loss of vestibular function influences heading perception. Furthermore, visual stimulus reliability influences multisensory integration. Attempts to modify the inertial stimulus reliability using vibration has been shown and has demonstrated the vestibular cue can be weighed great than Bayesian predictions based on reliability. It is unclear that adding vibration is more than just a distractor, and a unilateral lesion is a physiologically and clinically relevant mechanism of decreased vestibular reliability. Studying visual-inertial integration in subjects with chronic unilateral lesions will give valuable insight in this area. Hypothesis: Inertial heading perception will be more deviated towards visual headings with a greater difference in heading direction being perceived as having common causation. Stimuli and Task: Will be similar to experiments IA and IB to facilitate direct comparison with results in normal controls. The subjects will be recruited from the otolaryngology clinics at the University of Rochester. Subjects with unilateral lesions due to labyrinthectomy for removal of benign tumors such as acoustic neuromas will be included. Some of these subjects are already involved in experiments in the lab, and more will be recruited during the study period. Outcomes and Interpretation: As with experiments IA and IB we will determine if stimuli the same or different and how far apart they are perceived. Unlike normal subjects we anticipate that this behavior might change as these subjects recover and will also consider that performance may be predicted by standard clinical tests such as vestibulo-ocular reflex function as measured with the video head impulse test and clinical measures such as the dizziness handicap inventory (DHI). Power Analysis: We anticipate these subjects may have more variation due to clinical factors related to the underlying nature of human unilateral lesions. However, for a human disease population, those with unilateral vestibular lesions are relatively homogeneous. Ten subjects will likely be sufficient to demonstrate the differences relative to a control population. Potential Pitfalls: These subjects are more difficult to recruit which means the experiments will need to be done over a longer period of time. The nature of human vestibular lesions (e.g. slow growing tumors) can make difficult to know the effective duration of the lesion but use of chronic lesions will decrease this effect. The method of compensation and effects on heading integration may not be uniform across subjects which itself would be an interesting finding.

F7: Aim II: Adaptation of heading perception. An important feature of neural systems is plasticity, and this is especially important for visual motion perception. Plasticity is also an important mechanism of the VOR. It is unclear how plasticity in vestibular heading perception occurs, although there have been some studies focused on rotation heading adaptation has not been studied. Rationale: Although, adaptation has been studied in many neural systems, heading perception has some interesting qualities which make it potentially unique. One interesting finding is that with gaze shifts cause shifts in visual heading perception but not inertial heading perception. These types of gaze shifts occur regularly during daily behavior in multiple directions, which may be the reason this does not lead to adaptation. Furthermore, misalignment of visual-inertial motion is a factor in motion sickness and simulator sickness. Understanding how to adapt visual or inertial heading perception has clinical and scientific relevance.

Experiment IIA: Heading perception adaptation using offset visual and inertial headings. Hypothesis: Experience with visual and inertial headings that are systematically offset from each other will adapt inertial heading perception and heading association. Stimuli and Task: Adaptation will occur while subjects will do a task in which they are asked to report if headings are right or left of straight ahead. During this task, the visual and inertial headings will be offset from each other in such a way that the offset is not likely to be noticed (e.g. visual will be 20 deg to the right of the inertial stimulus) and this offset will not be known to the subject. Although the subject will be asked report their heading, this is used mainly as an attention task. The analyzed data will be the baseline perception (measured prior to adaptation) and a task afterwards to measure the effect of adaptation. Multiple variations on this experiment are planned with regard to which sensory modality is measured after adaptation (visual or inertial), range of stimuli used during adaptation and testing (e.g. does adaptation induced over a narrow range of stimuli extends to a wider range if testing afterwards), and direction of adaptation (left or right). Two methods of measuring adaptation will be tested: Using a forced choice task (e.g. left or right of midline) will be the main method of assessing adaptation although, estimation task (e.g. point in the direction of perceived motion) will be used in a subset of experiments to test the range of adaptation beyond straight ahead, or a combination of such as that described in exp. I, where subjects are asked to report if the visual and inertial stimuli are the same and the relative direction of one of them. Outcomes and Interpretation: There are two related outcome measures that will be determined - how visual heading perception is influenced, and how inertial perception is influenced. Using some variations on the experiment we hope to define the range of headings in which adaptation occurs as related to the range of angles that are adapted (e.g. does adapting angles near straight ahead influence

the full range of headings). Power Analysis: We anticipate focusing on 15 normal subjects, and plan to use subjects who potentially can participate for a longer period of time so performance across sessions can be explored. We have demonstrated robust adaptation in some subjects using this technique although significant variation between individuals is expected. Potential Pitfalls: There will likely be some variation between individuals with some task variations that induce adaptation in some subjects but not others. Adaptation may be limited to the range of headings adapted, which will be tested and the method can be modified to use as wide of range of headings as needed.

Experiment IIB: Heading adaptation using rotational velocity offset in virtual reality environment. Hypothesis: Exposure to a rotating environment will shift heading perception towards the direction of implied inertial rotation. Stimuli and Task: Subjects will be exposed to a virtual reality environment consisting of a rotating star field with decreased coherence (i.e. stars disappear and are regenerated at a random new location) to decrease use of landmarks. To encourage head rotation subjects will be encouraged to turn their head look for objects (e.g. aliens) in the virtual environment. We have found that after a minute or two rotations of 40 deg/s are not perceived by subjects and this type of stimulus induces robust adaptation of inertial heading perception. Afterwards subjects will have visual and inertial heading perception tested using methods similar to exp. IIA. In addition, we plan to measure thresholds of potential biases in inertial rotation perception before and after adaptation. Methods for doing this have previously been described in the current laboratory. Outcomes and Interpretation: Similar to IIA, outcome measures that will be determined - how visual heading perception is influenced, how inertial perception is influenced, and the range of headings that are adapted. In addition, we will look at potential effects of rotation perception before and after testing. Power Analysis: We plan to focus on 15 subjects and will try to use some of the same subjects included in IIA. Potential Pitfalls: Rotation will be more likely induce motion sickness symptoms in some subjects than previous protocols, although this has not been a major issue in collecting the preliminary data in about 10 subjects. Adaptation may also depend to some degree on how much subjects move during the trial and their attention to the ask. Techniques could be used to standardize this such as requiring a minimum amount of motion (or minimum velocity) before the search object appears.

Aim III: Long term heading adaptation. There is growing evidence that errors of heading perception are clinically significant. Vestibular and balance symptoms are the primary factor determining quality of life in vestibular schwannoma patients. Heading perception and navigation are known to be impacted by unilateral vestibular lesions as well as central vestibular lesions. After an acute vestibular lesion, it is common to have a perception of rotation towards the intact side, but this perception normalizes quickly even though asymmetry in the VOR persists presumably due to central compensation.

Experiment IIIA: Characterization of heading bias in subjects with unilateral lesions. Rationale: After unilateral vestibular lesions patients often perceive rotatory vertigo towards the intact side which unlike vestibulo-ocular reflex asymmetries, resolves after compensation. However, even after rotation is no longer perceived, heading bias is common and is such that straight forward motion is perceived to be towards the side of their lesions. Unlike rotatory vertigo, this heading bias does not appear to be something that recovers spontaneously with time or convention vestibular rehabilitation. Initially this bias is masked by a compelling sensation of rotation, and it is not clear how it develops or how stable it is. It is also unclear if it is related to unilateral loss of otolith function or if it is an effect induced by a prolonged sense of rotation, and may be a pathological adaptation. Hypothesis: Heading bias occurs once rotatory vertigo subsides. This may be related to asymmetric otolith function vs central rotation compensation. Stimuli and Task: Subjects with unilateral vestibular hypofunction will be recruited, preference will be to recruit acute patients (e.g. after acoustic neuroma surgery, vestibular neuritis, and Meniere's disease recently treated with gentamicin). Subjects will undergo psychometric testing to measure heading bias (similar to healthy controls, Fig. 3A), and measure the bias and thresholds of yaw rotation and sway translation as previously done in the current laboratory. These responses will be measured weekly for the first month, then once per month for 6 months, and then at 9 months, and 1 year. These measures will also be correlated with video head impulse testing, calorics, and VEMP which are routine clinical tests in these individuals as well as symptoms measured using the DHI. Outcomes and Interpretation: Bias and thresholds will be measured using established curve fitting Initially, after an acute loss subjects will likely perceive spinning towards their intact ear. Preliminary results indicate the heading is acutely deviated towards the intact side due to the perception of rotation. Likewise, the yaw rotation perception will be strongly biased while sway translation may be more balanced. Over time the pathological rotation perception will decrease as the vertigo subsides with natural adaptation. Observing the pattern of biases during recover will be helpful in determining the origin of the heading deviation that is observed after chronic lesions. If this is due to otolith asymmetry it should be manifest with a bias or asymmetric threshold in perception of sway translation. If it is due to exposure and adaptation to rotatory vertigo, sway translation asymmetry should be minimal. We will also examine the stability of these asymmetries over time. Power Analysis: We anticipate there will be variation between subjects due to the nature of human lesions, the lesion may not have occurred at a single time point (e.g. with a growing tumor that is eventually removed), subject's experience outside the laboratory will be varied, there will be effects of age, and other factors which may contribute to variation between subjects. However, in the preliminary data all subjects with unilateral lesions develop heading deviation although the cause and time course of this may not always be the same. Previous studies of this type have looked at 30 subjects with unilateral lesions, but due to the robustness of preliminary responses seen it is anticipated that 20 or fewer subjects will be enough. Potential Pitfalls: Patients seen at the University of Rochester with unilateral lesions often come from a long distance which can make it difficult to test them serially. Some, that enroll may not be able to come to all the visits or may be lost over time. The dropout rate is anticipated to be similar to established clinical trials at about 50%. Thus, there will be some missing data. As previously mentioned, the nature of lesions and experience after the lesions will vary between subjects.

Experiment IIIB: Using adaptation to remove heading bias in subjects with stable unilateral vestibular lesions. Rationale: Heading adaptation is possible, but in normal subjects is likely to be transient due to experience with aligned visual and inertial stimuli during ordinary activities outside the adaptation sessions. Longer term adaptation may be possible in subjects who have an asymmetry in the otolith system due to vestibular loss. If this can be done it could form the basis of a future rehabilitation tool. Hypothesis: Heading bias is common in individuals with unilateral vestibular hypofunction. Long term correction of this heading bias maybe possible. Stimuli and Task: Subjects with unilateral vestibular hypofunction will be recruited (e.g. those with transtympanic gentamicin treatment of Meniere's disease or those with vestibular schwannomas). Only individuals who have had a unilateral lesion for at least a year will be included, these will likely include some subjects who completed exp IIIA. Subjects will undergo standard clinical testing to establish the nature of their lesion including calorics, VEMP, video head impulse testing and DHI to measure symptom severity. Each testing session will include heading perception task based on forced choices (left vs. right of midline) using a staircase to focus stimuli near the point of subjective equality. This will be fit with a cumulative distribution function to determine the bias in their perception of heading. A similar task will also be used to determine biases in rotation and sway translation perception during the same visit. These subjects will also complete the dizziness handicap inventory (DHI) at each visit to gauge their symptoms and insure that the experimental intervention is not associated with worsening symptoms as a safety factor. Both heading offset adaptation (exp IIA) and rotational adaptation (exp IIB) tasks previously proposed in aim II will be used but not at the same time in the same individuals so both tasks can be assessed independently. The adaptation task used will likely depend on the time of enrollment with early subjects doing the rotation task and later subjects doing the heading offset task. Both tasks have potential advantages. The rotation task does not require a HMP so it would be more practical as a future clinical intervention. However, rotation may be more likely to cause discomfort in this population. Heading adaptation using offsets in visual inertial headings is more equipment intensive as it uses the HMP in the current, but potentially could be adapted to virtual reality headsets. Subjects will always be adapted in the direction that will eliminate their heading bias. Adaptation sessions will be once per week with baseline measurements of both visual and inertial heading perception before each session. Preliminary data demonstrate all 3 subjects had adaptation during the first session to nearly eliminate their bias. The residual bias was reduced at the start of the session a week later in 2 of 3 subjects. The amount of sessions needed may vary across subjects based on tolerance and the amount of adaptation observed. If a subject is found to no longer have an inertial bias or the bias has reversed direction further adaptation will not be performed but the subject will continue with subsequent sessions to assess the stability of their heading perception. Outcomes and Interpretation: These experiments will determine if durable adaptation of heading can occur with two methods. Although the main goal is to adapt inertial perception, it is possible that visual heading perception may be impacted and this will be monitored. We will also assess if this adaptation can be performed safely without causing increased dizziness symptoms as measured with the DHI. Power Analysis: We anticipate being able to enroll about one new subject with chronic unilateral vestibular loss per month, in addition to testing about ten patients who are known to us and willing to participate. The effect is likely to be most robust in subjects will heading deviations >10 deg so these individuals will be preferred. The heading bias in chronic unilateral vestibular patients is a robust effect which is consistent in the 5 subjects already tested. The strength of the adaptation and its long-term effect on symptoms are unknown. It is likely that an effect that cannot be demonstrated in 20 patients is not clinically significant. Potential Pitfalls: In human subjects the nature of the lesion will be unclear in some subjects because of clinical attempts to preserve vestibular function when possible, and when not possible (some tumor resections) other structures such as the brain stem may not be completely normal. It is possible the adaptation may worsen symptoms which would make it less feasible, but parameters could be adjusted (e.g. duration of sessions, speed of visual rotation) to improve feasibility. This this is an important clinical problem, so even if the strategy is not successful it is worth taking a risk to investigate.

4.2.b. Primary Purpose: Basic Science

4.2.c. Interventions

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Heading direction adaptation	Will adapt subject's perceived heading direction using exposure to visual environments that include rotation and situations where visual and inertial heading direction are systematically offset.

4.2.d. Study Phase: Early Phase 1 (or Phase 0)

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model: Single Group

4.2.f. Masking ○ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation Non-randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	Heading Perception	Through out funding period	Heading perception will be measured using two alternative forced choice and magnitude estimation procedures.
Secondary	Dizziness Handicap Inventory (DHI)	Through out funding period	The (DHI) will be measured in subjects with unilateral vestibular hypo function to ensure symptoms are not worsening.

4.4. Statistical Design and Power Crane_Statistical_design2.pdf

4.5. Subject Participation Duration Will vary depending on the experiment. Some subjects can participate for multiple years if they desire.

4.6. Will the study use an FDA-regulated intervention? ○ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan Crane_Dissemination_plan.pdf

Statistical Design and Power

Perception will be determined in two ways: By collecting a forced choice response (e.g. right vs. left) or using continuous data such as the angle of a perceived heading reported using a dial. In some experiments both methods will be used. **Discrete responses:** Forced choice data will be analyzed by fitting a cumulative Gaussian function to these data using a Monte Carlo maximum-likelihood criteria which allows confidence intervals to be determined. A lapse rate of ≤ 5% will be permitted by the fitting algorithm. This involves resampling and fitting data points from each subject 2,000 times so that multiple estimates of the mean are generated, and 95% confidence intervals determined. This technique can be applied independent of the staircase used to collect the responses. A modification of this technique will be used to determine if the sets of responses from different test conditions are significantly different (e.g. before and after adaptation). This is done by determining a set of 2,000 means using random resampling of one set of responses and comparing these with means calculated from another set. If the means from one data set are always lower or higher than the other then the p-value is <2 x (1/2,000) or $p < 0.001$. If the means of the two datasets overlap then an exact p-value can be calculated using $p = 2*n/2{,}000$ where n is the number of fits where the relationship between the means is the less common situation. It has previously been demonstrated in the current laboratory that $p \leq 0.01$ is a conservative criterion for significance using this method. This technique has the advantage that it can be used to determine significance in individual subjects (as would be need for a clinical test) as well as from data combined across subjects. **Dial responses:** Heading estimates will be collected as an exact angle reported by subjects using a freely rotating dial. The laboratory has developed an efficient technique for analyzing such responses. This method involves choosing a reference heading and fitting a psychometric function from the responses collected for stimuli within ±90°. Classifying the fraction of responses that are right or left of the reference and fitting them with a cumulative distribution function. This technique allows the response precision to be determined even when each direction is only presented once. Continuous responses can be analyzed using established general methods such as ANOVA and T-test. We will repeat the same trial block at least 3 times in each subject so that the precision of the responses can be assessed.

Using this psychometric curve fitting methods, we are frequently able to determine performance was significantly different between two tasks for an individual subject. However, it is understood that a single subject is not always representative of a population and the amount of variation in a population can be considerable.

This is a basic science study in which we measure perception of visual and inertial heading stimuli. Several effects will be examined including the effect of stimulus parameters (e.g. offset, reliability, timing) as well as effects of previous experience and adaptation on these parameters. We have some preliminary data demonstrating robust effects, but there will be some variation between subjects and the novelty of the experimental paradigm makes it difficult to know the exact number of subjects needed. With all the proposed experiments it will be possible to change the number of subjects recruited as data is collected but we have provided our best estimates. In all the experiments we plan to look at effects of sex as a biological variable, although sex is not anticipated to have a significant effect and include enough subjects to ensure scientific rigor and reproducibility. We also anticipate there will be effects of age and want to include subjects over an appropriate range.

Experiment IA: Causal Inference (CI) will be studied in normal controls. Preliminary data indicates that heading biases of about 15° are present even when there is no perception of common causation when averaged across heading angles. Within each subject the standard deviation of reported headings is about 20°. We would like to be able to look for significant effects for single heading angles and capture potential outliers in the normal population. Thus, we plan to include 20 subjects. Using a sample size of 20 subjects, a standard deviation of 20° for each subject, an average bias of 15°, using a one-tailed test (it is not expected that the bias would occur in the opposite direction, and this has never been observed), and alpha confidence level of 5%, this would give us a statistical power of 96%. Because we are repeating the test multiple times in each subject, and the responses will be similar between test the actual power will be greater.

Experiment IB: This is similar to Experiment IA, except some of the parameters of testing will be varied: Visual field size, timing, and duration. These experiments will include subjects from exp 1A if they are available. Because we hope to compare results within the same subjects, we hope to minimize effect variation between individuals. The effect sizes are unknown, but will likely be between no effect and the effect seen in IA. We anticipate a similar sample size to exp IA.

Experiment IC: This essentially the same experiment as IA but in subjects with unilateral lesions. We expect a similar sample size of 20 subjects will be adequate.

Experiment IIA: Heading adaptation using offset visual and inertial headings. The preliminary data demonstrates the adaptation is about 16° with a sigma of 11°. In the preliminary data we were able a significant effect in an individual subject. Power calculation assuming a one-tail test, alpha error level of 5%, and a sample size of five subjects gives 97.3% statistical power. We plan to include about 15 subjects so that we can compare effects of age and gender within the normal population. Gender is not expected to have an effect, and adaptation may not be as robust in older subjects.

Experiment IIB: Heading adaptation using a rotating virtual environment. Preliminary data demonstrates a 12° shift in mean and sigma of 6°, with the ability to demonstrate a significant effect in a single subject. Thus, although the shift in heading was a smaller shift than seen with exp IIA, subject responses were tighter. Using the assumption of a one-tail test, alpha of 5%, and a sample size of five subjects the statistical power is 99.8%. Again, we plan to include about 15 subjects, with some subjects from exp IIA so that effects of age and gender in the population can be determined.

Experiment IIIA: Characterization of heading bias in subjects with unilateral lesions. Preliminary results in five subjects demonstrated heading biases of 4-13° in patients with chronic lesions. Thus, a mean ± standard deviation of 7±4. This was already a significant heading deviation for the 5 subjects in the preliminary sample. However, this experiment looks to see how this develops over time which will likely demonstrate variation between subjects, which is not currently known but there is likely to be variation. We plan to include about 20 subjects with some likely dropping out before being followed a year.

Experiment IIIB: Chronic heading adaptation in subjects with unilateral vestibular lesions. Acute adaptation is expected to be similar to normal controls in exp IIA & B. Preliminary data indicates that in two out of three individuals some of this acute adaptation was still apparent after a week. If a similar long-term adaptation is possible a small study population (<10 subjects) will likely yield significant results. However, the protocol for best inducing long term adaptation is not yet know and will depend on earlier experiments. Preliminary data also indicates no change in dizziness handicap index (DHI) in three subjects. We plan to examine possible variation in performance based on age, gender, and type vestibular lesion which will require a larger population, and we anticipate about 20 subjects over the course of the study.

Dissemination plan

If funded the study will be registered at ClinicalTrials.gov prior to starting data collection

This is a basic science study, and primary method of disseminating the data will be through publication in peer reviewed journals. During the previous funding period papers were published in the *Journal of Neurophysiology*, *Otology and Neurotology*, *Experimental Brain Research*, and the open access journal *PLoS One*. We anticipate publishing in these or similar journals in the future.

The findings with also be presented at national meetings including the Association for Research in Otolaryngology, the Society for Neuroscience, the American Neurotology Association, and the American Academy for Otolaryngology. In addition, some of the results may be discussed with more patient centered groups such as the Acoustic Neuroma Society.

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

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Resource Sharing Plan

The current proposal does not use model organisms or genomic data. Although, a data sharing plan is not technically needed since the direct costs do not exceed [redacted] per year we do plan to continue to share data with any interested parties. The primary method of data sharing will publishing the processed data in peer reviewed journals. Raw data (de-identified to protect human subject privacy) has been provided to interested parties (for instance those interested in developing or testing models) in the past and we anticipate this will continue in the future. Data sharing will be through our institutional file sharing website [redacted]