HoverBoard

Date: Thursday, October 10, 2019 12:51:09 PM Print Close

View: SF: Basic Information

Basic Information

1. *** Select research team:**
   Fetz

2. *** Title of protocol:**
   VNS and neuroplasticity

3. *** Short title:**
   2326-09: VNS and neuroplasticity

4. *** Summary of research:**
   The goal of the proposed work is to establish a protocol for noninvasive vagus nerve stimulation (VNS) that will augment targeted neuroplasticity and enhance cognitive performance in normal nonhuman primates (NHPs). Specifically, we propose to use left and/or right auricular branch VNS (abVNS) to promote targeted synaptic plasticity between specific areas of the cerebral cortex and to enhance behavioral performance in a cognitive task that involves these areas. This NHP study will be directly applicable to the development of noninvasive VNS technology that can be used to enhance neuroplasticity and cognitive performance in healthy adults.

5. *** Principal investigator:**
   Eberhard E Fetz

6. *** What is the intention of the animal protocol?**
   Experimental Research

View: SF: Experimental Research Protocol Addition

Experimental Research Protocol Addition

1. *** Will the protocol include breeding?**
   ○ Yes ● **No**

View: Custom SF: Protocol Team Members

Protocol Team Members

1. **Identify each additional person involved in the design, conduct, or reporting of the research:**

Name	Role	Involved in Animal Handling	Authorized To Order Animals	E-mail	Phone
[redacted]	Student/Volunteer	yes	no	[redacted]	
[redacted]	Graduate Student	yes	no	[redacted]	
[redacted]	Graduate Student	yes	yes	[redacted]	
[redacted]	Student/Volunteer	yes	yes	[redacted]	
Greg D Horwitz	Co-Investigator	yes	yes	ghorwitz@uw.edu	+1 206 616-0731
[redacted]	Student/Volunteer	yes	no	[redacted]	
[redacted]	Student/Volunteer	yes	no		
Samira Moorjani	Postdoctoral Fellow	yes	yes	moorjani@uw.edu	
Steve I Perlmutter	Co-Investigator	yes	yes	perl@uw.edu	+1 206 616-8520
Irene Rembado	Research Scientist	yes	yes	ireremba@uw.edu	
WaNPRC Research Support	Other	yes	no	wanprc@uw.edu	(206)543-0440
Robert Robinson	Research Scientist	yes	yes	roberr2@uw.edu	+1 206 221-0973
Lucia Shumaker	Research Scientist	yes	yes	lrshu@uw.edu	
Stavros Zanos	Co-Investigator	yes	yes	zanos@uw.edu	+1 206 553-9047

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2. **If veterinary care will be provided by individuals outside of DCM or WaNPRC, provide the name, credentials and contact information below:**
N/A

View: Custom SF: Funding Sources

Funding Sources

1. **Identify each organization supplying funding for the protocol:**

Funding Organization	eGC1 Number(s)

	Funding Organization	eGC1 Number(s)
View	Other	A117687

View: Custom SF: Scientific Aims

Scientific Aims

1. *** Scientific aims of the research:**

The goal of the proposed work is to establish a protocol for noninvasive vagus nerve stimulation (VNS) that will augment targeted neuroplasticity and enhance cognitive performance in normal nonhuman primates (NHPs). Specifically, we propose to use left auricular branch VNS or invasive left VNS to promote targeted synaptic plasticity between specific areas of the cerebral cortex and to enhance behavioral performance in a cognitive task that involves these areas. This NHP study will be directly applicable to the development of noninvasive VNS technology that can be used to enhance neuroplasticity and cognitive performance in healthy adults.

2. *** Using language understandable to non-scientists, describe the goals and significance of the protocol to humans, animals and science:**

The impact of this work will be three-fold. First, since this work will be conducted in the NHP, its results will be directly translatable to the human condition. Second, it will generate unique, never before obtained, data and insights into several key unexplored issues: the effects of VNS in different cortical areas and their timescales, the mechanisms and anatomical substrates of synaptic plasticity and the modulation of neuroplasticity by VNS. We expect this data to inspire further basic science research in neuromodulation, and to be directly applied to human trials, in a variety of disease conditions. Third, it will result in one or more noninvasive VNS protocols that are optimized both physiologically, with regards to augmenting targeted cortical plasticity, and behaviorally, with regards to augmenting sensory discrimination performance, with minimal side effects. These protocols can be directly tested in healthy adults for the purposes of cognitive enhancement. We estimate that this study will be implemented with a total (direct+indirect) cost of less than 1 million dollars and will be completed in fewer than 28 months from the time animals are acquired (table I).

3. *** Provide a statement to address the potential harm to the animals on this study (e.g., pain, distress, morbidity, mortality) relative to the benefits to be gained by performing the proposed work:**

This project aims at investigating mechanisms of cortical plasticity in non-human primates and at developing methods and techniques for inducing and controlling adaptive plasticity via stimulation of a peripheral nerve. The knowledge and technology generated by this project are vital for the development of neurorehabilitation treatments after stroke and brain injury. During this project, animals receive invasive brain and peripheral nerve implants. These invasive implants are used to record neural signals and to deliver electrical stimulation to the nervous system. The use of invasive implants is essential to our studies, as noninvasive techniques cannot reach an acceptable level of accuracy in recording from and stimulating the nervous system. We have had no indications that these implants, under normal circumstances, cause distress to the animal post-surgically or that they impair the animalâ€™s mobility, appetite, task performance and social engagement. These implants have been designed to be as minimally invasive as possible, given the goals of their use, and special care has been taken to avoid or minimize their contact with pain-sensing tissues and organs. Implantation procedures are performed under anesthesia and post-surgical analgesics are administered. The skin around some of the parts of these implants that are exposed (e.g. head chamber, halo) may, at times, show signs of inflammation. Daily cleaning of those skin sites, regular trimming of hair and topical administration of antibiotics are measures we take to reduce inflammation. In rare occasions, some of the indwelling implants become infected; in those cases, aggressive treatment with systemic antibiotics is administered by the vet staff. If the animal does not show signs of the infection resolving swiftly, and after consultation with the vet staff regarding the animals clinical condition, the implant is either removed or the animal is euthanized.

View: Custom SF: Experiments

Experiments

Note: If you will be administering cells, cell lines, sera or other biologicals to rodents, contact the Rodent Health Monitoring Program (RHMP, rhmp@uw.edu). Testing may be required prior to administration to rodents.

1. *** Define the experiments to be used in this protocol:**

Name	Species	USDA	Count	Count by Pain Category	Procedures	Husbandry Exception Types
VNS and neuroplasticity	NHP - Rhesus/Pigtail Macaques	yes	7	B: 0 C: 0 D: 7 E: 0		NHPs - Food treats, as outlined in the policy, are not acceptable for part or all of the study. NHPs - Standard social contact housing, as outlined in the policy, is not acceptable for part or all of the study.

2. **Will any single animal undergo more than one survival surgery? (include any animal that underwent surgery prior to use on this protocol)** ● **Yes** ○ No

3. *** Describe the order of and time interval between surgical procedures on a single animal:**

Animals on this project may undergo 3 or 4 surgeries (not including repairs), depending on if a "Halo" restraint device is used.

Surgery 1: Head stabilization implant ("Fetz: (8) Halo") combined with Vagus nerve implant - OPTIONAL -

Surgery 2: Skull surgery (brain implant). If the halo is used, the **remainder of the halo device is also implanted** ("Fetz: (8) Halo" option B).

Surgery 3: Vagus nerve implant and subcutaneous electrode.

Surgery 4: Forearm sensory nerve implant.

Minimal time between surgery 1 and surgery 2: 1 month

Minimal time between surgery 2 and surgery 3: 1 month

Minimal time between surgery 3 and surgery 4: 1 month

Repair surgery (after veterinary consultation): when required

A single repair surgery for each animal is included in the description of the multiple survival surgeries. Additional repair surgeries require IACUC approval, which will be requested through a significant change. This is in accordance with UW Guidelines of Non-human Primate Neuroscience Studies.

* Provide scientific justification for multiple survival surgical procedures on a single animal:

One of the reasons why multiple survival surgical procedures, rather than one, have to be performed on a single animal is the duration of these surgical procedures. Typically, a brain implant surgery lasts between 6-10 hours, a VN implant surgery between 4-6 hours, and a forearm sensory nerve implant surgery between 3-5 hours. Surgical operations that exceed 8-10 hours are potentially risky for the health of the animal because of the effects of anesthesia on the animal's physiology and because of increased physical and mental exertion of the surgeon, which predispose to surgical errors.

Another reason is that the lifetime of these implants is oftentimes limited, and could be shorter than the total duration of the experiment. For example, a VN or a peripheral nerve cuff implant may last for 1 year. If the cuff implant surgeries happen at the beginning of the experiment, the associated implants may be unusable by the time the experiment reaches the corresponding stages, which start past the 1-year mark.

One or more repair surgeries may be required in a given animal during the lifetime of this project. Implant repair surgeries are used to correct malfunction of an implant (failure, infection etc). Before any repair surgery, the research team will asked for a pre-surgical veterinary consultation. **A single repair surgery for each animal is included in the description of the multiple survival surgeries. Additional repair surgeries require IACUC approval, which will be requested through a significant change.**

* Specify how many animals will undergo multiple survival surgeries:

Seven (7) animals.

View: SF: Procedure Personnel Assignment

Procedure Personnel Assignment

1. * Select the team members who will be performing each procedure:

Procedure	Species	Is USDA Species	Team Members

Procedure	Species	Is USDA Species	Team Members
Behavioral Testing (with Food or Fluid Restriction): Fetz: VNS and neuroplasticity behavioral training and testing, ver. 3 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Euthanasia: Anesthetic Overdose, Pentobarbital or Pentobarbital Solution, ver. 1 (Standard)	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support

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Procedure	Species	Is USDA Species	Team Members
Implants: Fetz: Brain Electrodes, ver. 2 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Implants: Fetz: EOG Electrodes v2, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Implants: Fetz: Head Restraint, Recording Chamber and/or Electronics Housing v2, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Implants: Fetz: Nerve cuff implant at forearm peripheral nerves, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Implants: Fetz: Subcutaneous electrode implant for auricular branch VNS, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Implants: Fetz: Transcutaneous delivery of auricular branch VNS, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Implants: Fetz: Transcutaneous delivery of electrical stimulation at forearm nerves, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Implants: Fetz: Vagus nerve electrode cuff, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Non-Survival Surgery: Fetz: Perfusion, ver. 2 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter

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Procedure	Species	Is USDA Species	Team Members
Other: Fetz: A14229 Repair Surgery (2 & 3), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter [redacted]
Other: Fetz: A14229 Repair Surgery (4), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Other: Fetz: A16229 Repair Surgery (2), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Other: Fetz: A16230 Repair Surgery (2 & 3), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Other: Fetz: A16230 Repair Surgery (4), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Other: Fetz: A16230 Repair Surgery (5), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter

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Procedure	Species	Is USDA Species	Team Members
Other: Fetz: Primate Jackets/Shirts, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Other: Fetz: Sedated Implant Maintenace, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Physical Restraint: Fetz: Chair Restraint, ver. 1 (Team) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Substance Administration: Analgesia, WaNPRC Standard (at least 48 hours), ver. 1 (Standard) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support
Substance Administration: Anesthesia, General, WaNPRC Standard (v.2), ver. 1 (Standard) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support

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Procedure	Species	Is USDA Species	Team Members
Substance Administration: Anesthesia, Sedation/Injectable Anesthesia, WaNPRC Standard , ver. 1 (Standard) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Substance Administration: Anesthesia, Terminal, Pentobarbital or Pentobarbital Solution, ver. 2 (Standard)	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support

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Procedure	Species	Is USDA Species	Team Members
Substance Administration: Antibiotics, Prophylactic Surgical, WaNPRC Standard, Cephalosporins, ver. 1 (Standard)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Substance Administration: Fetz: Saccharin solution (0.1% w/v), v2, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani [redacted] Greg D Horwitz [redacted] Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]
Survival Surgery: Fetz: (2) Skull Surgery (v.3), ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support [redacted] Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker [redacted] Steve I Perlmutter [redacted]

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Procedure	Species	Is USDA Species	Team Members
Survival Surgery: Fetz: (4) Implantation of subcutaneous electrode for auricular branch VNS, ver. 1 (Team) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter
Survival Surgery: Fetz: (4) Nerve cuff implant at forearm peripheral nerve surgery (v3), ver. 1 (Team) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter

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Procedure	Species	Is USDA Species	Team Members
Survival Surgery: Fetz: (4) Vagus Nerve Cuff Electrode Implant, ver. 1 (Team) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Greg D Horwitz Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter
Survival Surgery: Fetz: (8) Halo Implant , ver. 1 (Team) [Archived]	NHP - Rhesus/Pigtail Macaques	yes	Samira Moorjani WaNPRC Research Support Eberhard E Fetz Irene Rembado Robert Robinson Stavros Zanos [redacted] Lucia Shumaker Steve I Perlmutter
Survival Surgery: Fetz: Repair Surgery, ver. 1 (Team)	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support Greg D Horwitz Lucia Shumaker Steve I Perlmutter

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Procedure	Species	Is USDA Species	Team Members
Tissue/Blood Collection: Blood collection, peripheral vein (Sedated), ver. 1 (Standard)	NHP - Rhesus/Pigtail Macaques	yes	WaNPRC Research Support Irene Rembado Stavros Zanos Lucia Shumaker Steve I Perlmutter

2. Team member training:

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First Name	Last Name	Training
[redacted]		

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	12/26/2017	12/26/2022
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	12/26/2017	12/31/2020
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	9/12/2018	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	1/17/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	3/30/2018	

No experience data to display

First Name	Last Name	Training
[redacted]		

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	12/31/2018	12/31/2023
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	1/14/2019	1/31/2022
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	6/28/2019	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	7/5/2019	

No experience data to display

[redacted]

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	5/11/2017	5/11/2022
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	6/11/2018	6/30/2021
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	1/8/2016	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	9/5/2014	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	9/10/2014	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	
WaNPRC Vivarium Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	

No experience data to display

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[redacted]

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	6/8/2018	6/8/2023
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	2/22/2019	2/28/2022
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	12/18/2017	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	7/29/2016	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	7/19/2016	

No experience data to display

Eberhard E Fetz

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	12/15/2014	12/15/2019
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	5/22/2019	5/31/2022

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Rat Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	10/3/2011	
Rat Online Course: Working with Rats at UW	Animal Handling	Online	Basic Course	Stage 1	11/14/2007	
Surgery Laboratory Part 1B - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Laboratory Part 2 - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	7/6/2016	7/6/2017
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	

Greg D **Horwitz**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	12/30/2016	12/30/2021
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	3/19/2018	3/31/2021
Sedation Certification, NHP - Waived	Procedure	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, NHP Major - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, NHP Minor - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	7/8/2016	7/8/2017
WaNPRC Vivarium Clearance	Orientation	In Person	Basic Course	Stage 1	1/6/2016	

No experience data to display

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Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
6th Floor Facility Orientation, Rodent Users	Orientation	In Person	Basic Course	Stage 1	7/9/2019	
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	10/14/2018	10/14/2023
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	5/14/2019	5/31/2022
Annual DCM Facility Access Training (Rodent)	General	Online	Basic Course	Stage 1	5/7/2019	5/31/2020
Mouse Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	5/14/2019	

No experience data to display

[redacted]

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	12/18/2017	12/18/2022
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	1/8/2018	1/31/2021
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	1/7/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	1/29/2018	

No experience data to display

Samira Moorjani

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	8/3/2016	8/3/2021
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	5/24/2017	5/31/2020
Annual DCM Facility Access Training (Rodent)	General	Online	Basic Course	Stage 1	8/28/2019	8/31/2020

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Cervical Dislocation, Mouse Anesthetized	Procedure	In Person	Basic Course	Stage 1	8/26/2011	
Foege Facility Orientation	Orientation	In Person	Basic Course	Stage 1	10/13/2011	
Mouse Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	8/26/2011	
Rat Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	5/19/2016	
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	2/18/2016	
Surgery Laboratory Part 1A	Surgery	In Person	Basic Course	Stage 1	6/22/2016	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	12/5/2014	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	12/17/2014	
T-Wing Facility Orientation	Orientation	In Person	Basic Course	Stage 1	8/30/2016	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	6/21/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	2/2/2018	
WaNPRC Vivarium Clearance	Orientation	In Person	Basic Course	Stage 1	2/2/2018	

Steve I **Perlmutter**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
6th Floor Facility Orientation, Rodent Users	Orientation	In Person	Basic Course	Stage 1	11/8/2011	
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	9/18/2019	9/18/2024
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	7/2/2018	7/31/2021

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Annual DCM Facility Access Training (Rodent)	General	Online	Basic Course	Stage 1	11/1/2015	11/30/2016
Brotman Facility Orientation, Rodent Users	Orientation	In Person	Basic Course	Stage 1	3/26/2009	
Foege Facility Orientation	Orientation	In Person	Basic Course	Stage 1	3/19/2009	
Mouse Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	7/5/2011	
Rat Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	7/12/2007	
Surgery Certification, NHP Major - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, NHP Minor - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, Rodent - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	8/9/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	7/8/2016	7/8/2017

Irene **Rembado**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	4/2/2018	4/2/2023
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	8/20/2019	8/31/2022
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	10/7/2016	

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Surgery Certification, NHP Major	Surgery	In Person	Basic Course	Stage 1	6/12/2019	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	5/3/2013	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	6/28/2013	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	11/9/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	
WaNPRC Vivarium Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	

WaNPRC **Research Support**

No training data to display

No experience data to display

Robert **Robinson**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
6th Floor Facility Orientation, Rodent Users	Orientation	In Person	Basic Course	Stage 1	11/5/2012	
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	4/13/2017	4/13/2022
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	6/27/2019	6/30/2022
Annual DCM Facility Access Training (Rodent)	General	Online	Basic Course	Stage 1	11/15/2018	11/30/2019
Brotman Facility Orientation, Rodent Users	Orientation	In Person	Basic Course	Stage 1	2/6/2014	
Foege Facility Orientation	Orientation	In Person	Basic Course	Stage 1	8/24/2009	

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Mouse Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	1/23/2015	
Rat Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	8/28/2009	
Sedation Certification, NHP - Waived	Procedure	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, Rodent	Surgery	In Person	Basic Course	Stage 1	7/9/2014	
Surgery Laboratory Part 1A - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	8/3/2012	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	8/7/2012	
T-Wing Facility Orientation	Orientation	In Person	Basic Course	Stage 1	1/6/2015	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	1/18/2018	

Lucia **Shumaker**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	7/12/2018	7/12/2023
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	8/23/2018	8/31/2021
Annual DCM Facility Access Training (Rodent)	General	Online	Basic Course	Stage 1	7/1/2019	7/31/2020
Mouse Hands-On Laboratory	Animal Handling	In Person	Basic Course	Stage 1	7/30/2018	
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	11/13/2018	

No experience data to display

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	11/2/2018	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	11/9/2018	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	9/14/2018	
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	9/21/2018	

Stavros **Zanos**

Course	Category	Source	Stage	Stage Number	Completion Date	Expiration Date
Animal Use Laws & Regulations	General	Online	Basic Course	Stage 1	6/26/2017	6/26/2022
Animal Use Medical Screening	General	Online	Basic Course	Stage 1	4/17/2018	4/30/2021
Sedation Certification, NHP	Procedure	In Person	Basic Course	Stage 1	10/18/2012	
Surgery Certification, NHP Major - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Certification, NHP Minor - Waived	Surgery	Other	Basic Course	Stage 1	1/1/1950	
Surgery Laboratory Part 1B	Surgery	In Person	Basic Course	Stage 1	6/15/2012	
Surgery Laboratory Part 2	Surgery	In Person	Basic Course	Stage 1	6/26/2012	
WaNPRC Necropsy Room Clearance	Orientation	In Person	Basic Course	Stage 1	8/2/2016	8/2/2017
WaNPRC Surgery Suite Clearance	Orientation	In Person	Basic Course	Stage 1	2/23/2018	
WaNPRC Vivarium Clearance	Orientation	In Person	Basic Course	Stage 1	2/23/2018	

No experience data to display

View: Custom SF: Animal Details

Animal Details

1. *** How are animals acquired?**
   Purchased

2. **Describe the acquisition for:**
   a. **Not purchasing through DCM or WaNPRC:**
      N/A

3. **Identification of individual animals (other than cage cards):**
   a. **Method(s) (e.g., ear punch/tag, tattoo, tagging/banding, radio collar, etc.) (Note: If method is implantation (e.g. PIT tag), create or select an Implant procedure to describe the details. If method is surgical (e.g., satellite tag), create or select Survival Surgery procedure to describe the details):**
      Tattoo

   b. **Will external identification be replaced if it falls off/out? If yes, describe the plan for replacement:**
      N/A

   c. **Will external identification be removed as part of the protocol (e.g., radio collars on field animals)? If yes, describe the plan for removal:**
      No.

4. **Identify strain/stock for rodents and genetically modified animals:**

Species	Is USDA Species	Strain	Genetically Modified Strain	Phenotype Description

There are no items to display

View: Custom SF: Animal Number Adjustments

Animal Number Adjustments

â€œAnimals Identified in Experimentsâ€ is the total number of animals per pain category listed in all experiments on this protocol. If more or fewer animals will be used on the protocol (see Help Text for examples), click Update to enter this new number in the corresponding â€œAdjusted Animal Countâ€ column. **Only input numeric values in this field; 0 is acceptable.**
If no adjustment is required, the values in the â€œAnimals Identified in Experimentsâ€ and â€œAdjusted Animal Countâ€ columns must match. Click Update in each Pain Category row to input the matching value.
For questions about adjusting animal numbers, contact OAW.

1. *** Click Update to adjust the number of animals to be used or produced for this protocol:**

	Species	USDA Covered Species	Pain Category	Animals Identified in Experiments	Adjusted Animal Count
View	NHP - Rhesus/Pigtail Macaques	yes	Pain Category B	0	0
View	NHP - Rhesus/Pigtail Macaques	yes	Pain Category C	0	0
View	NHP - Rhesus/Pigtail Macaques	yes	Pain Category D	7	7
View	NHP - Rhesus/Pigtail Macaques	yes	Pain Category E	0	0

2. If you adjusted the number of animals for this protocol, explain why:

N/A

3. If you will be using animals to train personnel or to practice procedures included in this protocol, describe below:

N/A

4. Supporting documents:

Document Name	Date Modified
There are no items to display	

View: Custom SF: Alternatives

Alternatives

Display Procedures that cause pain or distress:

- Survival Surgery: Fetz: (2) Skull Surgery (v.3), ver. 1 (Team)
- Survival Surgery: Fetz: (4) Implantation of subcutaneous electrode for auricular branch VNS, ver. 1 (Team) [Archived]
- Survival Surgery: Fetz: (4) Nerve cuff implant at forearm peripheral nerve surgery (v3), ver. 1 (Team) [Archived]
- Survival Surgery: Fetz: (4) Vagus Nerve Cuff Electrode Implant, ver. 1 (Team) [Archived]
- Survival Surgery: Fetz: (8) Halo Implant , ver. 1 (Team) [Archived]
- Other: Fetz: A14229 Repair Surgery (2 & 3), ver. 1 (Team)
- Other: Fetz: A14229 Repair Surgery (4), ver. 1 (Team)
- Other: Fetz: A16229 Repair Surgery (2), ver. 1 (Team)
- Other: Fetz: A16230 Repair Surgery (2 & 3), ver. 1 (Team)
- Other: Fetz: A16230 Repair Surgery (4), ver. 1 (Team)
- Other: Fetz: A16230 Repair Surgery (5), ver. 1 (Team)
- Implants: Fetz: Brain Electrodes, ver. 2 (Team)
- Implants: Fetz: EOG Electrodes v2, ver. 1 (Team)
- Implants: Fetz: Head Restraint, Recording Chamber and/or Electronics Housing v2, ver. 1 (Team)
- Non-Survival Surgery: Fetz: Perfusion, ver. 2 (Team)
- Survival Surgery: Fetz: Repair Surgery, ver. 1 (Team)
- Implants: Fetz: Vagus nerve electrode cuff, ver. 1 (Team)

1. **Date of alternative search for procedures causing pain or distress:**
   1/1/2017

2. **Databases searched (select more than one):**
   PubMed/Medline
   Other
   If other, provide databases searched:
   1) Health Sciences Library, University of Washington. Health Sciences, Libguides
   2) ISI Web of Knowledge
   3) Neuroscience Literature

3. **Describe the search strategy used:**

   1. (alternative OR "animal testing alternatives" OR "animal testing" OR "non- animal alternatives") AND (primate OR monkey OR macaque) AND neuroscience.

   2. ("animal testing alternatives" OR "non-animal alternatives" AND (primate OR monkey OR macaque) AND "intraspinal stimulation" OR "spinal stimulation"

   3. paralyzed (arm OR hand) recovery

   4. ("animal testing alternatives" OR "non-animal alternatives" AND (primate OR monkey OR macaque) AHD "R-BCI" OR "machine implant".

4. **Time period covered by search (for triennial reviews, the start date should be the date of your last approval):**
   Start Date:
   1/1/1981
   End Date:
   1/1/2017

5. **Briefly describe the results of your searches and why you can or cannot incorporate the findings. Or, if a literature search was not performed, describe the methods used to determine that alternatives are not available or feasible:**
   These experiments are designed to generate preclinical observations that will be used in a human subject study. In this regard, we found that the brains of mice, rats and even larger animals (like dogs or pigs) lack the functional and anatomical properties of the human brain and the human vagus nerve system. We found no alternative animal model to studying the brain and peripheral nerve processes that are pertinent to these experiments.

View: Custom SF: Refinement, Replacement and Reduction

Refinement, Replacement and Reduction

1. **Describe below how the three Râ€™s (refinement, replacement and reduction) have been employed on this project. Include alternatives that were considered for the procedures above**

that cause pain or distress:

* Refinement (use of methods to decrease animalsâ€™ sensitivity to pain)

Pain may be part of what animals are experiencing for a limited amount of time after each surgery. Appropriate analgesics are administered during that time. We don't have reasons to believe that any of the implants or procedures involved in the protocol are associated with significant pain sensation beyond that period.

* Replacement (include in vitro tests, use of less sentient animals)

The study concerns properties of neural systems mediating behaviors characteristic of the whole animal, and hence in vitro preparations are not adequate. Our goal is to understand how implantable brain-computer interfaces (BCI) and vagus nerve stimulation can be used to assist in the understanding of the effects of VNS on brain activity, motor function and brain plasticity. Species less sentient than monkeys are not good models for these studies, since their limbs and the movements that they make are too dissimilar from those of man.

* Reduction (use of fewer animals to attain statistical significance)

Two animals per experiment path is the minimum acceptable number of subjects in nonhuman primate neurophysiology research to derive useful information. Including only 1 animal in a research study does not allow us to investigate how reproducible the findings are, or assess the between-animal variability of our measurements.

2. **Describe the rationale for using animals and the appropriateness of the species proposed:**

Monkeys are essential subjects because of their ability to learn the motor behaviors required for study of voluntary limb movements. Their motor and cognitive systems are most similar to that of the human, so results should be directly applicable to mechanisms of clinical motor dysfunction and requirements for functional restoration. The macaque is the most widely studied animal for studies on control of voluntary limb movements, and thus there is a large body of information upon which these experiments will build from.

View: Custom SF: Housing and Use

Housing and Use

Housing and use outside of the vivarium is not allowed without strong scientific justification.

1. **Identify each location where animals will be housed:**

	Building	Room	Species	Justification for Housing Outside Vivarium
View	ARCF (Animal Research & Care Facility)	Vivarium ABSL2	NHP - Rhesus/Pigtail Macaques	
View	WaNPRC: I-Wing Vivarium	Vivarium ABSL2	NHP - Rhesus/Pigtail Macaques	

2. **Identify each location where animals will be used:**

	Building	Room	Use	Species	Justification for Use Outside Vivarium
View	WaNPRC: I-Wing Vivarium	Vivarium ABSL2	Surgery	NHP - Rhesus/Pigtail Macaques	
View	ARCF (Animal Research & Care Facility)	Vivarium ABSL2	Surgery	NHP - Rhesus/Pigtail Macaques	
View	WaNPRC: I-Wing Laboratory Spaces	I441	Behavioral testing, implant maintenance.	NHP - Rhesus/Pigtail Macaques	This location bears equipment (booths, amplifiers, stimulators etc) that is essential for this experiment, as well as supplies that are essential for implant maintenance; those are not available at the vivarium.
View	WaNPRC: I-Wing Laboratory Spaces	I553	Behavioral testing, implant maintenance.	NHP - Rhesus/Pigtail Macaques	This location bears equipment (booths, amplifiers, stimulators etc) that is essential for this experiment, as well as supplies that are essential for implant maintenance; those are not available at the vivarium.

View: Custom SF: Disposition

Disposition

1. **Disposition plans for the animals when this research is complete:**
(check all that apply)
Euthanasia

2. **If other, provide an animal disposition description:**
N/A

3. **If protocol involves fixing tissues, list agents (e.g., paraformaldehyde, formalin):**
Formaldehyde, glutaraldehyde for paraformaldehyde

View: SF: Supporting Documents

Supporting Documents

1. **Attach supporting files:**

Document Name	Date Modified
There are no items to display	

View: Custom: Create and Edit

1. *** Select the funding organization:**
   Other

   If Other was selected in question 1, provide Funding Organization:
   DARPA

2. *** All animal use projects must be reviewed for scientific merit prior to initiating animal use. Choose the required reviews for this project:**
   Has already been conducted and approved by a funding agency

3. **Provide name of the committee or the department reviewer** (Required if â€œHas been conducted by my department or school and has been found to be scientifically meritoriousâ€ was selected):
   Doug Weber, DARPA program officer

4. **eGC1 Number(s):**(assigned internally)
   A117687

View: Custom: Create and Edit

Experiments Appendix:

VNS and neuroplasticity

1. *** Experiment name:**
   VNS and neuroplasticity

2. *** Species:**
   NHP - Rhesus/Pigtail Macaques

3. **If other was selected, provide a species:**

4. **What is the scientific goal of this experiment:**
   The overall goal of our proposal is to determine, in NHPs, the optimal parameters of a noninvasive VNS protocol that promotes physiological neuroplasticity and augments behavioral performance in a sensory discrimination task. In order to realize that goal, we will:
   1) Develop a method for delivering noninvasive, left and/or right auricular branch VNS and invasive VNS in the NHP. The method for abVNS will involve chronic implantation of a subdermal stimulating electrode against the area of the auricle innervated by the left and/or right abVNS, or repeated placement of a gel-coated skin electrode directly on the skin aided by permanent skin marks. The method for iVNS will involve chronic implantation of a cuff electrode on the trunk of the left and/or right VN in the neck. When successfully developed, this method will allow the repeated, daily delivery of abVNS and/or iVNS in the behaving NHP, in a reliable and consistent manner.

iVNS and abVNS may be similar in the ways they affect brain function and plasticity, as there is histological evidence that they share much of the brain pathways they recruit; however, direct physiological evidence about their actions is lacking, in humans and animals. If they are shown to exert similar actions, abVNS may be used as a noninvasive alternative to iVNS in the treatment of epilepsy, depression and other indications of iVNS; in addition, abVNS, being noninvasive, may be used in normal human population for cognitive enhancement, a use for which an invasive implant would be hard to justify.

2) Compare abVNS and iVNS protocols with regard to cortical responses, changes in ongoing brain activity and cortical connectivity. We will characterize and quantify the evoked cortical responses and the changes in ongoing brain activity and cortical connectivity in several frontal cortical areas, elicited by different VNS protocols, both abVNS and iVNS. These measurements will allow us to rank different VNS protocols, and to directly compare abVNS and corresponding iVNS protocols, with regard to their cortical effects. The data collected will provide quantitative information of how VNS affects brain function and communication between cortical areas. It will provide a quantitative â€œmappingâ€ between abVNS and iVNS in terms of their effects on the brain and will allow us to use iVNS as a surrogate to abVNS in later experiments, in the case of technical issues with abVNS in the NHP. Finally, it will limit the range of VNS parameters that need to be tested in subsequent, more technically challenging, physiological and cognitive tests.

3) Rank abVNS and iVNS protocols with regards to their side effects (toxicity profile). We will characterize the type, frequency and severity of side effects of different protocols of abVNS and iVNS. Possible side effects include heart rate abnormalities (quantified by ECG recordings), gastrointestinal effects, like gagging, nausea and vomiting (quantified by direct observation and behavioral testing), and respiratory abnormalities (quantified by respiratory rate monitoring). The data collected will provide the first quantitative characterization of objective and subjective side effects of VNS in NHPs. The data will be valuable in ruling out and ranking stimulation protocols based on their toxicity profile before additional testing is performed.

4) Rank VNS protocols with regards to their neuroplasticity potential. We will characterize and quantify the magnitude and duration of cortical stimulation-induced targeted plasticity in the same frontal cortical areas, under different conditions of VNS. Synaptic plasticity will be induced by delivering closed-loop cortical stimulation (CLS) between specific cortical sites. The magnitude and duration of these plasticity effects will be quantified by measuring changes in functional connectivity between the cortical sites. These CLS sessions will be repeated for different VNS protocols so that direct comparisons can be made with regards to the protocolsâ€™ plasticity induction potential. Thus, we will have developed a quantitative measure of cortical plasticity targeted to specific cortical areas, under different VNS conditions. The data will be valuable in selecting a few VNS protocols with the highest neuroplasticity potential to be further tested in a cognitive task.

5) Retrospectively establish a test of the neuroplasticity potential of VNS that can be translated to a noninvasive human application. The â€œevoked activity dataâ€ (collected in goal 2) will be compared, on a per animal and per protocol basis, to

the â€œneuroplasticity dataâ€ (collected in goal 4). This comparison will establish the extent to which the former test, which is simple, reliable and can be implemented using noninvasive (EEG) methods in humans, is predictive of results in the latter test, which is more technically challenging and requires invasive cortical stimulation. Such knowledge can be directly used in the noninvasive testing of the neuroplasticity efficacy of VNS parameters in humans.
6) Determine a VNS protocol that significantly augments performance in a sensory discrimination task. We will quantify the effect of a selected number of VNS protocols on the performance of an electrotactile sensory discrimination task that depends on the same cortical areas in which physiological measurements were made in previous goals. Thus, we will determine the optimal VNS parameters for promoting enhanced performance in a well-controlled cognitive task in normal NHPs. This knowledge will direct the development of noninvasive VNS technology for cognitive augmentation in healthy humans.

5. *** Describe the animal experience in the experiment, from enrollment in the study to the final endpoint, including all procedures in chronological order and the minimum time between procedures. We encourage using bullet points, timeline, table, or a flow chart as appropriate:**

This project involves the following 9 stages. The stages are shown in the typical chronological order. All or only some of the procedures are performed on individual animal monkeys as described in Experimental Paths A-C further below.

Stage 1: Visual-guided task training. The animal (macaque) is operantly trained to perform visually-instructed arm and hand movements (approximately 6-10 months). **Details on this procedure are provided in Fetz - VNS and neuroplasticity behavioral training and testing.**

Stage 2: Brain implant. Electrodes are implanted in different sites of the brain to enable recording of electrical brain activity and delivery of electrical brain stimulation; wires are implanted subcutaneously around the orbit to record electrical activity associated with eye movements (electrooculography, EOG). A miniaturized electronic circuit or brain-computer interface (BCI) will be attached to the skull, housed inside a titanium head chamber, to control recording and stimulation.

If an acrylic-free "halo" head stabilization device is used, four plates will be implanted in an intial surgery - see "Fetz: (8) Halo Implant. Due to the simplicity of this initial surgery (maximum duration 3 hours) it may be combined with the vagus nerve implant (here described in Stage 4) - see "Fetz: (3) Vagus Nerve Cuff Electrode Implant".

If the "halo" head stabilization device is not used, the first surgery will be "Fetz: (2) Skull Surgery: Cranial Implant.

See multiple surgery info at bottom of Experiments page for additional information.

Stage 3: Brain neurophysiological testing. Daily experimental sessions involve recording and stimulating the brain. Recording and stimulation may be performed by implanted electrodes, electrode arrays, and/or by advancing moveable electrodes into the brain. Between these sessions, or in some animals exclusively, the BCI may perform similar operations while the monkey moves freely about the home cage for 24 hours a day (approximately 2 months). Details on these procedures are provided in Fetz - VNS and neuroplasticity behavioral training and testing.

Stage 4: Vagus nerve implant. A nerve cuff is implanted to the trunk of the left and/or right vagus nerve (VN), for invasive VN stimulation (VNS). A subcutaneous stimulating electrode is implanted behind the left and/or right auricle, for minimally-invasive auricular branch VNS (abVNS). Noninvasive VNS is delivered via a patch electrode placed on the left auricle.

Note: The tunneling will occur separately for the left- and the right-side electrode leads, so there will be no extra stress to the tissue from the implantation of one additional lead.

Stage 5: Brain neurophysiological testing during VNS. Daily experimental sessions involve recording and stimulating the brain, with or without concurrent VNS. Different protocols of invasive VNS, minimally invasive abVNS and noninvasive abVNS are delivered. Recording and stimulation of the brain may be performed by implanted electrodes, electrode arrays, and/or by advancing moveable electrodes into the brain. Between these sessions, or in some animals exclusively, the BCI may perform similar operations while the monkey moves freely about the home cage for 24 hours a day. Duration will be approximately 6 months. **Details on these procedures are provided in Fetz - VNS and neuroplasticity behavioral training and testing.**

Stage 6: Sensory nerve implant. A nerve cuff is implanted to a sensory or mixed sensorimotor peripheral nerve of the forearm. This implant enables the delivery of invasive electrotactile sensory stimulation (ETS).

Stage 7: Electrotactile stimulation-guided task training. The animal is operantly trained to perform arm and hand movements instructed by ETS-guided feedback (approximately 6 months). Details on this procedure are provided in **Fetz - VNS and neuroplasticity behavioral training and testing.**

Stage 8: Behavioral testing during VNS. Once trained, the animal performs the task under different conditions, e.g. different VNS protocols or no VNS (approximately 6 months). **Details on this procedure are provided in Fetz - VNS and neuroplasticity behavioral training and testing.**

Stage 9: Euthanasia. The animal is euthanized.

Notes:

a. In some monkeys, no trained behavior is used and all data are collected in the home cage or with the monkey sedated (e.g. experiment path C).

b. In some monkeys, not all of the devices are implanted.

c. In some monkeys, some stages may be omitted.

The 3 typical experimental sequences are as follows:

Experiment path A: Stages 1 to 9 (“Neurophysiological tests and cognitive task”)

Experiment path B: Stages 1, 4, 6, 7, 8, 9 (“Cognitive task only”)

Experiment path C: Stages 2, 3, 4, 5 (“Neurophysiological tests during free behavior only”)

In more detail, the experiment comprises the following stages.

Stage 1: Monkeys are first trained to perform hand, wrists, and arm movement tasks. Procedure: “VNS and neuroplasticity behavioral testing”.

Stage 2: Once an adequate level of performance is obtained, the animals undergo surgery to implant head restraint, recording and stimulating electrodes in the brain, head chamber, and BCI circuitry (depending on which one of the two alternative skull surgeries is performed at this stage).

Stage 3: In this stage, we record and discriminate activity from brain sites and identify units or field potentials that are modulated during the trained tasks. Such activity is then used to control electrical stimulation at other brain sites, or stimuli is delivered in predetermined intervals. Stimulation at some sites elicits cortically-evoked potentials (CEPs) at a number of other sites. These CEPs characterize the connectivity between brain sites and the excitability of the brain at the time of stimulation. Stimulation at sensorimotor sites may elicit motor evoked potentials (MEPs), which can be measured by registering the evoked movements. These MEPs are indicative of the excitability of the sensorimotor areas of the brain at the time of stimulation. When stimulation is triggered from appropriately detected neural activity, changes in cortical connectivity (seen as changes in the magnitude of CEPs) occur, an effect which is indicative of synaptic plasticity. In daily sessions, we will use CEPs, MEPs and their changes to characterize the connectivity between brain sites, the excitability of the brain as a function of stimulation parameters, task performance etc. and the plasticity effects between brain sites. Between these sessions, or in some animals exclusively (e.g. animals in path C), the BCI may perform similar operations while the monkey moves freely about the home cage for 24 hours a day. The rationale for free behavior experiments is to study these processes at different times of day and night, during different behavioral and brain states (wakefulness, movement vs. resting, slow wave sleep, REM sleep etc).

Stage 4: The animals undergo surgery to implant a cuff in the left and/or right vagus nerve and a subcutaneous electrode in the left and/or right auricle.

Stage 5: In this stage, we repeat many of the neurophysiological tests in stage 3, but this time with concurrent delivery of invasive, minimally invasive or noninvasive VNS of different stimulation parameters. The effects of VNS on brain activity, excitability and plasticity will be explored in these sessions, as well their dependence on the difference VNS parameters. The goal of delivering VNS during these neurophysiological measurements is (a) to study the brain effects of VNS, (b) to determine whether VNS enhances the magnitude or duration of cortical plasticity, (c) to compare the plasticity effects of different parameter sets of VNS. Based on these measurements, a small number of VNS parameter sets will be selected for further behavioral testing. Between these sessions, or in some animals exclusively (e.g. path C), we will make use of the implanted BCI device to deliver similar experiments under free behavioral conditions. The rationale for the free behavior experiments is to study these processes at different times of day and night, during different behavioral and brain states (wakefulness, movement vs. resting, slow wave sleep, REM sleep etc). During this stage, blood samples draws may be performed at regular intervals (once a month), to assess possible effects of VNS on hematological, biochemical and immunological parameters.

Stage 6: The animals undergo surgery to implant a cuff in a sensory or mixed sensorimotor peripheral nerve in the forearm, for delivery of electrotactile sensory stimulation (ETS) feedback.

Stage 7: The animals are operantly trained to perform arm and hand movements instructed by ETS-guided feedback.

Stage 8: The animals perform the ETS-guided feedback task under different conditions of VNS. In daily sessions, in separate runs of 30-100 trials each, VNS of a selected parameter set is delivered and the animal's performance is registered. Some runs involve no VNS. The effect of VNS on task performance is then examined by comparing performance on different subsets of runs: VNS parameter set 1 vs. no VNS, VNS parameter set 2 vs. no VNS, VNS parameter set 1 vs. VNS parameter set 2, etc. The rationale for this stage is to establish which VNS parameters enhance performance in a well-characterized cognitive task of sensory discrimination.

Stage 9: Animals are euthanized.

A14229 transfer from protocol 2326-08 to 2326-09

One of the animals on this study, A14229, will be transferred from protocol 2326-08 ("003. Vagus Nerve Stimulation") to this experiment.

As of the time of this request (09/21/2017), the animal has undergone 3 surgical procedures on protocol 2326-08: Halo head stabilization surgery (March 15, 2017), vagus nerve implant (May 17, 2017) and skull surgery for brain implant (August 10, 2017). The animal is healthy and is fully recovered. The animal has all of the hardware that it needs for the project on protocol 2326-09 and will not receive any additional surgeries, other than repair surgeries, after protocol transfer. **See attached document for additional information.**

Note: Subsequent to this request, it was determined in consultation with the USDA that an exemption under Animal Care Policy #14 is not required. Per the USDA, because the proposed major operative procedures are to repair hardware already in place, these surgeries would be considered veterinary care procedures.

Animal Sex:
Male

Animal Ages:
2.5-6 years

Animal Size:
4-12 kg

6. *** Select experimental procedures:**

Name	Type	Version	Scope
Fetz: VNS and neuroplasticity behavioral training and testing	Behavioral Testing (with Food or Fluid Restriction)	3	Team
Anesthetic Overdose, Pentobarbital or Pentobarbital Solution	Euthanasia	1	Standard
Fetz: Brain Electrodes	Implants	2	Team
Fetz: EOG Electrodes v2	Implants	1	Team
Fetz: Head Restraint, Recording Chamber and/or Electronics Housing v2	Implants	1	Team
Fetz: Nerve cuff implant at forearm peripheral nerves	Implants	1	Team
Fetz: Subcutaneous electrode implant for auricular branch VNS	Implants	1	Team
Fetz: Transcutaneous delivery of auricular branch VNS	Implants	1	Team
Fetz: Transcutaneous delivery of electrical stimulation at forearm nerves	Implants	1	Team
Fetz: Vagus nerve electrode cuff	Implants	1	Team

Name	Type	Version	Scope
Fetz: Perfusion	Non-Survival Surgery	2	Team
Fetz: A14229 Repair Surgery (2 & 3)	Other	1	Team
Fetz: A14229 Repair Surgery (4)	Other	1	Team
Fetz: A16229 Repair Surgery (2)	Other	1	Team
Fetz: A16230 Repair Surgery (2 & 3)	Other	1	Team
Fetz: A16230 Repair Surgery (4)	Other	1	Team
Fetz: A16230 Repair Surgery (5)	Other	1	Team
Fetz: Primate Jackets/Shirts	Other	1	Team
Fetz: Sedated Implant Maintenace	Other	1	Team
Fetz: Chair Restraint	Physical Restraint	1	Team
Analgesia, WaNPRC Standard (at least 48 hours)	Substance Administration	1	Standard
Anesthesia, General, WaNPRC Standard (v.2)	Substance Administration	1	Standard
Anesthesia, Sedation/Injectable Anesthesia, WaNPRC Standard	Substance Administration	1	Standard
Anesthesia, Terminal, Pentobarbital or Pentobarbital Solution	Substance Administration	2	Standard
Antibiotics, Prophylactic Surgical, WaNPRC Standard, Cephalosporins	Substance Administration	1	Standard
Fetz: Saccharin solution (0.1% w/v), v2	Substance Administration	1	Team
Fetz: (2) Skull Surgery (v.3)	Survival Surgery	1	Team
Fetz: (4) Implantation of subcutaneous electrode for auricular branch VNS	Survival Surgery	1	Team
Fetz: (4) Nerve cuff implant at forearm peripheral nerve surgery (v3)	Survival Surgery	1	Team
Fetz: (4) Vagus Nerve Cuff Electrode Implant	Survival Surgery	1	Team

Name	Type	Version	Scope
Fetz: (8) Halo Implant	Survival Surgery	1	Team
Fetz: Repair Surgery	Survival Surgery	1	Team
Blood collection, peripheral vein (Sedated)	Tissue/Blood Collection	1	Standard

7. **Monitoring protocol, including frequency and specific behavioral and clinical signs to be monitored. Include humane endpoints (criteria for euthanasia):**
Monitoring is described in the individual procedures.

Animals will be euthanized when they have reached the end of study or have become ill. At the termination of stages 1-5, electrolytic marking lesions may be made by passing DC current through electrodes in the brain. Animals will be euthanized if they are unresponsive to medical treatment or have severe neurological impairment as a result of experimental interventions.

8. If there is expected mortality (spontaneous death) in this experiment:

a. Procedure/condition associated with mortality:
N/A

b. Estimated mortality rate, i.e. percentage of animals expected to die spontaneously (not via euthanasia) or need to be euthanized as a result of the procedure. (Be sure to account for this in your animal number calculations):
N/A

c. Explain why euthanasia is not possible or appropriate:
N/A

9. **Will some animals live out their natural lifespan as part of this experiment? If so, indicate their use and describe the monitoring plan for aged animals (e.g., rodents >18 months of age), including frequency, behavioral and clinical signs to be monitored and criteria for euthanasia.**
No.

10. *** Total number of animals used in this experiment:**(including all the animals to be produced)
7

a. **Justify total number of animals used in this experiment:**

Two animals will be used in experiment path A. Two animals per experiment path is the minimum acceptable number of subjects in nonhuman primate neurophysiology research to derive useful information. Including only 1 animal in a research study does not allow us to investigate how reproducible the findings are, or assess the between-animal variability of our measurements.

Two animals will be used in experiment path B, for the same reason.

Two animals will be used in experiment path C, for the same reason.

One animal will be used only if one of the other animals needs to be terminated prematurely.

11. **Number of animals by pain and distress category:**(include each animal only once in the highest pain category)

B: 0
C: 0
D: 7
E: 0

a. **Justify the need for any animals in pain category E:**
N/A

12. *** Identify husbandry exceptions:**

	Exception Type	Description and Justification
View	NHPs - Food treats, as outlined in the policy, are not acceptable for part or all of the study.	On weekends and holidays, colony staff feeds and treats research animals according to posted instructions.
View	NHPs - Standard social contact housing, as outlined in the policy, is not acceptable for part or all of the study.	Unless adverse behavior within a pair inhibits the training process, all of our pre-surgical animals can be in run-through contact except during feeding times, as precise food restriction is used throughout behavioral training and experimentation. After surgical augmentation, tactile contact between animals pairs will be closed during recovery until it can be determined that the pairing will not cause injury to the implanted animal or damage the implant. Such decisions will be made with veterinary staff. Social contact decisions for animals fitted with primate jackets containing or protecting experimental devices (e.g. nerve cuffs, spinal chambers, and EMG wires) will be approached in a similar manner. Social contact arrangements are monitored by research staff, WaNPRC Behavioral Management, and veterinary staff and may be altered at any time to ensure the health and safety of the animals and their implants.

13. **Supporting documents:**

Document Name	Date Modified
Appendix 1 Implant Cleaning Protocol.pdf	1/10/2017 1:04 AM

Document Name	Date Modified
Appendix 2 Possible Prohylactic Antibiotics.pdf	1/10/2017 1:04 AM
Experiment path schematic	1/10/2017 1:01 AM
Transfer Exemption Request A14229.pdf	2/27/2018 4:55 PM
VVC 122 weight and dimensions of implants.pdf	1/10/2017 1:05 AM

View: Custom: Create and Edit

1. * Exception type:

NHPs - Food treats, as outlined in the policy, are not acceptable for part or all of the study.

2. Description and justification:

On weekends and holidays, colony staff feeds and treats research animals according to posted instructions.

View: Custom: Create and Edit

1. * Exception type:

NHPs - Standard social contact housing, as outlined in the policy, is not acceptable for part or all of the study.

2. Description and justification:

Unless adverse behavior within a pair inhibits the training process, all of our pre-surgical animals can be in run-through contact except during feeding times, as precise food restriction is used throughout behavioral training and experimentation. After surgical augmentation, tactile contact between animals pairs will be closed during recovery until it can be determined that the pairing will not cause injury to the implanted animal or damage the implant. Such decisions will be made with veterinary staff. Social contact decisions for animals fitted with primate jackets containing or protecting experimental devices (e.g. nerve cuffs, spinal chambers, and EMG wires) will be approached in a similar manner. Social contact arrangements are monitored by research staff, WaNPRC Behavioral Management, and veterinary staff and may be altered at any time to ensure the health and safety of the animals and their implants.

View: Custom: Add Vivarium Location

1. *Identify the location where animals will be housed:

Vivarium ABSL2

a. For locations that are lab managed, provide justification for housing outside of the vivarium:

b. If you cannot find the location above, identify it here and provide justification for housing outside of the vivarium:

2. * What species will be housed in this location?

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

View: Custom: Add Vivarium Location

1. *Identify the location where animals will be housed:

Vivarium ABSL2

a. For locations that are lab managed, provide justification for housing outside of the vivarium:

b. If you cannot find the location above, identify it here and provide justification for housing outside of the vivarium:

2. * What species will be housed in this location?

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

View: Custom: Add Animal Use Location

1. * Identify the location where animals will be used:

Vivarium ABSL2

a. For locations that are outside of the vivarium, provide justification for the use of this space:

b. If you cannot find the location above, identify it here and provide justification for the use of animals outside of the vivarium:

2. * What species will be used in this location?

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

3. Describe how this location will be used:

Surgery

4. *** If animals are left unattended in this location, provide an explanation and include maximum duration:**
   Animals are not left unattended.

5. **Describe how animals will be transported to and from this location, including container and route**
   (Note: use of private vehicles requires IACUC approval):

   Primate chairs (awake) or carts (sedated). For transportation across floors we use the I-wing elevators.

View: Custom: Add Animal Use Location

1. *** Identify the location where animals will be used:**
   Vivarium ABSL2
   a. **For locations that are outside of the vivarium, provide justification for the use of this space:**

   b. **If you cannot find the location above, identify it here and provide justification for the use of animals outside of the vivarium:**

2. *** What species will be used in this location?**

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

3. **Describe how this location will be used:**
   Surgery

4. *** If animals are left unattended in this location, provide an explanation and include maximum duration:**
   Animals are not left unattended.

5. **Describe how animals will be transported to and from this location, including container and route**
   (Note: use of private vehicles requires IACUC approval):

   Primate chairs (awake) or carts (sedated).

View: Custom: Add Animal Use Location

1. *** Identify the location where animals will be used:**
   I441
   a. **For locations that are outside of the vivarium, provide justification for the use of this space:**
   This location bears equipment (booths, amplifiers, stimulators etc) that is essential for this experiment, as well as supplies that are essential for implant maintenance; those are not available at the vivarium.

b. **If you cannot find the location above, identify it here and provide justification for the use of animals outside of the vivarium:**

2. *** What species will be used in this location?**

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

3. **Describe how this location will be used:**
Behavioral testing, implant maintenance.

4. *** If animals are left unattended in this location, provide an explanation and include maximum duration:**
Animals will not be left unattended.

5. **Describe how animals will be transported to and from this location, including container and route**
(Note: use of private vehicles requires IACUC approval):

Primate chairs (awake) or carts (sedated). For transportation across floors we use the I-wing elevators.

View: Custom: Add Animal Use Location

1. *** Identify the location where animals will be used:**
I553

a. **For locations that are outside of the vivarium, provide justification for the use of this space:**
This location bears equipment (booths, amplifiers, stimulators etc) that is essential for this experiment, as well as supplies that are essential for implant maintenance; those are not available at the vivarium.

b. **If you cannot find the location above, identify it here and provide justification for the use of animals outside of the vivarium:**

2. *** What species will be used in this location?**

Common Name	Scientific Name
NHP - Rhesus/Pigtail Macaques	M. mulatta/M. nemestrina

3. **Describe how this location will be used:**
Behavioral testing, implant maintenance.

4. *** If animals are left unattended in this location, provide an explanation and include maximum duration:**
Animals will not be left unattended in this location.

5. Describe how animals will be transported to and from this location, including container and route
(Note: use of private vehicles requires IACUC approval):

Primate chairs (awake) or carts (sedated). For transportation across floors we use the I-wing elevators.