IRB APPROVAL - Continuing Review

Date: May 31, 2017
From: Jary Larsen, PhD, IRB Chairperson
Investigator: Anthony J.W. Chen, MA, MD
Protocol: MERIT: Neural Bases of Cognitive Rehabilitation for Brain Injury
ID: 00599 Prom#: 4257 Protocol#: 10-08-00599
Expiration Date: 05/14/2018

The following items were reviewed and approved through Expedited Review:

- * Continuing Review Application - Amendments (05/05/2017)
  1. Remove Brian Curran, Jason Deitch, Matthew Schalles and Diane Swick from the research team.
  2. Close study to enrollment.
  3. Update recruitment totals for individuals enrolled between 2015-2016 (see enrollment table).
  4. Increase the length of the study 1 year for a total of 8 years.
- * Human Subject Enrollment Form - From 03/14/2014 to 11/28/2015 (02/24/2017)
- * Human Subject Enrollment Form - From 11/28/2015 to 03/08/2017 (02/24/2017)
- Project Data Sheet (04/03/2017)
- Research Security Plan (04/03/2017)
- Research Project Abstract (03/22/2017)
- Research Data Use and Security Plan - Investigator (04/03/2017)
- Offsite Data Storage Waiver (04/03/2017)
- Research Financial Conflict of Interest Statement - 2017
  Anthony Chen (03/08/2017); Mark D'Esposito (03/08/2017); Tajana Novakovic-Agopian (03/08/2017)

Continuing Review Application - Amendments (05/05/2017) was returned to you with stipulations. The following revised items incorporate the stipulations and are now approved:

- Continuing Review Application - Amendments (05/22/2017)
  1. Remove Brian Curran, Jason Deitch, Matthew Schalles and Diane Swick from the research team.
  2. Close study to enrollment.
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  4. Increase the length of the study 1 year for a total of 8 years.

Human Subject Enrollment Form - From 03/14/2014 to 11/28/2015 (02/24/2017) was returned to you with stipulations. The following revised items incorporate the stipulations and are now approved:

- Human Subject Enrollment Form - From 03/14/2014 to 11/28/2015 (05/22/2017)

Human Subject Enrollment Form - From 11/28/2015 to 03/08/2017 (02/24/2017) was returned to you with

stipulations. The following revised items incorporate the stipulations and are now approved:

- Human Subject Enrollment Form - From 11/28/2015 to 03/08/2017 (05/22/2017)

Expedited Approval [Expedited under Federal Regulation: 45 CFR 46.110(b)(1)(4) / VA Regulation: 38 CFR 16.110(b)(1)(4)] was granted on 05/31/2017 for a period of 12 months and will expire on 05/14/2018. Your Continuing Review is scheduled for 04/03/2018. This Expedited review will be reported to the fully convened IRB (Institutional Review Board/Human Studies Subcommittee) on 06/06/2017.

Since this continuing review was done after the current expiration date, the continuing review approval period changes to 05/31/2017 to 05/14/2018.

The following other committee reviews are scheduled:
Research & Development Committee [06/28/2017]

Approval by each of the following is required prior to study continuation (unless Exempt):
IRB (Institutional Review Board/Human Studies Subcommittee)
Research & Development Committee

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Jary Larsen

Digitally signed by Jary Larsen
DN: cn=Jary Larsen, o=VANCHCS, ou=Institutional Review Board, email=Jary.Larsen@va.gov, c=US
Date: 2017.05.31 16:02:34 -07'00'

Jary Larsen, PhD, IRB Chairperson

DEPARTMENT OF VETERANS AFFAIRS
NORTHERN CALIFORNIA HEALTH CARE SYSTEM
10535 Hospital Way • Mather & Martinez, CA

Conditions of IRB Approval

What Are the Conditions of IRB Approval?

1. Adhere to ethical principles: (1) Respect for persons - consent, privacy, confidentiality, (2) Beneficence - maximize possible benefits to the subject and minimize possible harms, and (3) Justice - equitable selection.

2. Obtain informed, written consent from each human subject or his legally qualified guardian or next-of-kin, unless specifically waived by the IRB. If the subject lacks decision making capacity or has been declared incompetent, surrogate consent is required. You are required to place the original, signed consent form in the medical record (and document it in the electronic record), provide a copy to the subject, provide a copy to the Research Office (if applicable), and keep a copy for your files.

3. Promptly report all Serious Adverse Events or Serious and Unexpected Events to the IRB (both events at the VA and sponsor reports of events at other sites). The FDA defines Serious Adverse Events as: (1) death, (2) life-threatening, (3) hospitalization - initial or prolonged, (4) disability, (5) congenital anomaly, (6) required intervention to prevent permanent impairment/damage, or (7) serious and unexpected severity or frequency of expected events.

4. Promptly report all deviations (including error and accidents) from the approved protocol and do not initiate any unapproved changes (amendments, consent form modifications, advertisements) without IRB review and approval, except where necessary to eliminate apparent immediate hazard to human subjects.

5. Report Emergency Use of unapproved test articles to the IRB within 5 days.

6. If applicable, provide a copy of each subject's consent form and the Investigational Drug Information Record (VA Form 9012) to the Investigational Pharmacist prior to your request to receive, store, and dispense study medications. (The Investigational Pharmacist is responsible for the storage and dispensing of investigational drugs.)

7. Submit Continuing Review information to the IRB by the date specified and inform the IRB when your study is completed (federal law requires that every protocol must be reviewed a minimum of once per year). File a final report upon completion or termination of a study.

What Are the Penalties for Non-Compliance?

1. Non-compliance may result in suspension of approval or a particular project. Serious or continuing non-compliance may result in suspension of your privilege to conduct research at this VAMC.

Department of Veterans Affairs

NORTHERN CALIFORNIA HEALTH CARE SYSTEM

CONTINUING REVIEW APPLICATION

- *Obtain a copy of the **"Continuing Review Submission Checklist"** for complete instructions on documentation required for VANCHCS IRB Continuing Review.*
- ***Complete this form if the research involves living human subjects, or their biological samples, or identifiable data about them.***
- ***All sections of the application must be completed. Do not leave any fields blank. All answers must be in complete sentences.***
- ***Handwritten and/or incomplete applications will be returned without IRB review.***

Principal Investigator:	Anthony Chen, M.D.
Title of Study:	MERIT: Neural bases of cognitive rehabilitation for brain injury
VA File Number:	10-08-00599

PRINCIPAL INVESTIGATOR PREFERS APPROVAL NOTIFICATION DOCUMENT

SENT TO: ☐ Principal Investigator OR ☒ Contact Person

SENT BY: ☒ VA Inter-Office Mail OR ☐ United States Postal Service

Principal Investigator:	Anthony Chen, M.D.	**Contact Person (if different from PI):**	
Phone:	925-372-2000 ext 2530	**Phone:**	
Pager or Cell Phone:	415-719-3824	**Pager or Cell Phone:**	
Email:	anthony.chen@va.gov	**Email:**	
Fax:	510-666-3440	**Fax:**	
US Mailing Address:	Martinez VA Research Service/151 150 Muir Rd Martinez, CA 94553	**US Mailing Address:**	
VA Site and VA Inter-Office Mail Code:	Martinez 127	**VA Site and VA Inter-Office Mail Code:**	

DESCRIPTION OF STUDY

A. RESEARCH STUDY STATUS

1. Study Activity

a. Is this study open to enrollment of new subjects, samples or charts?

☐ Yes ☒ No

b. Are any subjects in the process of receiving research related interventions or study procedures?

☐ Yes ☒ No ☐ N/A

c. Are any subjects being tracked for long term follow-up?

☐ Yes ☒ No ☐ N/A

d. Are any of the remaining research activities ongoing, including data analysis?

☒ Yes ☐ No

(If the answer to all of the above questions is "NO" or "N/A," complete the "Application for Study Closure" instead of this form.)

e. Is an original signed consent form in the study file for each subject entered into this study?
☒ Yes ☐ No

- *If "NO", is a waiver of consent and authorization approved for all subjects, samples or charts being used in this study?*
  ☐ Yes ☐ No

f. Is a progress note in the medical record of each VA subject entered into this study?
☒ Yes ☐ No ☐ N/A

2. Information from the Prior Approval Period

a. Total number of subjects, samples or charts entered into study since the last IRB Initial or Continuing Review: 6

b. Have one or more subjects claimed injury from participating in this study?
☐ Yes ☒ No ☐ N/A

c. Have any unanticipated problems, and/or adverse events related to the research occurred at this site?
☐ Yes ☒ No

d. Have any serious adverse events related to the research occurred at this site?
☐ Yes ☒ No

e. Have any participants withdrawn from this site since the last IRB review?
☐ Yes ☒ No

f. Have there been any complaints about the research at this site since the last IRB review?
☐ Yes ☒ No

g. Has there been any recent literature that may be relevant to the research since the last IRB review?
☐ Yes ☒ No

h. Have there been any relevant multi-center trial reports since the last IRB review?
☐ Yes ☐ No ☒ N/A

i. Has there been any other relevant information, especially information about risks associated with the research (updated Investigator's Brochure, etc.) since the last IRB review?
☐ Yes ☐ No ☒ N/A

j. Have there been any research findings since the last IRB review?
☐ Yes ☒ No

k. Has this study received any monitoring visits from the sponsor or other external compliance agencies?
☐ Yes ☒ No

If "YES":

1) **How many monitoring and/or compliance visits were conducted?**
2) **Were all monitoring and/or compliance visits reported to Research Service?** ☐ **Yes** ☐ **No**
3) **Please provide dates and outcome of monitoring/compliance visits.**

3. Additional IRB Oversight

Has the PI submitted this study to another IRB or IRBs?
☒ Yes ☐ No

- *If "YES":*

a. Provide name(s) of IRB(s): UC San Francisco Committee on Human Research (for UC Berkeley, per NOITR)

1) **Federal Wide Assurance Number:** 00000068

b. Status of study:
☒ Under Review ☐ Approved ☐ Disapproved

- *If Disapproved:*

1) **Provide details:**

B. CONFLICT OF INTEREST

1. Describe any personal or financial interest of the investigators and research staff in the study. n/a
2. Research Financial Conflict of Interest Statement submitted for all members of the research team. ☒ Yes ☐ No

C. INVESTIGATORS AND RESEARCH PERSONNEL

1. Principal Investigator	**Check if research personnel will perform informed consent process independently ****
Anthony Chen	☐
2. Co-Investigator(s) None ☐	
Mark D'Esposito	☒
Tatjana Novakovic-Agopian	☒
3. Research Staff None ☐	
Diane Swick	☒
Matthew Schalles	☒
Nicholas Rodriguez	☒
Fred Loya	☒
	☐
	☐

**NOTE: *Delegation of informed consent must be to an appropriate, suitably qualified member of the research team with a comprehensive understanding of the study and the ability to answer all research-related questions including those regarding risk, alternative treatments and therapies.*

4. Current number of open studies for this PI at VANCHCS/VACCHCS:	☐ 0	☒ 1-5	☐ 6-20	☐ over 20
a. Current number of open studies for this PI at other institutions:	☐ 0	☒ 1-5	☐ 6-20	☐ over 20

5. Describe the experience and training of the investigators and research staff. *(Do not answer with "Refer to CV")*

a. Expertise with study procedures.

__Mark D'Esposito, M.D., is Staff Neurologist at the VA, Director, Neurobehavioral Clinic and Brain Injury Rehabilitation Unit at the Martinez VA, Director of the Brain Imaging Center, UC Berkeley, Professor of Psychology, UC Berkeley, and Professor of Neurology, UCSF with extensive experience performing investigations of cognitive processes using functional MRI and other testing methods.

__Anthony Chen, M.A., M.D., is a Staff Neurologist at the VA, with fellowship training in performing investigations of cognitive neuroscience and cognitive rehabilitation, development of functional MRI methods for these investigations, Assistant Professor at UCSF, directing studies of cognition, recovery and rehabilitation of patients with brain injuries.

__Tatjana Novakovic-Agopian, Ph.D., is a specialist in Rehabilitation Neuropsychology, fellowship trained at UCSF and with extensive experience in clinical practice, Clinical Instructor in Neurology at UCSF, with expertise in the development of assessment measures for cognitive dysfunction affecting patients with brain injuries.

__Fred Loya, PhD is a psychologist with expertise in neurocognitive assessment and clinical interventions who will conduct neurocognitive assessments and will be involved in research design and cognitive training.

__Nicholas Rodriguez, BA is a research associate who will screen potential subjects, explain research activities to subjects, assist in research design and manage study data.

b. Provide information on how the training and expertise of the principal investigator, sub-investigators and other research personnel are relevant to the study.

The study addresses how executive control functions such as selective attention may be improved through clinically-relevant cognitive training in patients with brain injury, as well as which neural changes support such improvements in executive control functions. The investigators and other research staff all have training and experience relevant to the study's purpose and design, including: cognitive rehabilitation of patients with brain injury and the development of clinical research protocols for assessment (using imaging, functional, and cognitive outcomes) of patients with brain injury.

c. Describe the qualifications *(training and experience)* **of all individuals who will be involved in the informed consent process.**

Mark D'Esposito, MD, is a staff neurologist at the VA. Co-investigators who will obtain informed consent include Anthony Chen, MD (staff neurologist at the VA) and Tatjana Novakovic-Agopian, PhD (rehabilitation neuropsychologist). Fred Loya, PhD, Nicholas Rodriguez, BA, and Erica Pool, BA are study staff who will also be involved. All have extensive experience working with patients and performing neuroscience studies. Drs. D'Esposito and Chen are trained in neurology, behavioral neurology and neurologic rehabilitation and cognitive neuroscience. Dr. Novakovic-Agopian is trained in neuropsychology and cognitive neuroscience. Fred Loya is a psychologists with extensive experience in neurocognitive assessment and research. Erica Pool, and Nicholas Rodriguez have BAs in Psychology and over 2 years research experience. Brian Curran has a BS in Physiological Psychology and is a Health Research Specialist with over 30 years experience in neuroscience research, with extensive experience screening and consenting subjects.

d. If applicable, include information about relevant licenses/medical privileges.

Mark D'Esposito and Anthony Chen are licensed physicians. Tatjana Novakovic-Agopian is a licensed neuropsychologists.

D. STUDY DESIGN AND MERIT

1. Estimated length of study: *(in years or months)*

7 years

2. Length of each participant's time in this study: *(in hours, days, weeks, months, or years)*

1 day to 9 months

3. Purpose of study:

a. State the research hypothesis.

Participation in the experimental interventions will enhance functioning in complex 'real-life' settings, result in improvements in attention and working memory (reflecting protection from distraction) and improvements on measures of sustained attention.

b. Describe the research objectives.

To determine the neural, neurocognitive and functional effects of attentional training protocols. We will use fMRI coupled with behavioral interventions to address the following questions: Question 1: What are the neural changes caused by brain injury that underlie behavioral changes in executive cognitive control? Question 2: What specific neural changes support improvements in cognitive abilities of executive control and attention in patients with brain injury? The studies will also investigate to what extent effects transfer to higher and lower levels of function and domains of cognitive functioning that are not explicitly trained; to what extent neural measures help to explain variability in behavioral effects; and to what extent effects are maintained at 6 months follow-up.

c. Describe in detail the purpose of this study.

Aim 1. To determine the neural, neurocognitive and functional effects of a theory-driven, strategy-based intervention that trains goal-oriented attention with intensive application through accomplishment of personally relevant projects. Hypothesis: Participation in the experimental intervention will enhance functioning in complex 'real-life' settings, relative to an educational intervention matched for time and attention.

Aim 2. To determine the neural, neurocognitive and functional effects of a computer-assisted game-based protocol designed to intensively train the target process of re-direction of selective attention when distracted.

Hypothesis: Participation in the experimental intervention will result in improvements in attention and working memory (reflecting protection from distraction), relative to a comparison intervention matched for time and computer usage.
Aim 3. To determine the neural, neurocognitive and functional effects of a computer-assisted training task that targets basic tonic and phasic attention functions. Hypothesis: Participation in the experimental intervention improves sustained attention, relative to a comparison intervention matched for time and computer usage.
Each study will also investigate to what extent effects transfer to higher and lower levels of function and domains of cognitive functioning that are not explicitly trained; to what extent neural measures help to explain variability in behavioral effects; and to what extent effects are maintained at 6 months follow-up.

Describe the importance of resulting knowledge from this study.

d. This research is designed to contribute to improving care by (1) providing a neuroscientific framework for understanding neurorehabilitation therapies and their effects on brain functions, (2) aiding in the development of informative fMRI biomarkers that will be useful in rehabilitation treatment studies and (3) aiding in the design of novel therapeutic interventions that more directly target the underlying neural bases of dysfunction. Completion of the proposed studies will provide an essential foundation for the immediate next steps -- directly targeting the elucidated neural pathways using improved behavioral, physiological and pharmacologic modulation treatment interventions.

4. Check types of study design:

☒ **Chart/Medical Records Review**
- ☒ Prospective
- ☒ Retrospective

☒ **Observational (the investigator observes the events without altering them):**
- ☒ Cross-sectional study (each participant examined only once)
- ☒ Longitudinal study (each participant followed over a period of time)

☒ **Experimental Intervention (the investigator observes the effect of the intervention on outcome):**
- ☒ Randomized
- ☒ Blinded
- ☐ Retrospective
- ☒ Prospective

5. Describe statistical methods *(For example: sample size estimation, power calculation, statistical tests or descriptive statistics, data analysis tools, etc.)*

Analyses of cross-sectional data will include (a) across-group comparisons using univariate statistics and (b) within group correlational analyses testing the relationships between behavioral and neural measurements. Tests of repeated measures will be used to assess the effects of the training interventions on pre- and post- intervention measurements. Intervention group x time interactions will be assessed using ANOVA and specific relationships will be tested using paired T-tests.

6. Describe appropriateness and rationale for elements warranting special attention *(placebo, washout period, challenge study, radiation exposure, deception study, deviation from accepted standard of care).*

n/a

7. Have there been IRB approved protocol amendments modifying the study *(including sponsor amendments)* **since the last review?**

☒ Yes ☐ No

- *If "YES", list approval date and summarize the nature and purpose of all protocol amendments made since the time of last Initial or Continuing Review:*

Approval Date	Amendment Description
1011/04/2016	Approved letter to request signed authorization

E. AMENDMENT REQUEST AT CONTINUING REVIEW

1. Are any protocol amendments modifying the study *(including sponsor amendments)* **being proposed at the time of this continuing review?**

☒ Yes ☐ No

- *If "YES", complete the rest of this section, If No, skip the rest of this section*

2. Purpose and/or reason for modifying the protocol.

Remove personnel from research team, close study to enrollment, update recruitment totals

3. Brief Description of Amendment.

- **Remove Brian Curran and Jason Deitch from protocol**
- **Close study to enrollment**
- **Update recruitment totals for individuals enrolled between 2015-2016 (see enrollment table)**

F. SUBJECT POPULATION

1. Human Subject Enrollment

a. How many total participants did VANCHCS IRB originally approve for accrual (sign consent forms) at VANCHCS/VACCHCS? **210**

b. How many total participants are currently approved for accrual at VANCHCS/VACCHCS? **210**

c. How many total participants did VANCHCS IRB originally approve for accrual at other sites under your responsibility? **n/a**

List other initial site names _____

d. How many total participants are currently approved for accrual at other sites under your responsibility? **n/a**

List other current site names _____

e. If this is a Multicenter trial with different sites and different PIs, how many total participants are currently planned to be enrolled for the entire project? **n/a**

f. No contact with participants, authorization and consent waived: ☐

1) Enter total number of samples or charts originally approved **n/a**

2) Enter total number of samples or charts currently approved **n/a**

3) Enter total number of records extracted from VA Data Mart or VA Data Warehouse (National, Regional, or VISN) originally approved **n/a**

4) Enter total number of records extracted from VA Data Mart or VA Data Warehouse (National, Regional, or VISN) currently approved **n/a**

2. Status of subjects

a. Number of subjects, samples or charts entered into study **since project began**? **54**

b. Number of subjects, samples or charts entered into study **since last report** to the IRB? **6**

3. Since the **last report**, to the IRB indicate:

a. Number of female subjects:**0**

b. Number of male subjects **6**

c. Number of subjects in each of the following groups:

Caucasian: 4	African-American: 1	Hispanic: 1
Asian:	Other: *(indicate minority status and number)*	

d. Number of subjects in each of the following vulnerable groups:

☒ None	Children:	Persons with HIV:
Economically Disadvantaged:	Employees:	Prisoners:
Educationally Disadvantaged:	Homeless/Shelter:	Students/Trainees:
Impaired Decision Making Capacity:	Mentally Disabled:	Terminally Ill Patients:
Pregnant Women & Fetuses:	Non-English Speaking:	Others:

e. Number of subjects who signed consents but were dropped from study ("screen failures"):**1**

f. Total number of patients who withdrew or were withdrawn from the study: **0**

1) Summarize the reasons for withdrawal.

g. Did all research subjects give written informed consent? ☒ **Yes** ☐ **No** ☐ **N/A - consent waived**

1) If no, provide explanation:

4. Which of the following groups will be recruited for this study? *(check all that apply)*

☒ Inpatients	☒ Outpatients	☐ Pre-Operative patients
☐ Nursing home patients	☒ Non-VA participants *	☒ Healthy volunteers

**** Recruitment of Non-VA Participants***

a. Non-veterans may be entered into VA-approved research studies only when there are insufficient veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92.

b. You must document how you will attempt to enroll veterans and outline how you will provide verification to Research Service that recruitment resulted in insufficient veteran enrollment.

5. Are you recruiting and enrolling Non-VA participants?

☒ Yes ☐ No

- *If "YES", complete the following information:*

a. Document how you will attempt to enroll veterans.

Veterans are being referred by VA clinicians. Recruitment activities will also be extended to VA Outpatient Clinics, Veteran Centers, State of California Department of Rehabilitation veteran services programs, Employment Development Department disabled veterans outreach programs, community college disabled student programs and veteran affairs offices, adult school programs for individuals with brain injury, University of California and California State University programs for veterans, Travis AFB Transition Service Center, and neurology clinics at local hospitals. Recruitment activities will include presentations to individuals or groups associated with these service providers, distribution of approved letters, brochures and flyers, and posting of an approved advertisement on Craigslist.

b. Outline how you will provide verification to Research Service that recruitment resulted in insufficient veteran enrollment.

Researchers will make extensive efforts to enroll veterans, including providing IRB-approved recruitment material to VA Outpatient clinics, Veteran Centers, State of California Department of Rehabilitation Veteran services programs, State of California Employment Development Department disabled veterans outreach, State of California County veterans services, community college veteran affairs offices, University of California and California State University programs for veterans, Travis AFB Transition Service Center, and a Craigslist advertisement.

6. Selection Criteria

a. What are the inclusion/exclusion criteria?

Inclusion criteria: Patients with acquired brain injuries at the VANCHCS will be studied. Patients will be age 18-75 and have a clinical history of brain injury from stroke, brain tumor, surgery or trauma. Patients will be screened for evidence of mild residual dysfunction in executive control functions based on reports of real-world difficulties by self and/or significant other (Cognitive Failures Questionnaire, Patient Competency Scale, Mayo-Portland Adaptability Inventory) and/or evidence of executive cognitive deficits on neuropsychological tests (Auditory Consonant Trigrams, Trailmaking B, D-KEFS Stroop, Strategy application). All patients will be in the chronic, stable phase of recovery (>1 week from initial injury), and able to consent for themselves. Only patients who are deemed to have capacity for decision making by physicians caring for the patients will be asked to participate. If there is additional uncertainty, the clinicians on the research staff, Mark D'Esposito, MD, Anthony Chen, MD, or Tatjana Novakovic-Agopian, PhD will interview the patients, provide information on the risks and benefits of the study and ascertain whether the patient understands and has the capacity to make an informed decision.

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Exclusion criteria: Severely apathetic/abulic, aphasic, or unable to participate with the training tasks, history of neurodevelopmental abnormalities, illicit drug use, severe depression. Pacemakers, electronic or metallic implants, shrapnel, claustrophobia, that render MRI unsafe will exclude patients from participating in MRI studies. There will be no restriction in regard to gender, race and socioeconomic status. As safety for MRI during pregnancy is not well established, patients who are pregnant will be excluded. Only English-speaking subjects will be recruited as the neurocognitive tests are only available in English.

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Healthy Volunteers: All healthy volunteers will be screened for past psychiatric problems, severe medical disorders and drug or alcohol abuse history. Screening will be self-report and/or significant other-report. Healthy volunteers will also be screened for evidence of executive cognitive deficits on neuropsychological tests (Auditory Consonant Trigrams, Trailmaking B, D-KEFS Stroop, Strategy application). tests (Auditory Consonant Trigrams, Trailmaking B, D-KEFS Stroop, Strategy application).

b. How do the inclusion/exclusion criteria reflect the purpose of the study?
The study seeks to investigate neural changes associated with clinically relevant cognitive training of patients with acquired brain injury. Variability in cognitive performance is a significant problem in the interpretation of many rehabilitation studies. Limiting the study to patients with stable, chronic deficits will facilitate the detection of changes related to the parameters of interest. Acute recovery presents a phase of high variability and ongoing neural and vascular changes, therefore only patients in chronic stages will be included. Studies at this stable phase will facilitate detection of otherwise subtle changes in these 'proof-of-principle' studies. Findings are less likely to be confounded by 'spontaneous' recovery or vascular changes.

c. How do inclusion and exclusion criteria impose fair and equitable burdens and benefits?
The purpose of the inclusion/exclusion criteria is to limit the study to patients with stable, chronic deficits who are not severely abulic or aphasic, as the results of this research might benefit individuals in the general population who meet the inclusion criteria and is not expected to benefit individuals who are severely abulic or aphasic. Patients who are severely abulic or aphasic are already burdened by other factors (e.g., major difficulty in activities of daily living) and should not also be burdened by participating in research tasks they will not be able to perform. In addition, the informed consent process requires capable decision makers and patients who are severely abulic or aphasic are likely to be decisionally impaired.

d. Describe the science and ethics of excluding groups that might benefit from the research. *(If women or minorities are excluded, explain reasons for exclusion.)*
Patients who are severely abulic or aphasic will not be able to perform the tasks involved in these studies and are therefore excluded.

7. Research Setting:

a. Describe the research setting in context of equitable selection of subjects.
The research will be conducted at the Martinez VA and the University of California, Berkeley.

b. Where will participants be screened, enrolled, and followed?

☐ **VANCHCS Outpatient Clinics - Check all that apply:**
- ☐ Chico VA Outpatient Clinic - Specify Clinic:
- ☐ Fairfield VA Outpatient Clinic - Specify Clinic:
- ☐ Mare Island VA Outpatient Clinic - Specify Clinic:
- ☐ McClellan VA Outpatient Clinic - Specify Clinic:
- ☒ Martinez VA Outpatient Clinic - Specify Clinic: **Neurobehavioral Neurology**
- ☐ Oakland VA Outpatient Clinic - Specify Clinic:
- ☐ Oakland VA Mental Health and Substance Abuse Clinic - Specify Clinic:
- ☐ Redding VA Outpatient Clinic - Specify Clinic:
- ☐ Sacramento VA Mental Health Clinic - Specify Clinic:

☐ **Sacramento VA Medical Center – Check all that apply:**
- ☐ Outpatient Clinic: Specify:
- ☐ Inpatient Ward: Specify:
- ☐ UC Davis CTSC Clinical Research Center (CCRC)

☒ **VANCHCS Martinez: Center for Rehabilitation and Extended Care (CREC)**

☐ **VANCHCS Martinez: UC Davis Alzheimers Disease Center (UCD ADC)**

☒ **VANCHCS Research Space - Specify Site:** Martinez Research Building 4 and Brain Health Building

☐ **UC Davis Medical Center - Specify:**

☒ **University or College Campus - Specify:** UC Berkeley Neuroscience Institute

☐ **VACCHCS Outpatient Clinic - Specify Clinic:**

☒ **VACCHCS Research Space - Specify Site:** Martinez VA Research Building 4; Martinez VA Center for Integrated Brain Health and Wellness

☐ **Other - Specify:**

8. How will participants be recruited for taking part in the study? *Please review "Important Information for Researchers" for more information about acceptable recruitment methods.*

a. Check all that apply:

☒ **Investigator's patient population:** Study investigators recruit their own patients directly in person and/or nurses working with researchers approach patients.

☒ **Scheduled visit:** Study investigators provide their colleagues with an IRB approved "Dear Patient" letter describing the study. This letter can be signed by the treating health care provider and would inform the patients about how to contact the study investigators. The study investigators may not have access to patient names and addresses.

☒ **Physician referral:** Study investigators send an IRB approved letter to colleagues asking for referrals of eligible patients interested in the study. The investigators may provide the referring physicians an IRB approved Information Sheet about the study to give to patients. If interested, the patient will contact the PI. Or, with documented permission from the patient, the PI may be allowed to talk directly with patients about enrollment.

☒ **Direct advertising:** Interested participants will initiate contact with study investigators. *(Submit an electronic copy of all recruitment media listed in this section to the IRB Coordinator who will forward it to VANCHCS Public Affairs Officer (PAO) for review prior to IRB review and approval.)*

☐ Newspaper: Name(s)

☐ Bulletin Board Poster: Posting Location(s)

☒ Flyers: Posting Location(s) **VA Clinics , Vet Centers, Dept of Rehab offices, Community Colleges veteran services offices, Employment Development Department Disabled Veterans Outreach offices, Travis Transition Service Center, UC and CSU Veteran services offices, adult schools with classes for brain-injured students, community bulletin boards, County Veterans Service Offices and community organizations that provide services to disabled veterans.**

☒ Internet: Web site address **Advertisements on http://sfbay.craigslist.org**

If using the media above, see VANCHCS Policy Statement PS-00-9 "Local Publications" or call VANCHCS HRPP at 916 366-5369.

☐ Radio: Station Name(s)

☐ Television: Station Name(s)

If using the media above, see VANCHCS Policy Statement PS-00-7 "Public Affairs Program."

☒ Other: **Letter to Potential Subjects, Letter to Clinicians, Brochure, Letter to Service Provider, Craigslist advertisement**

☒ **Waiver of Authorization and Consent for recruitment purposes:** This waiver is an exception to the policy but may be requested in exceptional circumstances such as:

☐ Minimal risk studies in which participants will not be contacted, for example chart/database review only (Describe who and how):

☒ Review of charts/database is needed to identify prospective participants who will then be contacted (Describe who and how): **Drs. Chen and Novakovic-Agopian will review medical charts of prospective participants.**

☐ Large-scale epidemiological studies and/or other population-based studies when participants may be contacted by someone other than personal health care provider (Justify and describe by who and how):

☒ **Direct contact:** Potential participants have previously given consent to be contacted for participation in research. Clinic or program develops an IRB approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form from a different study that was approved by the IRB.

☒ **Potential participants unknown to investigators:** Study investigators recruit potential participants who are unknown to them. Examples include direct approach in public situations, random digit dialing, use of social networks, Please explain here: **In the case of physician referral or self-referral, investigators may not know the potential participants.**

☐ **NO contact:** This study does not involve participant contact for recruitment. Examples include record review, use of specimens.

b. Are participants being paid *(includes all types of reimbursement, such as parking fees, etc.)* **for participation?**

☒ Yes ☐ No

Note: VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's care and when it makes no special demands on the patient beyond those of usual medical care.

- *If "YES", continue to question 1), 2), 3), 4), 5) and 6) below.*
- *If "NO", skip to Section F.9.*

1) Payment may be permitted in the following circumstances
Check all that apply

☒ **No Direct Subject Benefit:** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer participant is being treated, and when the standard of practice in affiliated non-VA institutions is to pay participants in this situation.

☐ **Others Being Paid:** In multi-institutional studies, when human participants at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

☐ **Comparable Situations:** In other comparable situations in which payment of participants is appropriate. Describe:

☒ **Transportation Expenses:** When transportation expenses are incurred, by the participant that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

2) Payment Amount:
Total Amount $ **120-780**
Prorated as follows: **$20/hour**

3) Method of Payment:

☒ Cash	☐ Check	☐ Gift certificate	☐ Other:

4) Payment Schedule:

☐ Each visit	☒ Study completion	☐ Other:

5) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the participant.
Participants are being compensated for the inconvenience and time spent in a study that may provide no direct benefit to them. They will undergo 6 - 36 hours of cognitive, functional, and imaging assessments, up to 3 hours at a time.

6) Substantiate that proposed payments are fair and appropriate and that they do not constitute undue pressure or influence to participate.
Participation in the study will require a substantial amount of time. During the Informed Consent process, participants will review the nature, risks, benefits, alternatives, and requirements of the study. The rate of $20/hour is not excessive, given wage rates in the local vicinity, and therefore would not constitute an undue inducement to participate in the study.

9. **Which of the following vulnerable populations will be recruited for this study?** *(Check all that apply).*		
☒ None	☐ Children*	☐ Non-English Speaking
☐ Economically Disadvantaged*	☐ Employees	☐ Persons with HIV
☐ Educationally Disadvantaged*	☐ Fetuses*	☐ Prisoners*
☐ Impaired Decision Making Capacity*	☐ Homeless/Shelter	☐ Students/Trainees
☐ Pregnant Women*	☐ Mentally Disabled*	☐ Terminally Ill Patients
☐ Others:		
* *listed in the Federal regulations; VHA Handbook 1200.5 Appendix D lists special requirements*		

a. Describe the scientific and ethical reasons for including vulnerable populations in the research. *(Why are vulnerable populations necessary in this research study?)*
n/a

b. Describe the extra protections and additional safeguards that protect the rights and welfare of vulnerable groups. *(How are the vulnerable populations being protected?)*
n/a

c. Describe the procedures that you have devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent participants or persons with impaired decision-making capacity.
n/a

G. RESEARCH PROCEDURES

1. **Check all procedures to be performed on human participants, samples or charts:**	
☐ Analysis of Existing Biological Specimens	☒ Interview
☒ Analysis of Existing Data	☐ Invasive Procedures – Diagnostic (e.g. biopsy, catheters, etc.)
☐ Biological Specimen Collection (urine, sputum, tissue, etc.)	☐ Invasive Procedures – Therapeutic (e.g. infusions, catheters, etc.)
☐ Blood Collection	☒ fMRI: Clinical Research
☒ Chart Review	☐ MRI: Clinical Research
☒ Cognitive or Perceptual Experiment	☐ MRI: Diagnostic
☐ Commercial Product Development Potential from Human Biological Specimens	☐ Placebo
☐ Deception	☐ Physical Measurements: Non-Invasive (e.g. vitals signs)
☐ Device(s): FDA approved	☐ Public Behavior Observation
☐ Device(s): Investigational	☒ Questionnaire
☐ Drug(s): FDA approved	☐ Radiation: Clinical Research (e.g. PET)
☐ Drug(s): FDA approved Controlled Substance	☐ Radiation: Diagnostic (e.g. X-ray)
☐ Drug(s): Investigational	☐ Radiation: Therapeutic
☐ Drug(s): Investigational Controlled Substance	☐ Specimen Collection for Future Use (tissue banking)
☐ ECG	☐ Specimen Use from Tissue Bank (stored samples)
☒ EEG	☐ Surgery
☐ EMG	☐ Survey
☐ Evaluation of Program or Services	☐ Taste Test

☐ Gene therapy	☐ VA Data Record Search (Data Mart, Data Warehouse, etc.)
☐ Genetic/DNA Research	☒ Other **neurocognitive testing and cognitive task training**

2. Describe research procedures to be performed on participants, samples or charts.

a. Describe all interactions with participants or their identifiable samples or data in detail.

Patients and Healthy Volunteers: The research involves (1) neurocognitive testing, (2) practice on cognitive tasks, and (3) performing MRI scans. All study procedures described will be done at the Martinez VA Research Building 4, Outpatient Clinic, Brain Health Building, and/or Center for Rehabilitation and Extended Care (CREC) except that patients will be referred either to the Brain Imaging Center, UC Berkeley or to Martinez VA for functional MRI scans.

__Neurocognitive measurements: Subjects (patients and healthy volunteers) will be asked to participate in a focused battery of neurocognitive (neuropsychologic) tasks. This testing will be done at the Martinez VA Outpatient Clinic, Brain Health Building and/or Center for Rehabilitation and Extended Care (CREC). During this session, subjects will sit in front of a computer screen and respond to visual stimuli using a keyboard or button press. The subjects will also be asked to do written tests and answer written questionnaires about their cognitive and emotional status.

__Cognitive task practice: Subjects (patients and healthy volunteers) participate in cognitive task practice requiring attention and memory. These may be of short, medium and long-term duration in 3 separate stages. In the first stage, subjects may be asked to practice tasks for a single session. The short-term practice tasks involve presentations of images or words on a computer during one session lasting up to 90 minutes. In the second stage, subjects may be asked to practice tasks over 2-4 weeks. This medium-term training also involves practicing computerized cognitive tasks that involve attention and memory for 30-60 minutes a day. Subjects will be randomized into groups doing the same tasks, but in a different order. In the third stage, subjects will be asked to participate in cognitive task practice that is designed to be a form of cognitive rehabilitation training. This long-term training includes computer-assisted and therapist-guided practice 1-2 hours each day for up to 6 weeks working on cognitive tasks that engage attention, working memory, goal management and other executive functions, and may also include up to 6 weeks attending education sessions about brain health, with a therapist on an individual basis and in groups. The long-term training will include sessions with staff at the Martinez VA Outpatient Clinic, Brain Health Building and/or Center for Rehabilitation and Extended Care (CREC) on a weekly basis. Subjects in this third stage are also randomized into groups that do the same tasks, but in a different order. Assignments and materials for practicing at home will be given to patients and healthy volunteers. For computerized tasks, software for practicing tasks at home will be offered to participants. Subjects may stop participating at any time. Typically, neurocognitive testing and fMRI studies are performed before and after training.

__Functional MRI measurements: In the MRI test, subjects (patients and healthy volunteers) are asked to lie on their backs in the MRI scanner and perform a cognitive task. When the subjects are ready to be scanned, an MRI imaging coil will be placed around the subject's head. The subject will not come into contact with the coil during the experiment. Foam pads will be placed around the subject's head to limit head movement during the study. Functional MRI will involve scanning during the performance of a cognitive task and during rest. The cognitive task will involve presentation of images or words on a computer monitor or sounds through headphones. The subjects are asked to respond to certain stimuli by pressing a button. Basic structural images will be taken for reference to align with the functional images (these are separate from the clinical structural MRI imaging done as standard of care). Scanning will be performed using a 3 Tesla Siemens or 4 Tesla Varian scanners under the supervision of the Director of the Brain Imaging Center, Dr. Mark D'Esposito or co-investigator Dr. Anthony Chen.. All MRI studies performed at the Brain Imaging Center are part of research protocols and are not intended to provide comprehensive clinical MRI examinations of the brain. If a potential abnormality is identified on an MRI scan, the PI will immediately notify the subject and the family physician.

__EEG studies: In EEG studies, EEG is recorded while concurrently monitoring behavior. Subjects (patients and healthy volunteers) are asked to sit in a soundproofed room and have EEG electrodes placed on their scalp with conducting paste. The experiments involve presentation of images on a computer monitor, sounds

through headphones, or taps to fingers. The subject is asked to respond to certain stimuli by pressing a button. All stimuli are presented at a comfortable level. A recording session typically takes 60-90 minutes. The subject is given breaks every 5-10 minutes, but may request a break or stop the experiment at any time. These will be done in Research Building 4 at VANCHCS Martinez. ___Follow-up contact: Researchers will contact subjects by telephone 6 months after other study activities to ask standardized questions about their post-participation level of functioning in various life domains. Telephone contact takes 30-60 minutes. Subjects may also be asked to return six months after their first visit for follow-up neurocognitive testing and MRI.

b. Describe the research methods, including how the study will be implemented locally.
The research involves (1) neurocognitive testing, (2) practice on cognitive tasks, and (3) performing MRI scans. (1) Neurocognitive testing will be done at the Martinez VA Research Building 4, Outpatient Clinic, Brain Health Building and/or Center for Rehabilitation and Extended Care (CREC); (2) practice on cognitive tasks will be done at the Martinez VA Research Building 4, Outpatient Clinic, Brain Health Building and/or Center for Rehabilitation and Extended Care or at home; and (3) performing fMRI scans will be done at the Brain Imaging Center.

c. Provide detailed information about all study procedures, including the approximate duration and frequency of each procedure. It is not necessary to repeat descriptions of non-human related procedures from the protocol narrative *(e.g. you should describe how much and how frequently blood is drawn, but not the methods for performing tests on the blood, if already stated elsewhere).*

___Neurocognitive measurements: This part of the experiment takes approximately 2 - 3 hours. The subject is free to take breaks throughout the session. Subjects may undergo neurocognitive measurements once if they do not undergo cognitive training, twice if they participate in short-term or medium-term training (pre- and post-training), and three times if they participate in long-term training (at baseline, 5 weeks, and 10-weeks)

__Cognitive task practice: These may be of short, medium and long-term duration in 3 separate stages. In the first stage, subjects may be asked to practice tasks for a single session. The short-term practice tasks involve presentations of images or words on a computer during one session lasting up to 90 minutes. In the second stage, subjects may be asked to practice tasks over 2-4 weeks. This medium-term training also involves practicing tasks that involve attention and memory for 30-60 minutes a day. Subjects will be randomized into groups doing the same tasks, but in a different order. In the third stage, subjects may be asked to participate in cognitive task practice that is designed to be a form of cognitive rehabilitation training. This long-term training includes practicing 1-2 hours each day for up to 10 weeks working on cognitive tasks that engage attention, working memory, goal management and other executive functions, or education sessions about brain health, with a therapist on an individual basis and in groups.

__ fMRI scanning: A session typically takes 60-90 minutes and the subject is given frequent breaks. The subject may stop the experiment at any time. Subjects may undergo fMRI once if they do not undergo cognitive training, twice if they participate in short-term or medium-term training (pre- and post-training), and three times if they participate in long-term training (at baseline, 5 weeks, and 10-weeks)

__EEG studies: A recording session typically takes 60-90 minutes. The subject is given breaks every 5-10 minutes, but may request a break or stop the experiment at any time. These will be done in Research Building 4 at VANCHCS Martinez.

___Follow-up contact: Researchers will contact subjects by telephone 6 months after other study activities to ask standardized questions about their post-participation level of functioning in various life domains. Telephone contact takes 30-60 minutes. Subjects may also be asked to return six months after their first visit for follow-up neurocognitive testing and MRI.

d. Distinguish procedures that are for research from those that are clinically indicated and/or standard of care. All the procedures are for research.

e. Will any study procedures *(including analysis of subject samples or data)* **be conducted at any site other than VANCHCS/VACCHCS?**

☒ Yes ☐ No

- *If "YES", complete the following information:*

1) Site(s): University of California, Berkeley and outpatient subjects' homes

2) What study procedures will be performed there? fMRI at UC Berkeley Brain Imaging Center. Outpatient subjects will have option to participate in computer-assisted cognitive training at home or in Research Building 4 at VANCHCS Martinez or the Martinez VA Center for integrated Brain Health and Wellness.

H. RISK

1. Expected risks

- *Describe all known risks to subjects of study-related procedures and products and their expected frequency and severity.*
- *Assess the likelihood and seriousness of identified risks.*

a. Physical Risks: The research procedures involved in this study present minimal physical risk to the subjects. MRI Studies: Subjects will be repeatedly queried about metal in their bodies and claustrophobia before undergoing MRI. The risks for 3T and 4T MRI are the same as for clinical MRI scans, typically at 1.5T. The risks of this procedure will be attenuated for those patients who have undergone acute MRI as verified by the acute images or notes in their charts. If CT rather than MRI was taken acutely, the reasons will be established before considering that patients participation in the MRI portion of this project. Although MRI scanning is painless, subjects may experience discomfort. In particular, subjects may be bothered by the beeping and hammering sounds made when the scanner is collecting measurements. Some people become claustrophobic inside the magnet. Subjects may also experience peripheral stimulation, manifested as a gentle tap or sensation of mild electric shock. Because the MRI scanner attracts certain metals, it could move metallic objects within the MRI room which could possibly harm a subject. Further, because of the high magnetic field, people with pacemakers, heart rhythm disturbances, permanent cosmetics or certain metallic implants will be excluded. Finally, because the risks to a fetus from MRI are unknown, all women will have a pregnancy test immediately prior to scanning. Disposable earplugs will be provided to diminish the noise. Subjects with a history of claustrophobia will be excluded. Precautions have been taken to prevent metallic objects from moving within the MRI room. If a subject is uncomfortable for any reason, the experiment will be stopped. They will be warned about claustrophobia and will be given earplugs or headphones in fMRI study to reduce the noise intensity. They will also be given a hand held buzzer that sounds in the exterior room when pressed to indicate that they are uncomfortable or want to discontinue the imaging procedure. When this occurs subjects will be immediately removed from the scanner.

EEG Studies: Conventional EEG recording with standard subject grounding procedures are always employed. Subjects may become bored or anxious during the course of EEG measurements. The anxiety infrequently encountered can be immediately addressed and the EEG recording will be aborted, if requested.

b. Psychological Risks: The research procedures involved in this study present minimal psychological risk to the subjects. The primary risk in this study is the potential for anxiety, discomfort or boredom associated with completing neuropsychological testing, fMRI or EEG testing, and treatment intervention. The behavioral test battery is relatively brief and is non-invasive. It consists of instruments (neuropsychological and functional assessments, and self-report questionnaires) that have been previously administered to different patient populations, thus the potential for creating undue anxiety or frustration is minimal. There is a possibility of fatigue or boredom from performance of cognitive tasks. Participants are allowed frequent breaks during training. For patients, training will be adjusted for the fatigue level, and training sessions will stop if patients are frustrated or fatigued.

c. **Social Risks:** There are no perceived social risk.

d. **Economic Risks:** There are no perceived economic risks.

e. **Legal Risks:** There is a real, but small risk of breach of confidentiality. This risk will be minimized by controlling data storage.

2. Risk minimization

a. **Describe the impact of study design on risk.** *(e.g. does observational design impact on risk; or does observational design only impact privacy risks; or does placebo controlled design impact risk, or do all patients receive therapy; or does single blind placebo washout period increase risk of uncontrolled symptoms?)*

The study is designed in a series of parts. First, participants are enrolled in a cross-sectional study involving neurocognitive and functional MRI testing. Risks associated with this portion are related to time consumption, potential boredom and risks to privacy. Additional portions of the study include an experimental cognitive task practice interventions, in which participants are randomized prospectively to different groups which do the same tasks, but in different orders. The risks of boredom and fatigue increase.

b. **Describe study procedures that minimize risks.**

Psychological:

__The behavioral test battery is relatively brief and is non-invasive. It consists of instruments (neuropsychological and functional assessments, and self-report questionnaires) that have been previously administered to different patient populations, thus the potential for creating undue anxiety or frustration is minimal.

__Cognitive training: There is a possibility of fatigue or boredom from performance of cognitive tasks. Participants are allowed frequent breaks during training. For patients, training will be adjusted for the fatigue level, and training sessions will stop if patients are frustrated or fatigued.

Physical:

__MRI: The risks of this procedure will be attenuated for those patients who have undergone acute MRI as verified by the acute images or notes in their charts. If CT rather than MRI was taken acutely, the reasons will be established before considering that patients participation in the MRI portion of this project. Although MRI scanning is painless, subjects may experience discomfort. In particular, subjects may be bothered by the beeping and hammering sounds made when the scanner is collecting measurements. Some people become claustrophobic inside the magnet. Subjects may also experience peripheral stimulation, manifested as a gentle tap or sensation of mild electric shock. Because the MRI scanner attracts certain metals, it could move metallic objects within the MRI room which could possibly harm a subject. Further, because of the high magnetic field, people with pacemakers, heart rhythm disturbances, permanent cosmetics or certain metallic implants will be excluded. Finally, because the risks to a fetus from MRI are unknown, all women will have a pregnancy test immediately prior to scanning. Disposable earplugs will be provided to diminish the noise. Subjects with a history of claustrophobia will be excluded. Precautions have been taken to prevent metallic objects from moving within the MRI room. If a subject is uncomfortable for any reason, the experiment will be stopped. They will be warned about claustrophobia and will be given earplugs or headphones in fMRI study to reduce the noise intensity. They will also be given a hand held buzzer that sounds in the exterior room when pressed to indicate that they are uncomfortable or want to discontinue the imaging procedure. When this occurs subjects will be immediately removed from the scanner.

__Conventional EEG recording with standard subject grounding procedures are always employed. Subjects may become bored or anxious during the course of EEG measurements. The anxiety infrequently encountered can be immediately addressed and the EEG recording will be aborted, if requested.

__Privacy: We recognize the need to guaranteed participants confidentiality in order to protect individual participants from potential embarrassment, as well as to obtain maximally valid data. All information will be kept confidential in accordance with all regulations as specified by the Department of Veterans Affairs. All patient data will be depersonalized after initial screening and enrollment into the study. All personally identifying information will be kept in locked cabinets or password protected files.

c. Describe standard of care procedures that minimize risks.

There is no clear national standard of care for rehabilitation treatments for patients with brain injuries. However, most of our subjects receive high quality medical care at the VANCHCS by qualified professionals including physicians, psychologists and therapists. Neurologic and neuropsychologic evaluation, CT and/or MRI scans are all part of standard of care in our practice.

I. RISK BENEFIT RATIO

1. Risks in Relation to Benefits

a. What are the direct benefits to the participants?

There are no definite direct benefits to the subjects. The findings from these studies may potentially make a major impact in improving rehabilitation for patients with brain injuries, leading to a direct benefit to society.

b. Why do you believe the risks are reasonable in relation to the potential benefits to the participants?

The risks of this research to subjects are minimal. There are no definite direct benefits to the subjects.

c. What are the benefits to society?

As noted in the introduction, improved treatments for executive control dysfunction would potentially make a major impact in improving outcomes after brain injuries. The findings from these studies will be presented to health care workers and to other scientists in the field, and this is expected to influence both clinical care and future scientific investigations.

Why do you believe the risks are reasonable in relation to the potential benefits to society? The risks of this research to subjects are minimal, and therefore the risk is reasonable in relation to the potential benefits to society.

2. Alternatives to participation

a. Describe appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the participant. *(If no alternatives exist or if this is not a treatment study, state so.)*

This is not a treatment study. Subjects may decline participation in these studies, or discontinue participation at any time. Declining to participate in the studies will not have any effect on standard clinical care.

J. MONITORING SAFETY

1. Describe the Data and Safety Monitoring Plan that ensures the safety of participants in this research study. *(e.g. what labs to monitor for abnormalities, what questionnaire responses to monitor for suicide)*

All patients will be seen by the PI or his research staff. Research subjects will continue to receive usual care. Although this is a minimal risk study, the PI and investigators will monitor study subjects for adverse events during the study. Monitoring will occur continuously during study activities. Although the only interventions are behavioral, a standard grading scale will be used to describe AEs if the need arises: 0=none, 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=fatal. The attribution scale is 1=definitely not related, 2=probably not related, 3=possibly related, 4=probably related, 5=definitely related to the study interventions. The PI will promptly report any serious adverse events or unanticipated problems involving risks to study subjects in accordance with regulations: reportable adverse effects arising from any of the research procedures will be submitted promptly to the IRB. Although they are not anticipated to occur, unanticipated problems (involving risks to subjects) or Serious Adverse Events in subjects will be reported to the IRB within 5 working days of awareness of the event. Copies of reports will be submitted to the IRB so that they are received no later than 15 calendar days after the event. In addition, adverse events in all categories will be included in the PIs reports to the IRB as required by the federal regulations. All reportable adverse events will be compiled, and reported in summary form, on an annual basis to the IRB, and at the conclusion of the study. The PI reviews and reports on the progress of the study on an annual basis. The PI will monitor study progress, outcomes and participant safety, and may make recommendations on changes to the study protocol. The PI will review safety on an ongoing basis. Dr. Anthony Chen will perform the safety monitoring.

2. Does this study have a Data and Safety Monitoring Board (DSMB)?

☐ Yes ☒ No

- *If "YES":*

a. What is the nature and expected role of the DSMB?

b. How often will the findings of the DSMB be reported to the IRB?

3. Explain how researchers will manage adverse events and research-related injuries.

All research staff have been directed to document adverse events and to notify the Principal Investigator of any adverse event. Investigators will follow up with subjects until the resolution of the adverse event and will ensure that appropriate medical care is provided.

4. Describe the circumstances under which a participant may be withdrawn prematurely from the study and the potential risks of such early withdrawal.

A participant may decide to withdraw or be withdrawn for a variety of medical and personal reasons, such as lack of interest, non-participation, or change in medical condition. A potential risk of early withdrawal would be the possible adverse effect on the participant's self-esteem (e.g., feeling like a failure). This risk would be addressed by supportive counseling of participants who are withdrawn prematurely.

5. Describe the procedures for reporting adverse events.

Researchers will complete an adverse event report and notify the Principal Investigator, who will report the event to VANCHCS. All unanticipated problems involving risk to subjects or others related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

K. SAFETY REPORT

1. Adverse Events

a. Local (Internal) Adverse Events and Serious Adverse Events (AE/SAE): Have ALL complications, untoward side effects, or adverse events related or possibly related to research at this site been reported to the IRB since the last review?

☐ **Yes** ☐ **No** ☒ **N/A = none occurred**

- *If "YES":*
  Attach a Local Adverse Event spreadsheet summarizing all AE/SAE's which occurred at this site since the last report to the IRB.
- *If "NO":*
  Submit the missing report to the IRB and attach a Local Adverse Event spreadsheet summarizing all AE/SAE's which occurred at this site since the last report to the IRB.

b. Global (External) Adverse Events and Serious Adverse Events (AE/SAE): Have any complications, untoward side effects, or adverse events been reported at other sites (SAE or IND Safety Reports) since last report?

☐ **Yes** ☐ **No** ☒ **N/A**

- *If "YES":*
  Attach a Global Adverse Event spreadsheet summarizing all AE/SAE's which occurred at other sites since the last report to the IRB.

NOTE: Definition of SAE and AE:

- *Serious Adverse Event – any adverse experience that results in the following: Death; Hospitalization; Disability/Incapacity; Congenital Anomaly/Birth Defect; Requires Intervention; or is Life-threatening*
- *Adverse Event – any adverse experience temporally associated* with the investigational treatment not meeting the definition of serious adverse event.*

* ***temporally associated*** *– during the time period the subject participates in the study*

2. Have unanticipated problems* *(local or global)* **involving risks to subjects or others, or significant new findings** *(that have not been previously reported)* **been discovered since the previous IRB review that might affect the subject's willingness to continue participation?**

☐ Yes ☒ No

- *If "YES", complete the following:*

a. Attach a spreadsheet summarizing all unanticipated problems which occurred since the last report to the IRB.

b. Explain the risks or findings in detail: *(a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem)*

c. Describe any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem:

d. Do these risks or findings require modification of the informed consent form?

☐ Yes ☐ No

- *If "YES", have the modifications been submitted to the IRB?*

☐ Yes ☐ No

e. Were subjects notified of these risks or findings?

☐ Yes ☐ No

f. Were subjects re-consented?

☐ Yes ☐ No

3. Have other unanticipated problems (not related to adverse events) been discovered since the previous IRB review?

☐ Yes ☒ No

- *If "YES", complete the following:*

a. Attach a spreadsheet summarizing all unanticipated problems which occurred since the last report to the IRB.

b. Explain the findings in detail:

c. Describe any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem not related to an adverse event:

*** NOTE: Unanticipated problems are any incident, experience, or outcome that meet all of the following criteria:**

- *Is unexpected in terms of nature, severity, or frequency*
- *Is related or possibly related to participation in the research*
- *Suggests that the research places the subject or others at a greater risk of harm than was previously known or recognized*

4. Describe any complaints about the research since the last IRB review.

☒ N/A – none occurred

5. Describe any unanticipated protocol deviations (including errors and accidents) since the last review.

☒ N/A – none occurred

L. PRIVACY AND CONFIDENTIALITY

1. Research Data

a. Identifiers: Please indicate all identifiers that may be used by researchers or included in study research records.

☐ NO identifiers used by researchers *(skip to item L.1.d. "Medical Records or Health Information")*

Check all that apply:

☒ Names	☒ Social Security Number	☐ Device Identifiers
☒ Dates	☒ Medical Record Number	☐ Web URLs
☒ Postal Addresses	☐ Health Plan Numbers	☐ IP Address Numbers
☒ Phone Numbers	☐ Account Numbers	☐ Biometric Identifiers
☐ Fax Numbers	☐ License/Certificate Numbers	☐ Photos and Comparable Images
☒ Email Addresses	☐ Vehicle ID Numbers	☐ Any Other Unique Identifier

b. Source of Identifiers Listed Above: Please indicate the sources of the information listed in part 1(a) above

Check all that apply:

☒ Medical Records (created as part of health care, collected as part of health care, added to the medical record, extracted from the medical record, or used to make health care decisions)
☒ Directly from the Participant, including Interviews, Questionnaires
☐ Records Open to the Public
☐ Other:

c. Describe how identifiers will be used to screen and/or recruit participants for the trial.

Referring providers may provide information to patients on how to contact research staff, but may also ask permission for research staff to contact the patient. This includes permission by the patient to release basic information, including name and contact information, to research staff. To accomplish this, the study will use a Partial Waiver of Authorization and Consent for recruitment. PHI will be accessed by the PI, co-investigators, and research staff in order to contact participants for screening. Screening and eligibility data will initially be reviewed with personal identifiers included.

d. Medical Records or Health Information: Please indicate all information that may be used by researchers or included in study research records.

☐ NO medical record or health information used by researchers *(skip to Section M. "Research Data Security")*

Check all that apply:

☒ History and Physical Exam	☒ Progress Notes
☒ Operative Report(s)	☒ Discharge Summary(ies)
☒ Diagnoses	☒ Drugs/Medications
☒ Radiology Images	☒ Radiology Reports
☒ Pathology Reports	☐ Laboratory Reports
☐ ECG Reports	☒ Consult Reports
☒ Drug Abuse	☒ Alcoholism or Alcohol Abuse
☐ Testing for or Infection with HIV	☐ Sickle Cell Anemia
☒ Psychological Tests	☒ Mental Health (not psychotherapy notes)
☒ Patient Demographics	☐ Only the following records of types of health information:

e. Describe who will access protected health information (PHI) *(i.e. medical record)* **and for what purpose.**

PHI will be accessed by the PI, co-investigators, and research staff in order to contact participants for screening as well as scheduling of studies (e.g. making appointments for neurocognitive testing).

f. Disclosure of Protected Health Information (PHI): Please indicate to whom or where you may disclose any of the information listed above as part of the study process.

Check all that apply:

- ☐ We do not plan to share any of the PHI listed above outside the research team.
- ☒ VANCHCS/VACCHCS Research & Development Committee and Subcommittees
- ☐ VANCHCS/VACCHCS Designated Non-Profit Corporation
- ☐ U.S. Food and Drug Administration (FDA)
- ☒ U.S. Department of Health and Human Services Office for Human Research Protection (OHRP)
- ☒ U.S. Government Accounting Office (GAO)
- ☐ Participant's Medical Record
- ☐ Study Sponsor:
- ☒ Others **UC Berkeley, UC San Francisco, VA San Francisco**

g. Identify who will disclose information.

Anthony Chen, MD and authorized members of the research team.

2. Data Protection

a. Describe the provisions that exist to protect participant privacy during and after the research.

We will collect only the minimum amount of the individual's private information required to complete our study. To protect privacy, we will advise potential subjects of the minimum amount of personal information that would be required of them in order to participate in our study. Furthermore, we will provide information about the logistics of participating in our research study (e.g., location of testing) to ensure that each subject can decide whether logistics will impinge on his/her privacy. Finally, all participants will be informed regarding how information is secured and stored to protect confidentiality. Based on this information, the potential subject can determine for him/herself if he/she wishes to provide this information to us and whether he/she wishes to participate in our research study.

Subjects are contacted with discretion. Consenting and testing take part in private settings. To protect privacy, all subject interviews will be held in a closed room. Information will be discussed between the subject, interviewer, and PI only. None of the information reported by the interviewee will be discussed outside of the enclosed room and all information will be kept confidential.

b. Describe the provisions in place to protect participant confidentiality during and after the research.

Patient data will be kept confidential after initial screening and enrollment into the study. No personally identifying information will be used for data analyses. Collected data will include questionnaire results, neurocognitive testing data, and MRI data. Data will be stored in a database with personally identifying information removed. All personally identifying information, including patient name, and contact information will be kept in locked cabinets or password protected files. A key will be kept to match personal information with data in the case that patients need to be identified and contacted. Patients who receive computer-assisted training at home will be provided with a training website link as well as a secure login (divorced from personal information) and password once their training phase has begun.

M. INTERIM FINDINGS

1. Provide a summary description of study progress, subject experiences, research results obtained thus far, and any new information since the IRB's last review.

1. Training goal-oriented attention self-regulation amongst Veterans with chronic TBI. Twenty-two Veterans with history of chronic TBI (> 6 months) and functional complaints have completed this research protocol after having been randomized into active training (GOALS) or a comparison intervention involving brain health education (BHE). Results. GOALS participants demonstrated improvements on composite measures of attention and executive functions ($p < 0.01$) and a simulated, ecologically-valid 'real world' task ($p < 0.01$), as well as reported improvements on multiple aspects of cognition as it relates to daily functioning (i.e., within domains of working memory, sequencing and switching of attention, and awareness, self-monitoring, planning, task execution, learning, managing fatigue/energy, and anxiety; $p<0.05$). BHE participants did not demonstrate or report similar changes..

2. Development and preliminary testing of a cognitive training system for goal-directed self-regulation: "From Startup-to-CEO". We developed a fully manualized cognitive training system consisting of therapist-administered training and specially designed game scenarios to help illustrate, practice, and develop training concepts.

3. Preliminary data lend support to the plausibility of the hypothesized moderation and medication mechanisms under investigation in this protocol. Data also support that these approaches to training goal-oriented self-regulation are feasible and may help with transfer of skills to daily life contexts and individual goals.

Provide a summary of any relevant recent literature since the IRB's last review. *(Attach copies of any relevant publications.)*

2. Attach any relevant multi-center trial reports.

N. INFORMED CONSENT PROCESS

1. Will all participants taking part in this study be consented on VA Form 10-1086?

☒ Yes ☐ No

- *If "YES", continue to question #2 and #3 below.*
- *If "NO", submit the document entitled "Request to Waive Consent and Authorization for a Research Study" and skip Sections O2 and O3.*

2. Describe the process of obtaining informed consent.

a. Describe who conducts the consenting process.

Anthony Chen, MD, Tatjana Novakovic-Agopian, PhD, Fred Loya, PhD, MA, Erica Pool, Sahar Yusef, and Nicholas Rodriguez will conduct the consenting process.

b. Describe when it occurs.

After a preliminary determination that a candidate meets the inclusion/exclusion criteria, the candidate is contacted by the PI or Co-investigators, who explain the study in great detail. The contact may be at the Martinez VA Outpatient Clinic and/or Center for Rehabilitation and Extended Care, or if necessary, by telephone. The explanation of the study includes a description of the behavioral studies and MRI scanning. The participants are explicitly told that there are no treatment benefits to the proposed research and all participants are told that they can withdraw from the research at anytime. Risks of the behavioral testing, task practice and functional MRI imaging are explained. Candidates are given as much time as needed to consider participation in the study and ask questions. If they are agreeable to the study after initial discussions, candidates are brought to VANCHCS and the studies are again described in detail, with risks and benefits explained. Informed consent is then obtained.

c. Describe where it occurs.

At the Martinez VA Outpatient Clinic, Center for Integrated Brain Health and Wellness, Research Building R-4, Center for Rehabilitation and Extended Care, or UC Berkeley Brain Imaging Center.

d. Describe how you will assure an acceptable level of comprehension before consent.

In order to meet eligibility criteria, patients need to be able to demonstrate understanding of the potential risks, potential benefits, and voluntary nature of the study. Only patients deemed to have capacity by the patient's clinicians will be accepted into the study.

e. For participants who may have impaired decision-making capacity to give informed consent:

1) Describe the likely range of impairment.

n/a

2) Describe how the participants' decision-making capacity to consent will be determined.

The PI (Anthony Chen) and clinician co-investigators (Mark D'Esposito, Novakovic-Agopian), all of whom are experienced clinicians, will interview the patients and ascertain whether the patient understands and has the capacity to make an informed decision. Candidates are given as much time as needed to consider participation in the study and ask questions. Potential participants are asked to restate the description of the study, risks, and benefits. Informed consent is then obtained.

3) Who will determine whether or not the participant has decision-making capacity to consent?

The PI (Anthony Chen) and clinician co-investigators (Mark D'Esposito, Novakovic-Agopian).

f. If any vulnerable populations will be recruited, describe what precautions will be taken to insure their protection from undue influence.

No vulnerable populations will be recruited. Patients with brain damage of the types that are described in this study typically retain the ability to make informed decisions. They are able to understand and repeat study procedures, risks, and benefits. Patients with severe damage may not retain this capacity, but as we are only including patients with mild problems this will not be an issue.

g. If surrogate consent is likely to be required, describe your procedure for obtaining consent from the legally authorized representative.

n/a

3. After Hours Contact Information *(to be included in the consent form)*

a. The VA approved after-hours telephone number for research studies is (916) 843-7000 extension 6051.

b. This study will use the VA approved after-hours telephone number for research studies.

☐ Yes ☒ No

- *If "YES", complete the following:*

1) Designated Service (department):

OR

1) Designated Contact Person:

2) After-hours telephone number for the designated contact person (to be given to the VA after-hours operator):

b. This study will use a Designated Contact Person.

☒ Yes ☐ No

- *If "YES", complete the following:*

1) Designated Contact Person: **Anthony Chen, MD**

2) After-hours telephone number for the designated contact person: **925-580-2806**

O. PRINCIPAL INVESTIGATOR'S KNOWLEDGE ATTESTATION

Initial beside each statement to confirm your knowledge and agreement.

1. I assure that the rights and welfare of human subjects participating in this research project will be protected at all times and that the benefits to be gained from this study are commensurate with the risks involved.
2. I will obtain, (unless a waiver of consent and authorization is approved) an authorization to use PHI for research and a fully documented research informed consent on a VA Form 10-1086 for each subject enrolled.
3. I will document the consent process in the progress notes for each research subject, unless a waiver of consent and authorization is approved.
4. I certify that I will report all serious adverse events and unexpected adverse experiences as required.
5. I acknowledge that I will immediately report any complications arising from this study to the Human Studies Subcommittee/IRB through the Research Office.
6. I understand that any research project utilizing VA resources (i.e. space, personnel, services) must be approved by VANCHCS/VACCHCS Research and Development (R&D) Committee prior to commencement of the project.
7. I understand that any research involving VANCHCS/VACCHCS patients must be approved by VANCHCS/VACCHCS R&D Committee.
8. I will not begin any research project using human subjects before it has been fully approved by VANCHCS IRB and VANCHCS/VACCHCS R&D Committees.
9. I understand that I am required to annually complete an educational course or web-based training on both the protection of human subjects in research and Good Clinical Practice (GCP). ORD and Collaborative IRB Training Initiatives (CITI) have developed a VA training curriculum to satisfy this annual training requirement. (http://www.appc1.va.gov/resdev/fr/PRIDE/training/)
10. I understand that the research staff working for me who are involved in human studies are required to annually complete an educational course or web-based training on both the protection of human subjects in research and Good Clinical Practice. A single combined course will satisfy this requirement.
11. I understand that there may be specific training requirements for me and my research staff regarding animal research, laboratory safety, and security.
12. I understand that I am to cooperate fully with VANCHCS Research Compliance Officer regarding compliance in research.
13. I understand that any research involving radiation must be approved by VANCHCS Radiation Safety Committee.
14. I agree to abide by the requirements of VHA Handbook 1200.18, *Intellectual Property.* (http://www.va.gov/publ/direc/health/Handbook/1200-18hk.pdf)
15. I agree to abide by the requirements of VANCHCS PS-151-9, *Publication of Professional Papers* (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html) and VHA Handbook 1200.19 *Presentation of Research Results Handbook.* (http://www.va.gov/publ/direc/health/handbook/1200.19hk.pdf)
16. I agree to abide by the requirement of VANCHCS PS-151-7, *Administration of Non-VA Funded Research Grants.* (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html)
17. I agree to abide by the requirements of VANCHCS PS-151-2, *Detecting and Managing Conflicts of Interest in Research* (http://vaww.northern-california.med.va.gov/policies/ResearchIndex.html).
18. I agree to abide by the requirements of VHA Handbook 1200.8, *Safety of Personnel Engaged in Research* and the *Chemical Hygiene Plan* for Medical Research. (http://www.va.gov/publ/direc/health/Handbook/1200.8hk.pdf)

P. PRINCIPAL INVESTIGATOR'S ASSURANCE

As the Principal Investigator, I have ultimate responsibility for the performance of this study, the protection of the rights and welfare of the human subjects, and strict adherence by all co-investigators and research personnel to all requirements of the Human Subjects Subcommittee (IRB), the Research and Development Committee, federal regulations, and state statutes for human subjects research.

I hereby assure the following:

All named individuals on this project have read and understand the procedures outlined in the protocol. All experiments and procedures involving human subjects will be performed under my supervision or that of another qualified professional listed on this protocol.

I understand that, should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the description of human subjects used in the funding proposal(s) is identical in principle to that contained in this application.

I will submit modifications and/or changes to the IRB as necessary to ensure these are identical.

I and all the sub-investigators and research personnel agree to comply with all applicable requirements for the protection of human subjects in research including, but not limited to, the following:

- Obtain legally effective informed consent of all human subjects or their legally authorized representatives, and use only the currently approved, stamped consent form (if applicable);
- Make no changes to the approved protocol or consent form without first having submitted those changes for review and approval by VANCHCS Institutional Review Board;
- Within 24 hours of investigator awareness, communicate any Local Research Subject **Deaths** to the IRB and submit a written follow-up report to the IRB within 5 working days;
- Communicate other Local Serious Adverse Events, except death, in writing to the IRB within 5 working days after investigators learn of the event;
- Promptly provide the IRB with any information requested relative to the project;
- Promptly and completely comply with an IRB decision to suspend or withdraw its approval for the project;
- Submit an application for continuing review within 60 days prior to the date on which the approval for the study expires. I understand if I fail to apply for continuing review, approval for the study will automatically expire, and study activity must cease until IRB current approval is obtained;
- Submit a final report, within 60 days, to VANCHCS Research Office at the conclusion of this project;
- If I am unavailable to direct this research personally, I will arrange for an investigator to assume direct responsibility as principal investigator in my absence. I will submit a protocol amendment to the IRB in advance of such arrangements requesting this modification.

I understand my obligations as an investigator and agree to fulfill them.
The information contained in this application is complete to the best of my knowledge.
By signing this document, I attest that all the information I have provided is accurate to the best of my knowledge.

Principal Investigator  **Date 05/22/2017**