RECOVER-NEURO: A Platform Protocol for Evaluation of Interventions for Cognitive Dysfunction in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

By Sukanya Mohapatra and Daniel Thai
PIs: Dr. Linda Geng and Dr. Upinder Singh

Stanford MEDICINE | Center for Clinical Research

BACKGROUND

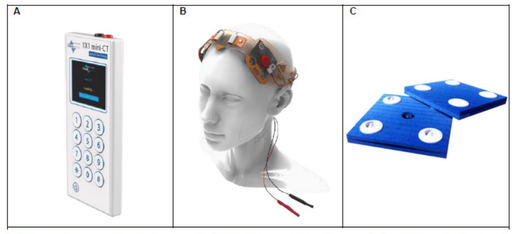
- PASC, also known as Long COVID, is a chronic condition present in up to 80% of SARS-CoV-2-infected, hospitalized patients and 40%-70% of non-hospitalized patients with COVID-19
- A common symptom is cognitive dysfunction, which can prevent patients' return to work and their daily lives
- There is an urgent and unmet clinical need to better understand PASC and develop interventions to restore patients' cognitive function
- This study is a part of the RECOVER (Researching COVID to Enhance Recovery) Initiative
- Data from the RECOVER initiative, as well as existing literature, highlight cognitive dysfunction as a frequently reported symptom
- The reason PASC involves cognitive dysfunction is not known but hypothesized mechanisms include neuroinflammation, loss of hippocampal neurons, microglial dysfunction, and neuronal mitochondrial dysfunction
- The impact of PASC-related cognitive dysfunction contributes to disability, poor quality of life, and psychological morbidity.
- This platform protocol aims to investigate interventions with prior evidence of improving cognitive function

OBJECTIVES AND ENDPOINTS

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary		
Evaluate the intervention's effect on self-reported cognitive function versus comparator	Everyday Cognition 2 (ECog2)	Change in average score from baseline to End of Intervention (EOI)
Secondary		
Assess the intervention's effect on cognitive patient-reported outcomes (PROs) versus comparator	PROMIS-cognitive function – short form 8a (PROMIS-Cog)	Change in total score from baseline to EOI and End of Study (EOS), defined as 90 days post-intervention
Compare the intervention's effect on an objective neurocognitive battery versus comparator	• Auditory Verbal Learning Tests • Symbol Digit Modalities Test • Verbal Fluency (lexical + semantic) • Digit Vigilance Test • Cogstate tests: Detection, Identification, One Back • NIH Toolbox Flanker Inhibitory Control and Attention Test	Change from baseline to EOI and EOS
Evaluate the intervention's durable effect on self-reported cognitive function versus comparator	ECog2	Change in average score from baseline to EOS
Characterize the intervention's safety	Serious Adverse Events (SAEs), Unanticipated Adverse Device Effects (UADEs), and/or Events of Special Interest (ESIs)	Proportion of SAEs, UADEs, and/or ESIs
Exploratory		
Assess the intervention's effect on exploratory PROs versus comparator	• PASC Symptom Questionnaire • Patient-reported Outcomes Measurement Information System (PROMIS)-29+2 • PROMIS-fatigue – short form 10 a (PROMIS-Fatigue) • PROMIS-8a sleep related impairment (PROMIS-SRI) • PROMIS-8b sleep disturbance (PROMIS-SD) • Modified DePaul Symptom Questionnaire Post Exertional Malaise (DSQ-PEM)	Change in total score from baseline to EOI and EOS

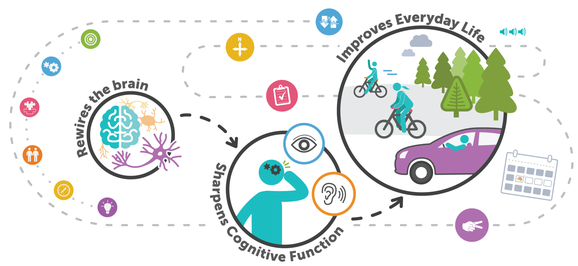
EXPERIMENTAL DESIGN AND INTERVENTIONS

- The study's design is a platform protocol created to be flexible so that it can be used for a wide range of settings within healthcare systems, remote settings, and in community settings
- This platform protocol is a prospective, multi-center, multi-arm, randomized, controlled trial evaluating treatment of PASC mediated cognitive dysfunction in patients previously infected with SARS-CoV-2
- Participants had an equal chance of being randomized to one of five intervention groups (Figure 5)
- Active study intervention means all or part of the study intervention could affect a participant's brain activity.
- Active comparator means the study intervention is not expected to affect brain activity.
- The primary outcome for this study uses a subjective assessment for cognitive function: the ECog2; a self-reported survey assessing a participant's ability to perform various everyday tasks related to memory, language, visual-spatial and perceptual abilities, and executive functioning.
- Aside from daily intervention activities, participants attend three clinic visits and one remote visit (Figure 4)
- During study visits, participants have vital signs recorded, give blood for biorepository samples, provide updates on medications and symptoms, complete survey questions, and complete a neurocognitive battery assessment with a licensed psychometrician



(A) 1x1 Mini-CT tDCS device; (B) SNAPstrap Headgear; (C) EASYpad Electrodes.

Figures 1-2. tDCS device and BrainHQ graphic



BrainHQ

BrainHQ is an online brain training program that targets memory, attention, and the time it takes to understand and respond to information. BrainHQ activities may include puzzles and games for brain training. In the active study intervention, the activities will adapt to each participant and will get a little easier or harder depending on the participant's progress.

The Active Comparator is a set of cognitive activities that are similar to the BrainHQ activities but do not adapt to a participant's progress. These activities are not the same as usual care.

BrainHQ + PASC-CoRE (PASC-Cognitive Recovery)

In addition to completing **BrainHQ** sessions, some participants will also complete **PASC-CoRE.** This is an online goal management training program for people with Post-Acute Sequalae of SARS-CoV-2 infection (PASC), including Long COVID. Participants will work with trained study staff to:

- Plan and manage personal goals
- Learn mindfulness-based ways to work through distractions
- Learn skills to focus on goal-oriented tasks
- Develop strategies to manage mental tiredness

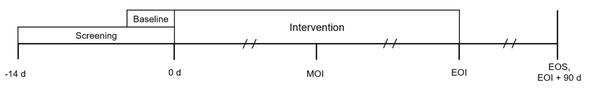
BrainHQ + transcranial Direct Current Stimulation (tDCS)

While completing **BrainHQ** sessions, some participants will also use **tDCS**, a safe and well-tolerated form of noninvasive brain stimulation currently under investigation for use in managing a variety of symptoms or as part of a rehabilitation program. Participants in the **BrainHQ + tDCS-active** group will wear a headset that directs a mild electrical current to specific parts of the brain. It is thought to have the most benefit when repeated daily or nearly daily over a period of time.

Participants in the **BrainHQ + tDCS-comparator** group will wear the tDCS headset that will briefly deliver a mild electrical current at the beginning of the BrainHQ session to mimic the active tDCS. However, no additional current will be delivered from the device during the session. Participants will not be able to tell whether electrical current is being delivered, and the tDCS-comparator is not expected to affect brain activity. This group is considered an active study intervention because because the BrainHQ part of the intervention is active, which could affect a participant's brain activity, while the tDCS part of the intervention is a comparator, which is not expected to affect a participants' brain activity.

Figure 3. Descriptions of interventions used in the study.

Figure 4. Schedule to study visits and duration



Abbreviations: MOI. Middle of Intervention; EOI. End of Intervention; EOS. End of Study

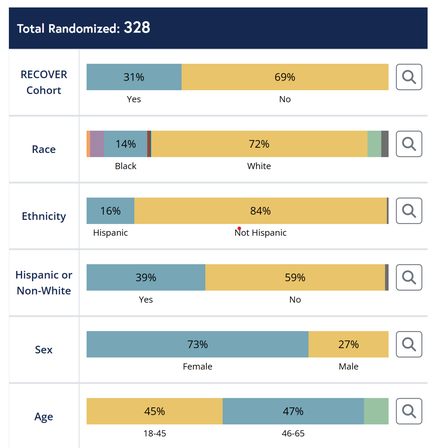
Figure 5. Five intervention groups of the study

Group	Type	Interventions Included
BrainHQ	Active study intervention	50 BrainHQ sessions only
BrainHQ active comparator	Active comparator	50 BrainHQ active comparator sessions only
BrainHQ + PASC-CoRE	Active study intervention	50 BrainHQ sessions and 12 PASC-CoRE sessions (9 group, 3 individual)
BrainHQ + tDCS-active	Active study intervention	50 BrainHQ sessions while using transcranial direct current stimulation (active)
BrainHQ + tDCS-comparator	Active study intervention	50 BrainHQ sessions while using transcranial direct current stimulation (comparator)

SIGNIFICANCE AND FUTURE DIRECTIONS

- The hypothesis is that PASC-associated dysfunction in cognitive domains may be improved by interventions that selectively focus on enhancing those domains
- BrainHQ and tDCS have been used to improve cognitive function in people with brain injuries. We want to learn if pairing BrainHQ with PASC-CoRE or BrainHQ with tDCS improves brain function more than using BrainHQ alone
- Results from this study will help us learn if BrainHQ, PASC-CoRE, and tDCS can improve cognitive dysfunction symptoms associated with Long COVID
- 328 participants enrolled in this study across 22 sites, demographics presented in Figure 6
- Our site enrolled 25 participants
- Study results will help inform future research, both within and outside of the RECOVER Initiative

Figure 6. Demographics of the 328 participants enrolled in NEURO nationwide



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CONTACT AND REFERENCES

Team TreatCOVID contact: treatcovid@stanford.edu

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