Enhancing Executive Functions after mTBI using Noninvasive Vagal Nerve Stimulation

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Type of Grant: Foundational II
Total Funding Requested: $49,995

Research plan

Introduction

The vagal nerve is the longest cranial nerve in the human body, and its fibers send sensory information from the body (e.g., digestive system, heart) to the brain[1]. In the last several decades, stimulation of the vagal nerve was used for the treatment of epilepsy, depression, and migraines, with good safety and clinical efficacy[2]. Yet, given that vagal nerve stimulation (VNS) is highly invasive and requires general anesthesia, non-invasive approaches have been gaining attention and were shown to be both safe[3] and effcticve[4]. These noninvasive techniques, referred to as transcutaneous vagal nerve stimulation (tVNS), apply an electrical current to branches of the vagal nerve on the skin, through commercially available, FDA-approved devices[5]. The hypothesized effect of tVNS occurs through the applied electrical current that leads to depolarization of the neurons along the nerve, resulting in the activation of subcortical nuclei and the parasympathetic nervous system[6].

Animal studies have consistently shown evidence for a positive impact of VNS on cognition and brain plasticity[7,8]. Recent non-invasive studies in humans have demonstrated that tVNS can enhance cognition in healthy individuals, particularly in the domain of executive function[9,10]. Executive functions (EF) is an umbrella term used to describe a series of higher-order cognitive abilities involved in controlling goal-directed behavior[11]. Executive deficits are common in patients with traumatic brain injury (TBI)[12], and have a profound negative impact on everyday functioning. Lower EF predicts poor rehabilitation outcomes[13,14], lower quality of life[15], and decreased participation[16].

There is a strong need for new therapies to enhance cognitive rehabilitation of EF after brain injury. While tVNS is considered a promising tool in the treatment of cognitive disorders in general[17] and executive functions specifically[18], it has not been studied in people with brain injuries for this purpose. Importantly, the technique has been used with patients after severe TBI for other purposes and was found safe and feasible in this patient population[19,20]. In summary, tVNS is a promising potential supplementary therapy for cognitive recovery after TBI, which is well tolerated, noninvasive, and easily available. The proposed study aims to establish safety and feasibility of this new method with patients with mild TBI (mTBI), with the long-term goal of conducting a randomized controlled trial to test its clinical effectiveness.

B. Specific Aims

1. Determine safety and feasibility of the use of tVNS in individuals with mTBI, as a tool to enhance executive functions post brain injury.
2. Assess the potential efficacy of tVNS in enhancing executive functions post brain injury.

C. Methods

Participants:

Given that the main aim of this study is to establish feasibility, it is not recommended to power the study with large sample size that is required for null hypothesis testing[21,22]. Therefore, based on the current literature guidelines[23] , 12 individuals will participate in this study. Participants will be recruited through referrals made by brain-injury physicians at SRAlab and surrounding hospitals. Inclusion criteria include (1) age between 18-80 (2) mild TBI confirmed by medical records (3) at least 6 months post-injury, and (4) ability to understand the experimental procedures and to give informed consent. Exclusion criteria include pre-morbid dementia, cardiac diseases, severe depression, and abuse of alcohol or drugs.

Study design

This is a single-blind sham-controlled randomized crossover pilot study. Participants will first be interviewed to establish eligibility and screen for depression (using the PHQ-9[24]) and dementia (using the Montreal Cognitive Assessment, MoCA[25]). Eligible participants will be invited to two sessions, 2-7 day apart. In each session either tVNS or sham stimulation will administer while the participants are preforming tasks of executive functions. The order of the sessions (tVNS vs Sham) will be counterbalanced across participants.

Transcutaneous vagus nerve stimulation

In line with the commonly reported procedure[4], transcutaneous electrical stimulation will be applied to the cymba conchae of the left ear, an area thought to be exclusively innervated by the auricular branch of the vagus nerve[5,6]. In the sham condition, the device will be applied to the left ear lobe, an area considered free of vagal innervation. To ensure stimulation over the entire task performance, the stimulation will be delivered continuously with a pulse width of 200–300 ms at 25 Hz. Stimulus intensity of the tVNS will be adjusted individually based on participant's self-report, so that it is above the detection threshold but do not cause discomfort[26].

Executive functions task

Participant will complete tasks of *set shifting* and *working memory*, core executive function which have shown to improve following tVNS in previous studies with healthy individuals[18,27]. Specifically, we will use the Trail Making Test (TMT-B[28]) to asses set shifting and, and the *N*-back[29] task to asses working memory. Given that these tasks have shown to have minimal practice effect[30,31], the same tasks will be administered on both sessions.

D. Primary outcome measures

To address the first aim of this study- **establishing safety and feasibility**- we will collect the following outcome measures: Total number of referrals, total number of eligible participants, reasons for ineligibility/refusal to participate, percent of individuals completing the study, type and frequencies of adverse events and participant's feedback about the treatment.

To address the second aim of this study- **preliminary evaluation of efficacy**- we will collect the following outcome measures: TMT B[28]: response accuracy and time to complete; *N*-back[29]: number of hits, number of false alarms and reaction time.

Data analysis: Visual aids such as histograms and QQ plots as well as statistical tests such as the Kolmogorov-Smirnov test will be used to assess data distribution. Given the small sample size, non-parametric tests (e.g., Mann Whitney U test) will be used to assess changes in executive functions in the tVNS condition vs. sham, with a significance level of α=.05. Effect size will be calculated to establish desired sample size for a larger trial.

E. Study Timeline: 0-14 Months: IRB approval; Patient recruitment, Data acquisition. 15-17 Months: data analysis; Local presentation of findings. 18-20 Months: National presentation of findings; Publication submission. 21-24 Months: Preparation of NIH R21 award application.

F. final deliverables will include research presentations and peer-reviewed publication, as well as a feasibility and preliminary efficacy data on the use of tVNS with patients with TBI. The results of this study will be necessary pilot data for a NIH R21 award application.

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