Repetitive mild traumatic brain injury (mTBI/concussion) and post-traumatic stress disorder (PTSD) have been called the "signature injuries" of the Iraq and Afghanistan wars and are major sources of morbidity, but diagnoses and treatment options are limited. Blast exposure is the primary source of mTBI and gives rise to a multi-factorial behavioral and pathophysiological syndrome highly comorbid with PTSD. We have previously reported increased PTSD, disinhibition, risky drinking (alcohol), and irritability symptoms by blast-mTBI Veterans. Likewise, we have demonstrated blood brain barrier disruption and neuroinflammation following blast exposure in a translationally relevant mouse model. Recently, vagus nerve stimulation (VNS) has garnered attention as a potential therapeutic for mTBI, due at least in part to its modulatory effects on inflammation and autonomic function.

The current study integrated behavioral, physiological, and biochemical approaches in mice to investigate whether non-invasive VNS (nVNS) could reduce blast-induced maladaptive outcomes. We used an established shock tube to model battlefield-relevant open-field blast forces generated by detonation of high explosives and a custom manufactured nerve stimulator (gammaCore) from electroCore, Inc. Male C57Bl/6 mice were exposed to either 1 or 3 blast treatments (one exposure per day) (or sham exposure) and nVNS (or sham stimulation) was given for one hour following blast/sham exposure (2-minute trains, every 15 minutes, for 1-hour). A behavioral and physiological battery of tests was conducted one month following injury/VNS and peripheral blood dynamics were assayed with flow cytometry.

Blast exposure increased a variety of maladaptive outcomes related to either/both mTBI and PTSD (e.g. decreased heart rate variability, shifted peripheral blood dynamics, weight changes, disinhibition, anxiety, dysphoria, and aggression) and many of these outcomes were reduced to control levels by prior nVNS treatment. These findings support the potential use of therapeutic nVNS following blast-induced mTBI and warrants additional attention and investigation.

Keywords: TBI, VNS, affect, inflammation

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VAGUS NERVE STIMULATION AS A STRATEGY TO AUGMENT PTSD REHABILITATION

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Exposure-based therapies help patients with posttraumatic stress disorder (PTSD) to extinguish conditioned fear of trauma reminders. However, controlled laboratory studies indicate that PTSD patients do not extinguish conditioned fear as well as healthy controls, and exposure therapy has high failure and dropout rates. An optimal adjunct to exposure therapy would promote extinction and attenuate the aversive stress response experienced in therapy in order to make the therapy more efficient and tolerable. However, anxiolytic medications are counter-productive because they can interfere with the consolidation of extinction memories. VNS enhances memory consolidation and we recently reported evidence that VNS enhanced the consolidation of extinction memory, and prevented reinstatement of conditioned fear in the single prolonged stress (SPS) rat model of PTSD. More recently, we discovered that VNS promotes generalization of extinction of fear across conditioned auditory cues when the conditioning occurred within the same session. Although the VNS was administered only during extinction of one of the cues, the presentation of cues during conditioning determined whether VNS promoted generalization. When fear conditioning for each cue was carried out on separate days or in separate contexts, VNS administration during extinction did not promote generalization. Other findings indicate that VNS given before testing naïve rats on the elevated plus maze increases time spent in open arms, suggesting that VNS has a rapid anxiolytic effect. However, a lasting anxiolytic effect of VNS is not a likely reason for extinction enhancement because non-contingent VNS does not enhance extinction. Taken together, these findings suggest that VNS possesses a rare combination of effects that include the enhancement of consolidation of extinction memories and rapid reduction of anxiety. These findings suggest that VNS may improve efficacy and tolerability as an adjunct to exposure therapy for the treatment of PTSD.

Keywords: VNS, extinction, Exposure therapy, Memory

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CLINICAL TRANSLATION OF VNS THERAPY FOR TINNITUS PATIENTS

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Animal studies demonstrated it is possible to drive plasticity in a controlled way by using vagus nerve stimulation (VNS) paired with tones. This reversed the tinnitus percept and pathological neural plasticity in noise-exposed rats with behavioral characteristics of tinnitus. In this talk, I will discuss the outcome of two human studies: (1) a Phase I safety and feasibility open label study and (2) a Phase II safety and efficacy placebo controlled multicenter study of VNS paired with tones. Overall the therapy was well tolerated, and no patient withdrew from both studies due to complications or side-effects for both studies. For the Phase I study, four of the ten patients exhibited clinically meaningful improvements in their tinnitus, both for the affective component and for the sound percept, as quantified by the minimum masking level. Of the ten patients, five were on medications that included muscarinic antagonists, norepinephrine agonists, and γ-amino butyric acid agonists, thereby possibly interfering with acetylcholine and norepinephrine release induced by VNS and essential for inducing plasticity. In the Phase II study 6 weeks of home therapy in medication free tinnitus patients, tone paired VNS improved on the affective component of the tinnitus and shows a clinically meaningful response. Clinical effect remained for one year follow-up. When combining the resting-state EEG data (Phase I and II combined) collected before and after one to three months of VNS-tone pairing in chronic tinnitus patients further showed that VNS paired with tone therapy induces changes in the auditory cortex that correlated with tinnitus loudness. VNS-tone pairing also reduced the phase coherence between the auditory cortex and areas associated with tinnitus distress, including the cingulate cortex. These results support the hypothesis that VNS can direct therapeutic neural plasticity in tinnitus patients. Targeted plasticity therapy might also be adapted to treat other conditions characterized by hypersynchronous neural activity.

Keywords: tinnitus, vagus nerve stimulation, EEG, auditory cortex

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EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION ON THE HUMAN BRAIN REVEALED BY INTRACRANIAL ELECTROCORTICOGRAPHY

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Transcranial magnetic stimulation (TMS) is increasingly used as a noninvasive technique for neuromodulation in research and clinical applications, yet the mechanisms of TMS are not well understood. This is, in part, due to limitations in the spatiotemporal resolution that are inherent in the methods used to study the effects of TMS on the human brain. In this study we evaluate a new approach of evaluating the effects of TMS using concurrent intracranial electrocorticography (ECoG) in neurosurgical patients. First, we evaluate safety of this approach using a gel-based phantom brain. Next, we test the TMS-ECOG approach in 7 participants using both single pulse and repetitive TMS, targeting structures in the frontal, temporal and parietal lobe, including directly over subdural electrodes. Our results show evidence for safety using the phantom brain with no electrode displacement, heating or excessive secondary induced currents. Our main findings include the demonstration of spatially specific evoked responses from TMS that differ depending on the frequency of stimulation (10Hz versus 0.5 Hz) and are greater in remote regions functionally connected to the stimulation site, based on individualized resting state functional connectivity MRI. These results open a new line of investigation into the mechanisms of TMS with intracranial electrodes in humans as a way to discover the effects of TMS with higher spatiotemporal resolution than currently available methods. We are optimistic that insights gained from this approach will aid in the rational development of novel therapies with TMS.

Keywords: Electrocorticography, ECoG, functional connectivity, electrophysiology