**Overview/Abstract** ICU delirium affects over 30% of hospitalized patients. At present, there is no FDA-approved therapy for delirium. Delirium likely results from neuroinflammation leading to aberrant functional connectivity of brain networks supporting attention and consciousness. The ideal intervention for delirium would therefore directly modulate neuroinflammation. Trans-auricular vagus nerve stimulation (taVNS), in which a wearable device on the ear delivers transcutaneous stimulation to branches of the vagus nerve, is reported to decrease neuroinflammation as well as to modulate neural activity in the dorsolateral prefrontal cortex (DLPFC). DLPFC dysconnectivity is implicated in the pathophysiology of delirium. We therefore hypothesize that taVNS will reduce clinical symptoms of delirium by reducing vagally-mediated neuroinflammatory changes that result in aberrant functional connectivity in the dorsolateral prefrontal cortex. Importantly, using a recently-developed technique known as diffuse correlation spectroscopy (DCS), we can interrogate the connectivity of DLPFC in individual patients. DCS is an optical imaging modality that measures functional connectivity via changes in blood flow in the brain. We have shown it to correlate well with invasive brain monitoring techniques in the critical care setting. Other imaging modalities, such as fMRI, are cumbersome in critically-ill patients who cannot leave the ICU and/or cannot tolerate lying still for prolonged studies. Additionally, taVNS stimulation parameters are currently determined by perception threshold as reported by the patient, which can be difficult for delirious or nonverbal patients to communicate. Thus, DCS will allow us to measure **target engagement** of neuromodulation therapy through measurement of quantifiable biological variables in an otherwise difficult-to-study patient population. We plan to use the OVPR seed grant funding for a two-part pilot study as follows:
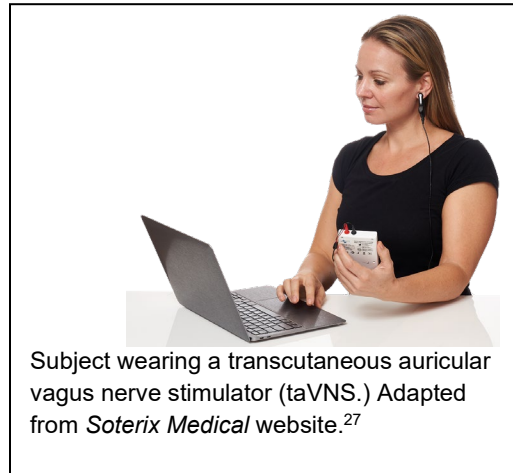


Subject wearing a transcutaneous auricular vagus nerve stimulator (taVNS.) Adapted from *Soterix Medical* website.[27]

**Aim 1. Monitor modulation of functional connectivity by taVNS in healthy controls with a combination of a biomarker and clinical assessments.** We hypothesize that **DCS-detected DLPFC connectivity will be a biomarker for target engagement** by taVNS. Specifically, we predict that taVNS will enhance both DLPFC connectivity as measured by DCS, as well as improving clinical measures of functional connectivity such as performance on validated neuropsychological tests of memory and cognition. We predict that effect size of clinical improvement in *healthy* volunteers will be small as it may not be possible to "super-charge" a healthy brain[1].

**Aim 2. Conduct a pilot study to treat delirious ICU patients with taVNS**. We hypothesize that **taVNS will enhance functional connectivity in delirious patients**, which will correlate with an improvement in clinical symptoms of delirium. We hypothesize this will be true in delirious ICU patients with brain dysfunction, *even* if we did not see a comparable increase in functional connectivity in healthy patients in Aim1.

We hypothesize that *delirious patients will demonstrate decreased functional connectivity.* If DCS is a reliable biomarker of functional connectivity in Aim 1, then we will utilize DCS to monitor target engagement. If DCS is *not* a reliable biomarker of functional connectivity, then we will utilize a combination of EEG and fMRI to study functional connectivity in delirious ICU patients.[2]