

Purpose of study Vagus nerve stimulation (VNS) is currently used to treat drug-resistant epilepsy and depression. There are results indicating that VNS may also be useful in treating a wide range of autoimmune, metabolic, and neurological disorders. Preclinical studies show that VNS can induce cortical plasticity and improve rehabilitation after stroke or SCI. Albeit showing tremendous potential, the underlying mechanism of VNS remains ambiguous. We aim to tease apart the specific circuitry that underlies VNS-induced cortical plasticity in a healthy mouse model. Identifying these specific anatomic pathways will help guide future research on the use of VNS in patients with motor deficits and may illuminate the mechanisms of other therapeutic benefits.

Methods used We used immunohistochemistry staining of an immediate early gene, cFos, to identify neuronal activation in key neuromodulatory centers such as the cholinergic basal forebrain and noradrenergic locus coeruleus. We then performed electrophysiological recordings in the basal forebrain during VNS and confirmed neural activity driven by vagal stimulation. To ensure that these changes reflected the state of a brain with increased cortical plasticity, we paired these experiments with behavioral investigations of a motor learning task.

Summary of results Our behavioral findings confirm that VNS, when paired to successful trials, increases learning of a skilled motor forelimb reach task in a healthy mouse model. Immunohistochemically, we see that following vagal stimulation there is increased activity in neuromodulatory regions, which is further solidified by our electrophysical findings that indicating that VNS affects the local field potential and firing rate in cholinergic basal forebrain.

Conclusions These results indicate that the enhancement of motor learning may be mediated by the excitation of basal forebrain, a neuromodulatory nuclei that widely projects to cortex. The projections from vagus nerve to the basal forebrain are still not fully defined, and may be mediated through locus coeruleus. To further dissect this, we will employ tracing experiments using a retrograde tracer in basal forebrain and an anterograde tracer in the Nucleus of Solitary Tract, where vagal afferents terminate.