Directing Synaptic Plasticity to Treat Neurological and Psychiatric Disorders

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Brain function and dysfunction result from network activity shaped by millions of synaptic connections across multiple brain regions. Substance abuse alters synapse strength and produces an uncontrollable desire to consume alcohol or drugs despite severe negative consequences. Synaptic changes can last a lifetime, which likely explains why addicts have a high vulnerability to relapse even after months or years of abstinence.

To effectively treat addiction, we need new tools to selectively target large numbers of synaptic connections. The core technical challenge is that the synapses related to drug craving and drug seeking are embedded in networks with billions of healthy synapses that we must avoid damaging.

This talk will describe a powerful new technology that can selectively alter synaptic strength in subsets of active neurons without deleterious side effects. Activating the vagus nerve triggers rapid transient activity in locus coeruleus and other modulatory nuclei that regulate synaptic plasticity. Repeatedly pairing a brief burst of VNS with a sensory or motor event drives consistent large scale and long-lasting changes in the corresponding sensory or motor networks of the brain. We know that VNS is safe because 80,000 people have received VNS to reduce seizure frequency. VNS pairing procedures use very short bursts and deliver 100 times less charge than FDA-approved VNS protocols.

Blocking acetylcholine or norepinephrine or serotonin release prevents the map plasticity caused by VNS event pairing. Delivery of VNS without pairing does nothing. The key to selectively changing networks is to repeatedly associate specific experiences with phasic bursts of neuromodulator release. This talk will summarize the evidence that pairing VNS with rehabilitation can trigger synaptic plasticity and enhance recovery in a wide range of animal models of spinal cord injury, tinnitus, PTSD, and stroke. The talk will also review the evidence from a series of human trials confirming the efficacy and safety of targeted synaptic plasticity therapy. Finally, preliminary evidence will be used to illustrate the potential of this new approach to benefit people with substance use disorders.