Targeted Neuroplasticity to Treat TBI, Tinnitus, and PTSD

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Military Relevance

•While traumatic injuries sustained on the battlefield are often treated in theater, many returning soldiers face chronic neurological manifestations of their war injuries. TBI is the signature injury of the wars in Iraq and Afghanistan. Over 100,000 cases each year occur in soldiers. (Glaser, 2007) The disabilities of TBI may include loss of motor control, decreased cognitive function, tinnitus, and PTSD. To date, there are no effective therapies for tinnitus and PTSD treatments often only work for 50% of the patients.

•According to the American Tinnitus Association, 30% percent of soldiers deployed in Iraq return with tinnitus, resulting from hearing loss, head injury or noise exposure. The VA is projected to pay over $1.1 Billion annually in tinnitus-related disability by 2011.

•The RAND survey from 2008 indicates that 20% of military service members returning from Iraq and Afghanistan report symptoms of PTSD with only half of these 300,000 servicemen seeking treatment. The economic cost is expected to exceed $3.1 Billion per year.

Why neuroplasticity works

•The clinical effects of TBI, including epilepsy, chronic pain, PTSD and tinnitus result from abnormal brain wiring subsequent to injury. The Nobel Prize winning work of Hubel and Wiesel refuted the notion that the brain is hard-wired and demonstrated that covering one eye for just a week early in life can cause a lifetime of impaired vision due to the ability of the brain to alter its neural circuits (Hubel and Weisel, 1977)

•We propose to develop the next generation treatment for neurological disease by precisely directed neural plasticity. Unlike current pharmacological or surgical interventions, our approach will provide the high spatial and temporal precision needed to guide endogenous neural plasticity mechanisms to restore pathological neural circuits that characterize many neurological disorders like tinnitus.

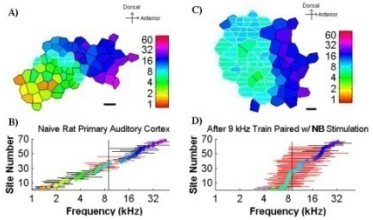
•The stimulation consists of discharging electrical current to the vagus nerve using an implanted electrode, lead and battery system. Such systems have been implanted in tens of thousands of refractory epilepsy patients with only minor side effects.

Scientific Support

•The motivation to use VNS pairing to stimulate plasticity stems from our earlier research using nucleus basalis (NB) stimulation.

•The most effective plasticity occurs when short bursts of NB stimulation are timed with specific experiences.

•Since the vagus nerve stimulates deep brain structures, including NB, VNS paired with specific experiences should also result in robust plasticity.

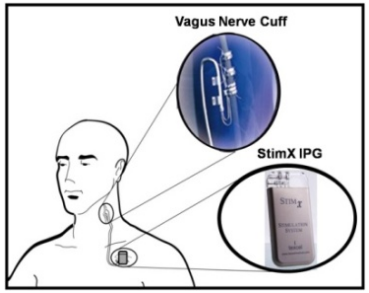


•The brain changes we have generated using VNS (above figure) are nearly identical to the changes we reported in *Science* in 1998 using NB stimulation *(Kilgard and Merzenich, 1998).*

•Repeated pairing of VNS with tones dramatically increased the representation of the paired tone.

•The left panels (A&B) show the normal tonotopic organization of primary auditory cortex from a naïve rat. The right panels (C&D) show the expansion of the 9 kHz region (light blue) after this tone was repeatedly paired with VNS stimulation.

VNS Therapy



•Besides the known clinical efficacy of VNS in treating refractory epilepsy and depression, VNS has been shown to improve memory consolidation (Clark et al., 1995, 1999, Hassert et al., 2004), decision making (Martin et al., 2004), mood (Harden et al., 2000), and cognition (Sjogren et al., 2002) in humans. VNS also enhances cognitive and motor recovery if therapy begins within 2 hours of brain injury (Smith et al., 2005; Clough et al., 2007).

•Our use of VNS therapy pairs sensory stimulation or motor therapy with simultaneous stimulation of the vagus nerve to induce precise changes in the abnormal cortical maps that characterize many of these disorders.

Tinnitus

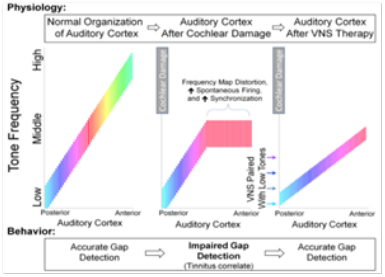
• Disturbing auditory sensation in the absence of external sound.

•There is no effective therapy to eliminate tinnitus.

• Pathological plasticity in the central auditory system is known to play a role

•Tinnitus arises from hyperactivity of neurons in the central auditory system subsequent to central or peripheral auditory system damage.

•Neurons deprived of auditory input begin to respond to the same frequencies as neighboring neurons that receive input from undamaged parts of the cochlear (center panel). When the number of neurons that respond to a given frequency increases beyond some critical level, synchronous spontaneous activity sets in, which is thought to account for tinnitus

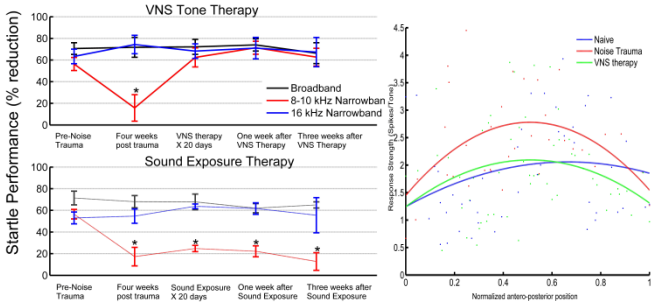


•In the proposed therapy, we will pair brief (0.5 second) episodes of VNS with low frequency tones to reorganize the auditory cortex as shown in the far right panel. Note that neurons still do not respond to high frequencies, as those inputs have been destroyed. However, the tonotopic map of the auditory cortex has now been redistributed and would thus be predicted to reduce or remove tinnitus.

•The therapy will be administered by a clinician who is monitoring both the tones and stimulation as depicted in the illustration below.

VNS -Tone Pairing Eliminates Tinnitus

•Our animal studies confirm that our method of using VNS paired with sounds is sufficient to reverse the tinnitus percept and the pathological plasticity that causes it.



•The top left plot indicates that we can reverse tinnitus in our animal model. After our tinnitus therapy, all signs of tinnitus are eliminated. The bottom left panel confirms earlier reports that rats with this level of noise exposure (115 dB SPL for 1 hr) experience tinnitus that persists indefinitely.

•The right panel shows the raw data revealing the abnormal frequency map of A1 neurons in noise exposed rats (red) and the significant restoration of the abnormal map after VNS-tone paring.

PTSD/ Motor Rehabilitation

•We are currently using VNS pairing protocols on our animal models for the treatment of PTSD and traumatic brain injury

•Our treatment method for PTSD would involve placing the soldier is in a virtual reality setting to mimic their fear triggers similar to exposure therapy and pair the trigger with VNS to enhance fear extinction.

•Using the Motek CAREN virtual reality system at Brooke Army Medical center would improve efficacy of the virtual reality therapy.

•The picture on the left indicates how VNS could be paired with the CAREN system for motor rehabilitation therapy to promote rapid motor skill recovery.

Conclusion

•Our preliminary data indicates that VNS pairing will improve the benefits of rehabilitation by stimulating the brain's natural ability to learn and remember (rewire itself), also known as neuroplasticity. By using brief periods of stimulation, our method will precisely guide neurons to generate more optimal recovery of function for our wounded soldiers, allowing them to return to active duty more rapidly or integrate more fully back into civilian life.