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Targeting Plasticity with Vagus Nerve Stimulation to Treat Neurological Disease

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Abstract

Pathological neural activity in a variety of neurological disorders could be treated by directing plasticity to specifically renormalize aberrant neural circuits, thereby restoring normal function. Brief bursts of acetylcholine and norepinephrine can enhance the neural plasticity associated with coincident events. Vagus nerve stimulation (VNS) represents a safe and effective means to trigger the release of these neuromodulators with a high degree of temporal control. VNS-event pairing can generate highly specific and long-lasting plasticity in sensory and motor cortex. Based on the capacity to drive specific changes in neural circuitry, VNS paired with experience has been successful in effectively ameliorating animal models of chronic tinnitus, stroke, and posttraumatic stress disorder. Targeted plasticity therapy utilizing VNS is currently being translated to humans to treat chronic tinnitus and improve motor recovery after stroke. This chapter will discuss the current progress of VNS paired with experience to drive specific plasticity to treat these neurological disorders and will evaluate additional future applications of targeted plasticity therapy.

Keywords

vagus nerve stimulation (VNS); cortical plasticity; recovery; neuromodulators; acetylcholine; norepinephrine; targeted plasticity

1 NEURAL PLASTICITY IN THE CONTEXT OF NEUROLOGICAL DYSFUNCTION

Plasticity provides an organism with the ability to adapt to a changing environment. Under normal physiological conditions, plasticity promotes acquisition of new knowledge and skills. In response to a pathological disturbance, insufficient or maladaptive plasticity prevents full recovery. After a stroke, reorganization of cortical motor representations occurs in the surrounding undamaged tissue and in the contralesional hemisphere (Calautti and

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Baron, 2003; Nudo, 1999). Reorganization of motor circuitry is observed after other types of brain lesions, such as traumatic brain injury (Axelson et al., 2013). Plasticity induced by rehabilitative training is thought to be the substrate for partial recovery; therefore, appropriately directed plasticity that enhances the robustness and specificity of reorganization could improve recovery. Similarly, targeted plasticity could be applied to specifically renormalize circuitry that exhibits maladaptive activity (Kilgard, 2012). One such instance of maladaptive plasticity is phantom limb pain. Following loss of a digit, deafferentation results in increased cortical representation of the remaining skin areas (Merzenich et al., 1984). In amputees, this cortical reorganization can often be accompanied by pain, which is correlated with the degree of overrepresentation (Flor et al., 1995). Some forms of chronic pain unrelated to limb loss display a similar manifestation, suggesting that aberrant plasticity in the central nervous system may underlie this percept of pain (Flor, 2003; Flor et al., 1997). Cochlear damage can produce changes in the tonotopy of the auditory cortex (Robertson and Irvine, 1989). This cortical reorganization and other accompanying changes in neuronal properties may produce tinnitus, a condition characterized by the perception of sound when no sound is present (Eggermont and Roberts, 2004). New methods are needed to drive specific circuit changes that can renormalize neuronal activity and thereby ameliorate a range of neurological disorders.

2 NEUROMODULATORY CONTROL OF PLASTICITY AND MEMORY

It is clear that neuromodulators strongly influence the expression of plasticity; therefore, control of neuromodulatory release during experience may serve as one method to direct plasticity. Cortical neuromodulatory systems, including acetylcholine and norepinephrine, all participate in cortical plasticity to varying degrees and have been the subject of extensive study (Gu, 2002). The cell bodies of neurons responsible for cholinergic innervation throughout the central nervous system are located in structures within the basal forebrain (Mesulam et al., 1983). These neurons release acetylcholine widely throughout the brain, which acts on ionotropic nicotinic receptors and metabotropic muscarinic receptors. Noradrenergic innervation originates in neurons in the locus coeruleus of the brain stem and projects throughout the central nervous system (Freedman et al., 1975). Norepinephrine released from these neurons stimulates α-adrenergic and β-adrenergic receptors, which fall in the metabotropic G protein-coupled receptor superfamily. The downstream effectors engaged by activation of both cholinergic and noradrenergic receptors (Gilman, 1987) enable these neuromodulators to have broad cellular effects that may be needed to drive the multifaceted mechanics of plasticity. Three primary lines of evidence that support the role of the cholinergic and noradrenergic systems in the expression of plasticity are discussed in the succeeding text.

2.1 Reduction of neuromodulatory transmission diminishes plasticity

Reduction of neuromodulatory transmission results in impaired experience-dependent plasticity. Lesions of the cholinergic system diminish topographical reorganization in motor, somatosensory, and auditory cortices (Baskerville et al., 1997; Conner et al., 2003; Kamke et al., 2005; Sachdev et al., 1998). Transient inhibition of neuromodulatory transmission with pharmacological antagonists of cholinergic receptors similarly reduces plasticity in

both motor and somatosensory cortices (Maalouf et al., 1998; Meintzschel and Ziemann, 2006; Sawaki et al., 2002). Lesions of the nucleus basalis and cholinergic antagonists also interfere with learning (Dunnett, 1985; Murray and Fibiger, 1985). Reduction of noradrenergic signaling by lesions or antagonism also diminishes experience-dependent plasticity in the visual system (Kasamatsu and Pettigrew, 1976; Kasamatsu and Shirokawa, 1985) and in the motor cortex (Meintzschel and Ziemann, 2006; Sawaki et al., 2003). Lesions of the locus coeruleus and adrenergic antagonists impair some forms of learning (Anlezark et al., 1973; Ögren et al., 1980). Together, these studies indicate that robust expression of experience-dependent plasticity requires cholinergic and noradrenergic transmission.

2.2 Enhancement of neuromodulatory transmission facilitates plasticity

Manipulations that enhance cholinergic and noradrenergic transmission facilitate plasticity. Direct exogenous application of acetylcholine to the auditory cortex during tone presentation promotes spectral plasticity (Ma and Suga, 2005) and application during presentation of visual stimuli induces receptive field plasticity in the visual cortex (Greuel et al., 1988). More indirect manipulations that also increase cholinergic transmission enhance plasticity, for example, electrical stimulation of the nucleus basalis paired with tones drives robust spectral and temporal plasticity in neurons of the auditory cortex (Kilgard and Merzenich, 1998a,b). Stimulation of the nucleus basalis paired with visual training increases visual acuity and improves performance on a visual task (Kang et al., 2013). Furthermore, cholinergic agonists enhance plasticity within the circuitry of the motor cortex when applied with motor training (Meintzschel and Ziemann, 2006). Similarly, local infusion of norepinephrine into the visual cortex and electrical stimulation of the locus coeruleus support ocular dominance plasticity (Kasamatsu et al., 1985; Pettigrew and Kasamatsu, 1978), and pharmacological manipulations that increase noradrenergic transmission increase training-dependent plasticity within the motor cortex (Meintzschel and Ziemann, 2006). Direct norepinephrine infusion into the visual cortex during visual stimulation promotes receptive field reorganization (Greuel et al., 1988). Synthesis of the results from these studies indicates that, when paired with experience, increased function of the cholinergic and noradrenergic systems can enhance neural plasticity.

2.3 Engagement of neuromodulatory systems during learning and attention

Neuromodulatory systems are engaged during the acquisition of a new task and during attentional processing. Participation in a new behavioral task triggers release of neuromodulators. Increases in acetylcholine levels are observed during the acquisition phase, but not the consolidation phase, of learning an operant task (Orsetti et al., 1996). Norepinephrine levels are transiently increased in the amygdala following inhibitory avoidance training, and the magnitude of increase correlates with memory retention (McIntyre et al., 2002). These temporally restricted increases suggest that neuromodulatory release supports learning. Attention is known to facilitate behaviorally specific plasticity and learning (Moucha and Kilgard, 2006). Neuromodulatory systems are involved in attention, as disruption of the cholinergic or the noradrenergic systems impairs attentional processing (Muir et al., 1993, 1994). As such, attentional engagement of neuromodulatory systems would be expected to facilitate plasticity. Indeed, behavioral tasks that require attending to

sensory stimuli drive plasticity within the relevant cortical circuitry. Adult owl monkeys trained on a tone discrimination task that required attention resulted in enhanced responses to behaviorally relevant tones, which correlated with task performance (Recanzone et al., 1993). Similar tone exposure in nonattending animals was insufficient to engender plasticity, demonstrating that sensory exposure alone is typically insufficient to drive plasticity. These studies suggest that release of neuromodulators during attentional processing facilitates plasticity.

Electrophysiological and computational modeling studies implicate high levels of acetylcholine in enhancing the effects of efferent inputs to cortical circuitry while minimizing the transmission through local connections (Hasselmo and McGaughy, 2004). In contrast, low levels of acetylcholine facilitate local circuit function and reduce the effects of extracortical inputs. Norepinephrine can control the state of cortical networks and can affect information processing (Constantinople and Bruno, 2011). This provides a theoretical framework for enhanced plasticity and learning whereby heightened neuromodulatory transmission makes cortical circuitry more receptive to inputs. While neuromodulatory input may facilitate plasticity, it is not sufficient by itself to drive neuronal changes. The expression of plasticity requires experience coincident with the release of neuromodulators. The broad innervation patterns of both the acetylcholine and norepinephrine result in diffuse neuromodulatory release (Eckenstein et al., 1988; Levitt and Moore, 1978); therefore, the effects acetylcholine and norepinephrine are restricted by the coincident network activity in the local circuitry. Temporal specificity is a product of the relative timing of neuromodulatory release and coincident neuronal activity. The temporal requirements for synaptic plasticity are well described, and small changes in timing of neuronal firing can have major impacts on spike-timing-dependent plasticity (STDP) (Dan and Poo, 2004). Neuromodulators influence the temporal rules that define STDP (Pawlak et al., 2010). The presence of acetylcholine or norepinephrine dictates the polarity of synaptic plasticity, and the ratio of these neuromodulators determines the temporal requirements for STDP (Seol et al., 2007). Studies using lesions and pharmacological antagonism have demonstrated that these neuromodulatory systems interact to facilitate plasticity and learning (Bear and Singer, 1986; Decker and Gallagher, 1987; Decker et al., 1990). As these neuromodulatory systems cooperate during processes that drive plasticity and learning, concurrent control of both acetylcholine and norepinephrine release would be useful to direct plasticity.

3 HARNESSING PLASTICITY WITH VAGUS NERVE STIMULATION

Targeted neural plasticity has potential to transform the ways in which neurological diseases are treated, but the complex dynamics of plasticity processes make it challenging to control. Under normal conditions, plasticity is fine-tuned to promote learning. However, in pathological conditions, the physiological processes driving plasticity are insufficient to restore function. Therefore, new techniques to direct robust and specific plasticity may overcome this insufficiency and provide clinically significant benefits.

A technique developed as a targeted plasticity therapy should exhibit four key characteristics. First, it should engage multiple neuromodulatory systems in a physiological or near physiological manner. Because neuromodulators act synergistically and the relative

concentration of each is crucial for the expression of plasticity (Bear and Singer, 1986; Seol et al., 2007), the ability to engage multiple neuromodulatory systems through physiological pathways will likely produce the most robust plasticity. Second, it must be able to be delivered in a safe, tolerable way. Fear-inducing or stressful stimuli can be potent modulators of plasticity (Joëls et al., 2006; Maren and Quirk, 2004; McIntyre et al., 2012), but clearly, their harmful effects limit their usefulness. Instead, a method would be effective if it could engage the same plasticity-promoting systems as aversive stimuli without the unfavorable sensory percepts to promote plasticity. Third, it should be able to be applied with a high degree of temporal precision, as timing is a critical regulator of plasticity and restricts plasticity to relevant events. Fourth, its plasticity-inducing properties should not decay or saturate during the course of therapy. Pharmacological manipulations can strongly effect neuromodulatory transmission but are unlikely to be successful as a method to target plasticity due to saturation and poor temporal control. It would be valuable for a targeted plasticity therapy to remain constant over time, thus permitting repeated exposures until the desired benefits are achieved.

Several manipulations that fit some or all of these criteria may be successful at specifically targeting plasticity to treat neurological disease. Deep brain stimulation, transcranial magnetic stimulation, optogenetic stimulation, or intensive repeated training could potentially trigger sufficient neuromodulatory release during experience to induce therapeutic plasticity. In this chapter, we will focus on one particular technique to drive targeted plasticity. This method uses stimulation of the vagus nerve paired with behavioral experience to drive specific forms of neural plasticity. Vagus nerve stimulation (VNS) engages multiple neuromodulatory systems and can be precisely temporally controlled. Additionally, VNS is a safe and approved method currently being used in over 60,000 patients for management of intractable epilepsy and depression (Ben-Menachem, 2002; Englot et al., 2011; Sackeim et al., 2001). Recent studies have demonstrated that VNS paired with sensory, motor, or cognitive training can drive specific forms of cortical plasticity that result in behaviorally relevant changes. As a result, VNS applied as a targeted plasticity therapy offers the potential to treat sensory, motor, and cognitive dysfunction.

3.1 Control of memory and neuromodulatory release by the vagus nerve

The vagus nerve is most widely recognized for its activation of parasympathetic “rest-and-digest” responses; however, it also acts as a conduit to relay ascending information from the periphery to the central nervous system. The vagus nerve communicates arousing information from the periphery regarding both favorable events, including a meal or deep breaths (Schwartz et al., 2000; Zagon, 2001), and aversive events, such as stress or inflammation (Maier et al., 1998). This information on peripheral status can enhance memory in the central nervous system, and a variety of studies have demonstrated that the vagus nerve is required for memory-enhancing influences of peripheral stimulation (Jensen, 1996). Vagotomy impairs the memory-enhancing effects of several substances that stimulate receptors in the periphery, including cholecystokinin (Flood et al., 1987), bombesin (Flood and Morley, 1988), gastrin-releasing peptide (Flood and Morley, 1988), 4-OH amphetamine (Williams and Jensen, 1991), substance P (Nogueira et al., 1994), and L-glucose (Talley et al., 2002). The variety of substances that influence memory suggests that the vagus nerve

relays diverse peripheral information. Transmission of information by the vagus nerve is not painful, stressful, or rewarding, but powerfully controls memory. Based on this memory-enhancing influence, the ability to precisely control the vagus nerve provides a potential method to selectively drive plasticity.

The vagus nerve regulates memory by exerting control over multiple neuromodulatory systems responsible for plasticity. Eighty to ninety percent of the left cervical branch of the vagus nerve is composed of afferent sensory fibers that project upward from the viscera into the medulla in the central nervous system (Berthoud and Neuhuber, 2000; Foley and DuBois, 1937; George et al., 2000; Leslie et al., 1982). These fibers synapse bilaterally on neurons within the nucleus tractus solitarius, which then project to the noradrenergic locus coeruleus and the cholinergic basal forebrain (Berntson et al., 1998; George et al., 2000; Henry, 2002; Semba et al., 1988; Van Bockstaele et al., 1999). Electrical stimulation of the vagus nerve drives neuronal activity within these regions and consequently induces release of neuromodulators throughout the cortex (Detari et al., 1983; Dorr and Debonnel, 2006; Follesa et al., 2007; Groves et al., 2005; Roosevelt et al., 2006). A reduction in either noradrenergic or cholinergic transmission reduces the effects of VNS in the central nervous system (Krahl et al., 1998; Nichols et al., 2011), suggesting that VNS is exerting its effects through both the locus coeruleus and basal forebrain.

3.2 Stimulation of the vagus nerve paired with tones drives reorganization in the auditory cortex

Because stimulation of the nucleus basalis or locus coeruleus paired with tones drives plasticity, it is reasonable to predict that stimulation of the vagus nerve paired with tones could engage the same neuromodulatory systems and subsequently enhance experience-dependent plasticity without the need for deep brain stimulation. Engineer and colleagues sought to investigate whether VNS paired with the presentation of tones could drive reorganization of the tonotopic map in the primary auditory cortex (Fig. 1A) (Engineer et al., 2011). Rats were presented with three hundred 9 kHz tones per day for 20 days either with or without paired VNS, followed by auditory mapping to derive the frequency map in the auditory cortex. As predicted from previous studies, repeated presentation of tones without VNS did not induce map reorganization. However, presentation of the same number of tones paired with VNS significantly increased the proportion of neurons that responded to frequencies near 9 kHz. A second cohort of rats was presented with 19 kHz tones, and a similar map expansion was observed corresponding to 19 kHz in rats that received VNS, suggesting that the observed reorganization is due to the specific event paired with VNS rather than a generalized effect in the auditory cortex. Interleaved 4 kHz tones that were not paired with VNS did not exhibit an increased response, suggesting that the transient burst of neuromodulators driven by VNS can label temporally specific stimuli. In addition to the robust changes in spectral properties, VNS can also enhance temporal response characteristics of neurons in the primary auditory cortex (Shetake et al., 2011). Presentation of rapid (15 pulses per second) trains of tones paired with VNS increased the maximal following rate of neurons within the primary auditory cortex compared to naïve controls. Alternatively, presentation of slow (5 pulses per second) trains of tones paired with VNS decreased maximal following rate compared to naïve controls. These findings indicate that

VNS can enhance the temporal plasticity of neurons in the primary auditory cortex. In summary, VNS repeatedly paired with specific auditory experiences can drive specific, long-lasting plasticity to change multiple characteristics of neuronal responses in the auditory cortex.

3.3 Stimulation of the vagus nerve paired with forelimb training drives reorganization in the motor cortex

Based on the robust enhancement of sensory experience-dependent plasticity conferred by VNS, Porter and colleagues sought to determine whether VNS was capable of enhancing event-specific plasticity within the motor system (Fig. 1B) (Porter et al., 2011). To this end, rats were trained to perform one of two skilled motor tasks. The first task was designed to primarily engage the shoulder and required the rat to rapidly press a lever located outside the cage twice within 500 ms. The second task was designed to primarily engage the forepaw and required the rat to reach through a small slot in the floor of the cage and spin a wheel 145° within 2 s. After reaching proficiency on one of the tasks, rats underwent an additional 5 days of training with or without stimulation of the vagus nerve delivered on the successful trials. Intracortical microstimulation mapping was then used to derive the area of motor cortex controlling specific movements. Rats that received repeated VNS paired with training on the lever press task demonstrated a major increase in areal representation of the shoulder, but no increase in forepaw compared to rats that did not receive VNS. Similarly, rats that receive VNS paired with training on the wheel spin task exhibited a significant increase in the area of motor cortex representing the forepaw with no expansion of the shoulder. Therefore, VNS facilitated robust expansion of the motor cortex representation of the specific movement that was paired with stimulation. Both tasks were designed such that reward pellets were delivered on successful trials and were typically consumed 1–2 s after the delivery of VNS. Despite the relatively close timing of pellet consumption and mastication with VNS, no increase was observed in the jaw representation, suggesting VNS must be precisely timed with an event to drive specific plasticity. These findings closely parallel the results observed in the auditory cortex and demonstrate that VNS paired with events can induce robust plasticity specific to the event with which stimulation is paired.

3.4 Stimulation of the vagus nerve during a cognitive task enhances memory retention

In addition to the topographical manifestations of plasticity, delivery of VNS after behavioral experience can enhance memory retention. Early studies provided evidence that a vagotomy impaired the enhancement of memory retention caused by peripheral pharmacological manipulations (Williams and Jensen, 1991). Based on this, Clark and colleagues investigated whether stimulation of the vagus nerve after inhibitory avoidance training would improve consolidation of avoidance memories (Clark et al., 1995). Rats were trained on a single-trial inhibitory avoidance task, followed immediately afterward by 30 s of VNS or no stimulation. Upon retest 24 h later, rats that had received VNS demonstrated a remarkable increase in retention compared to rats that did not receive stimulation. A similar increase in memory retention was observed in humans on a word recognition memory task. Clark and colleagues conducted a study in which subjects read paragraphs with some highlighted words and did or did not receive VNS immediately after reading (Clark et al., 1999). VNS immediately after reading significantly improved subjects' ability to recognize

highlighted words in a list of distracters. These findings provide support for the ability of VNS paired with experience to enhance memory retention.

4 APPLYING TARGETED PLASTICITY TO TREAT DISEASE

Because VNS paired with experience can drive event-specific plasticity, this technique may hold promise to direct beneficial plasticity in order to treat many manifestations of neurological disorders. A number of studies have provided proof-of-concept validity for the use of VNS paired with specific experience to treat an array of plasticity-related neurological disorders.

4.1 Chronic tinnitus

Chronic tinnitus is an alarmingly common disorder that causes minor to highly devastating reduction in quality of life (Davis and El Rafaie, 2000). Current treatments are largely ineffective, with great variability in patient response and adverse effects (Parnes, 1997). While the exact mechanism is still under debate, it is generally accepted that maladaptive plasticity within the central nervous system underlies the pathophysiology in many cases (Eggermont and Roberts, 2004). In the case of noise-induced hearing loss, the central nervous system fails to receive input from a region of the damaged cochlea. This loss of input causes destabilization of the normal excitatory and inhibitory balance within central auditory circuits that can lead to map distortion, increased receptive field size, and increased synchronous activity in quiet, which appears to be responsible for the tinnitus percept (Engineer et al., 2011).

As detailed previously, VNS paired with tones can drive specific plasticity to alter spectral and temporal response characteristics of the central auditory neurons (Engineer et al., 2011; Shetake et al., 2011). If map distortion and receptive field size lead to tinnitus, in principle, VNS paired with the appropriate presentation of tones could drive plasticity to restore the normal characteristics of the circuitry and alleviate the percept of tinnitus (Fig. 2A). Engineer and colleagues sought to evaluate the capacity of VNS to eliminate the behavioral correlate of chronic tinnitus in rats (Engineer et al., 2011). The rationale for the study was based on increasing the number of cortical neurons tuned to frequencies other than the tinnitus frequency to reduce the overrepresented tinnitus frequency. Noise trauma was induced to damage the high-frequency region of the cochlea, causing a large increase in the proportion of neurons tuned to middle frequency tones, a reduction in the proportion of neurons responding to high-frequency tones, and an increase in overall synchrony, all reflective of changes proposed to be responsible for tinnitus. Rats displaying a tinnitus percept centered on middle frequency tones were assigned to receive either VNS-tone therapy or sham therapy. The VNS-tone therapy consisted of VNS paired with randomly interleaved tones that spanned the rat hearing range but excluded the tinnitus frequencies. Sham therapy consisted of the same tone exposure without VNS. The VNS-tone therapy fully ameliorated the tinnitus percept 10 days after the therapy began. The behavioral improvements were observed for up to 3 months after the end of VNS-tone therapy, demonstrating that the effects of the therapy were long-lasting. Sham therapy did not improve the tinnitus percept at any of time points tested. Paralleling the behavioral improvements, VNS-tone therapy restored most electrophysiological correlates of tinnitus,

including map distortion and elevated synchrony. This study provides evidence that VNS paired with tones can reverse pathological plasticity and ameliorate chronic tinnitus. A clinical trial utilizing this implementation of VNS paired with tones was conducted to treat chronic tinnitus in patients and demonstrated promising results (Arns and De Ridder, 2011; Microtransponder, 2010).

4.2 Stroke

Stroke is a common cause of disability, affecting 795,000 people in the United States each year, with as many as 85% of cases leading to impairments in upper limb function (Dobkin, 2004; Roger et al., 2012). A stroke typically causes a unilateral disruption of blood flow to the brain, and because of the anatomy of the neurovasculature, the motor cortex is susceptible to cell death. The death of neurons in the motor cortex interferes with the circuitry responsible for controlling muscle groups, leading to a loss of coordinated motor function. The most common poststroke intervention, physical rehabilitation, leads to some functional gains, but in the majority of cases, the improvement is incomplete, leaving patients with chronic disability (Dobkin, 2004, 2005; Lai et al., 2002).

Notable reorganization of motor maps occurs after stroke, in both the surviving peri-infarct region and the undamaged contralateral motor cortex (Calautti and Baron, 2003; Nudo and Friel, 1999). Plasticity in these areas is believed to be the substrate for functional recovery (Hallett, 2001). As detailed earlier, a study from Porter and colleagues demonstrated that VNS paired with physical training can enhance plasticity within the motor cortex (Porter et al., 2011). Therefore, VNS paired with physical training after a stroke may enhance reorganization within spared circuitry of the motor cortex and improve function outcomes (Fig. 2B). Khodaparast and colleagues tested this hypothesis in two studies using a rat model of ischemic stroke (Khodaparast et al., submitted). In the first study, rats were trained on the bradykinesia assessment task, a skilled forelimb task that provides unbiased, quantitative measurements of multiple parameters of forelimb movement speed (Hays et al., 2013). All rats became highly proficient at the task. After induction of ischemic damage in the motor cortex contralateral to the trained limb, performance dropped significantly. Rats were then assigned to receive rehabilitative training with or without the delivery of VNS. VNS paired with rehabilitative training fully restored task performance by the second week of treatment and significantly improved performance compared to rehabilitative training without VNS. VNS paired with rehabilitative training also improved fore-limb movement speed compared to rehabilitative training alone. These findings demonstrate that VNS paired with physical rehabilitation can improve recovery of forelimb speed after stroke compared to rehabilitative training without VNS.

A second study by the same group extended these findings to recovery of fore-limb strength after stroke (Khodaparast et al., 2013). Rats were trained to proficiency on the isometric force task, an automated method to quantify forelimb strength (Hays et al., 2012). After induction of ischemic lesion, performance on the task and fore-limb strength were significantly reduced. VNS paired with rehabilitative training resulted in significantly better performance and stronger maximal pull force over the course of therapy compared to rehabilitative training without VNS. These benefits persisted after the cessation of VNS,

suggesting a long-term improvement. Highlighting the benefits of VNS, 100% of subjects that received VNS paired with rehabilitative training demonstrated a full recovery of forelimb strength, while only 22% of subjects that received rehabilitative training without VNS demonstrated a full recovery. In both studies, no difference in lesion size was observed, suggesting that VNS is not conferring a neuroprotective effect but rather improving recovery by enhancing plasticity. These findings provide initial evidence that VNS paired with rehabilitative training can restore clinically relevant parameters of forelimb function after a stroke. Based on these findings, a clinical trial applying VNS paired with physical rehabilitation in stroke patients is ongoing (Microtransponder, 2012).

4.3 Cognitive dysfunction

Aberrant plasticity is believed to underlie the hypersensitivity and abnormal memory retention that accompanies posttraumatic stress disorder (PTSD) (Bremner et al., 2007; Peña et al., 2012), and reversal of this maladaptive plasticity may erase fear memory (Sandkühler and Lee, 2013). As such, the ability to apply VNS to normalize the hypersensitive responses to stimuli may improve the symptoms of PTSD. A proof of principle study conducted by Peña and colleagues in a rat model of PTSD lends credence to this hypothesis. Rats were trained on an auditory fear conditioning task followed by extinction training with or without VNS (Peña et al., 2012). Testing was conducted 1 day later to assess conditioned fear retention. VNS paired with extinction training resulted in a significant reduction of conditioned fear retention compared to extinction training without VNS. Unpaired VNS delivered shortly after training failed to reduce conditioned fear retention, suggesting that VNS must be temporally aligned with the behavioral experience. The beneficial effects of VNS are long-lasting, as conditioned fear remains reduced 2 weeks after the cessation of treatment. Additionally, VNS paired with extinction training was similarly effective at reducing a remote fear memory compared to extinction training without VNS. Although chronic VNS is known to confer anxiolytic effects (Furmaga et al., 2011; George et al., 2008), this effect is not dependent on temporal specificity. Therefore, if VNS is exerting anxiolytic effects to reduce conditioned fear response, unpaired VNS delivery should be effective. However, because unpaired VNS fails to reduce the conditioned fear response, VNS is most likely acting through modulation of plasticity and memory rather than providing a generalized, nonspecific reduction in anxiety. Although much development remains, this study provides initial support that VNS paired with behavioral experience can improve extinction training.

5 MECHANISMS OF TARGETED PLASTICITY DIRECTED BY VNS

Anatomical, electrophysiological, and biochemical findings indicate that VNS engages the cholinergic and noradrenergic neuromodulatory systems (Detari et al., 1983; Dorr and Debonnel, 2006; Follesa et al., 2007; Groves et al., 2005; Naritoku et al., 1995; Nichols et al., 2011; Roosevelt et al., 2006). There is a high degree of similarity in the auditory plasticity evoked by VNS paired with tones (Engineer et al., 2011; Shetake et al., 2011) compared with direct stimulation of the nucleus basalis paired with tones (Kilgard and Merzenich, 1998a,b), indicating that these pathways may share a common mechanism. Several studies demonstrate that disruption of neuromodulatory transmission occludes the

effects of VNS. Nor-epinephrine is necessary, as lesions of the locus coeruleus prevent the antiepileptic effects of VNS (Krahl et al., 1998). Cholinergic antagonists abrogate the electrophysiological effects of VNS in the auditory cortex, implicating acetylcholine in the effects of VNS in the central nervous system (Nichols et al., 2011). These findings suggest that both the cholinergic and noradrenergic systems contribute to the ability of VNS to specifically direct plasticity.

VNS promotes several downstream changes in molecular signaling cascades that are known to underlie plasticity. VNS drives expression of brain-derived neurotrophic factor (BDNF), an important regulator of plasticity (Follesa et al., 2007). BDNF engages a variety of downstream effectors, including activation of cAMP response element-binding protein, that drive synaptic plasticity (Ernfors and Bramham, 2003; Mattson et al., 2004). Activity-regulated cytoskeletal protein (*Arc*) is regulated by BDNF and is strongly associated with plasticity (Bramham and Messaoudi, 2005; Bramham et al., 2008). Other downstream pathways affected by BDNF, such as Nogo receptor signaling, are known to contribute to recovery after motor cortex damage, suggesting a possible mechanism for VNS-dependent enhancement of recovery after stroke (Fang et al., 2010; Takei, 2009; Tsai et al., 2011). Consistent with increased BDNF expression, VNS increases phosphorylation of multiple sites in the BDNF receptor, TrkB (Furmaga et al., 2012). A compound that inhibits Trk autophosphorylation prevents the VNS-dependent increases in TrkB phosphorylation, indicating that VNS is driving activation of TrkB through the canonical mechanism. These phosphorylated sites on TrkB are associated with broad downstream effects, such as activation of mitogen-associated protein kinase, phosphatidylinositol-3 kinase, and phospholipase C-γ, which are linked to plasticity (Gottschalk et al., 1999; Thomas and Huganir, 2004). Additionally, VNS induces expression of interleukin-1β (Hosoi et al., 2000), which is associated with plasticity and memory (Avital et al., 2003). VNS also increases expression of the trophic factor basic fibroblast growth factor (Follesa et al., 2007), which is believed to promote recovery after motor cortex lesion (Rowntree and Kolb, 1997). VNS may even directly alter the expression of NMDAR and $GABA_AR$ expression levels, thereby influencing neuronal excitability (Zhang and Zhang, 2002). The extensive activation of signaling cascades demonstrates that VNS engages many molecular mechanisms that are known to enhance plasticity and memory.

The molecular changes induced by VNS translate into changes in neuronal and network properties. Low-intensity stimulation of the vagus nerve results in the activation of a slow hyperpolarizing current in the cortical neurons, suggesting that intrinsic neuronal properties may be modified by VNS (Zagon and Kemeny, 2000). Synaptic properties are also altered by VNS, as stimulation causes long-lasting strengthening of excitatory postsynaptic potentials in the hippocampal neurons (Ura et al., 2012). Additionally, VNS followed by weak tetanic electrical stimulation of the hippocampus enhances long-term potentiation (Zuo et al., 2007). The enhancement of hippocampal synaptic plasticity clearly provides a potential mechanism for VNS-directed targeted plasticity. Stimulation of the vagus nerve also causes large-scale changes in network activity. VNS rapidly induces desynchronization that can be observed in the EEG and in multiunit cortical recordings (Chase et al., 1967; Nichols et al., 2011). This desynchronization is dependent on cholinergic transmission

(Nichols et al., 2011). Chronic VNS induces long-term changes in the EEG power spectrum, increasing the power of low-frequency bands (Valdés-Cruz et al., 2008). Together, the findings suggest that VNS may promote neural plasticity by altering network state.

6 TARGETED PLASTICITY REQUIRES LESS VNS THAN APPROVED PROTOCOLS

VNS induces a variety of cellular- and circuit-level changes and effectively drives specific plasticity, but in order to be useful as a targeted plasticity therapy, it must be able to be delivered in a safe, tolerable manner. Standard FDA-approved protocols to treat epilepsy and depression using continuously delivered VNS are well tolerated with few adverse effects (Sackeim et al., 2001). VNS applied for targeted plasticity uses 100 times less current than these protocols and would be expected to have fewer adverse effects (Engineer et al., 2011). Continuously applied VNS for epilepsy and depression typically employs a 30 s “on” period every 5 min for 24 h per day (Handforth et al., 1998; Sackeim et al., 2001). The “on” cycle consists of 500 μs pulses delivered at 30 Hz at an intensity that is set at a tolerable level for each individual patient but does not exceed 3.5 mA. Variations on these parameters have been found to be safe and effective (Heck et al., 2002). The studies applying VNS with paired experience to drive plasticity use significantly less total current per day than the FDA-approved protocols. Stimulation parameters used to drive map reorganization in auditory cortex consisted of 300 daily stimulations of a 500 ms train at 30 Hz 0.8 mA of 100 μs pulses (Engineer et al., 2011). Similar amounts of stimulation were found to drive motor cortex reorganization and enhance recovery after stroke (Khodaparast et al., 2013; Khodaparast et al., submitted; Porter et al., 2011). The enhancing effects of VNS on extinction training and memory retention use even less stimulation, with one to four stimulation trains of 30 s consisting of 500 μs 0.4 mA pulses delivered at 20 Hz (Clark et al., 1995, 1998; Peña et al., 2012). In summary, the low levels of VNS current that effectively enhance plasticity and memory would be expected to be safe and tolerable.

The effectiveness of different parameters of VNS for continuously delivered and paired protocols likely arises from the different desired outcomes. For seizure suppression or antidepressant effects, a sustained, tonic increase in neurotransmitter levels may be desirable and could be achieved using the consistent 5 min off/30 s on stimulation cycle (Handforth et al., 1998; Sackeim et al., 2001). The antiepileptic effects of VNS are mediated by the locus coeruleus (Krahl et al., 1998), so a sustained increase in the level of norepinephrine may drive EEG desynchronization and seizure suppression. Consistent with this, lower amounts of current are less effective at preventing seizures (Handforth et al., 1998). The requirement of sustained neuromodulator levels for seizure suppression is further supported by the finding that treatment of epilepsy with VNS becomes more effective over time (Heck et al., 2002). Alternatively, for the plasticity-enhancing effects of paired VNS, a discrete, phasic release of neurotransmitter release is required to drive specific plasticity. Only events occurring coincident with VNS are reinforced while surrounding events are not (Engineer et al., 2011; Porter et al., 2011). Temporally precise release of acetylcholine and norepinephrine triggered by VNS coincident with an event may serve to “label” its importance and reinforce this event in comparison with other unlabelled events. Because of the temporal

requirements, a continuous delivery of VNS would not be expected to be effective in driving specific plasticity. The benefits of targeted plasticity using VNS persist for weeks or months after discontinuation of stimulation because targeted plasticity therapy drives long-lasting changes in neural circuits (Arns and De Ridder, 2011; Engineer et al., 2011; Khodaparast et al., 2013). In summary, the effectiveness of VNS is likely dependent on the temporal requirements for changes in neuromodulatory levels; therefore, sustained increases are efficacious for epilepsy and depression, and discrete, phasic increases are required for the enhancement of plasticity.

7 FUTURE APPLICATIONS

The low levels of current delivered for VNS-directed plasticity suggest that targeted plasticity therapy using VNS can be safely implemented into patients. The proof-of-concept experiments discussed in the preceding text demonstrate the efficacy of targeted plasticity therapy and suggest that it holds promise for treating tinnitus, stroke, and PTSD. In principle, the ability to specifically manipulate plasticity represents considerable potential for treating a variety of neurological disorders.

Pain disorders can be extremely debilitating and have massive economic, social, and personal consequences. Pain is typically treated with drugs that carry a significant risk of tolerance and dependency (Martell et al., 2007; Schnoll and Weaver, 2003), highlighting the significant clinical need for a safe, effective therapy. Targeted plasticity therapy may be effective in treating disorders related to sensory dysfunction, such as chronic pain, in the same manner as tinnitus. As chronic pain is thought to be related to an increased somatosensory cortical representation (Birbaumer et al., 1997; Flor, 2003; Flor et al., 1995, 1997), sensory input of non-painful areas paired with VNS may be effective in renormalizing the cortical representations and thereby reducing the percept of pain. A similar implementation may be effective for phantom limb pain.

The proof-of-concept evidence demonstrating the effectiveness of VNS paired with rehabilitative training to improve motor function after ischemic stroke opens the possibility that targeted plasticity therapy may drive plastic changes that are beneficial in other disorders of motor function (Khodaparast et al., 2013; submitted). Hemorrhagic stroke is a devastating subtype that has a mechanistically distinct pathophysiology compared to ischemic stroke and typically affects subcortical structures and white matter. It is not clear whether VNS will be effective after white matter damage, but VNS paired with rehabilitative training may be amenable for restoring function by driving plasticity in spared circuitry. Neuronal death from the initial impact of a traumatic brain injury or the resulting sequelae can impair motor function and may benefit from targeted plasticity therapy. Despite significantly different underlying pathologies, VNS paired with rehabilitation could be tested in models of spinal cord injury and Parkinson’s disease. Significant development is still required, but targeted plasticity therapy could potentially promote plasticity within intact motor circuitry to confer therapeutic benefits.

The memory-enhancing effects of VNS paired with training indicate that targeted plasticity therapy could potentially be applied to treat a range of cognitive disorders. Based on the

VNS-dependent enhancement of cued fear extinction in rats (Peña et al., 2012), it has been suggested that VNS may improve exposure therapy. Exposure therapy is beneficial for some patients experiencing generalized anxiety disorder and PTSD. The therapy aims to reduce the response to fear-inducing stimuli through habituation (Frueh et al., 1995). As VNS sped the reversal of a fearful memory in rats, similar principles may allow VNS to enhance the effects of exposure therapy in patients. Paired with the appropriate exposure, VNS may bolster the effects of the therapy and provide a more robust, rapid reversal of the fear response. Maladaptive plasticity is associated with a variety of other cognitive disorders, including anxiety, bipolar disorder, schizophrenia, depression, drug addiction, and attention-deficit hyperactivity disorder (Brunoni et al., 2008; Lozano, 2011). The complex cognitive aspects of these disorders have left them undermanaged, emphasizing the need for effective, flexible treatments that can address the underlying pathophysiology. VNS, if paired with the appropriate behavioral exposure, may be able to improve these disorders.

8 CONCLUDING REMARKS

The remarkable capacity for experience-dependent plasticity in the sensory, motor, and cognitive systems is a testament to its importance. In many neurological disorders, insufficient and maladaptive plasticity can hinder recovery. The ability to harness and specifically direct plasticity may reduce the suffering caused by these disorders. Targeted plasticity therapies, including VNS paired with relevant events, may represent such an intervention. While proof-of-concept studies have provided encouraging results, continuing studies should be directed at defining the optimal parameters to maximize benefit, delineating the factors that affect outcomes, and identifying other disorders that may respond to targeted plasticity therapy.

VNS is one of many potential tools that can drive specific plasticity and subsequently treat neurological disorders. Mirroring aspects of the development of vaccines, VNS acts as an adjuvant, while experience mimics the antigen (Fig. 3). Together, these elements synergistically provoke a significant biological response that surpasses the typical physiological response to the antigen alone. As such, VNS paired with experience enhances the brain’s response to experience and, when targeted appropriately in a disease state, can promote recovery or reversal of neurological disease. The development of other tools that can act as an adjuvant to reinforce the response to experience could also be applied as targeted plasticity therapies. Considering the transformative potential of targeted plasticity therapies, efforts should be focused on the development and translation of VNS and other methods for targeting plasticity to treat neurological disease and improve human health.

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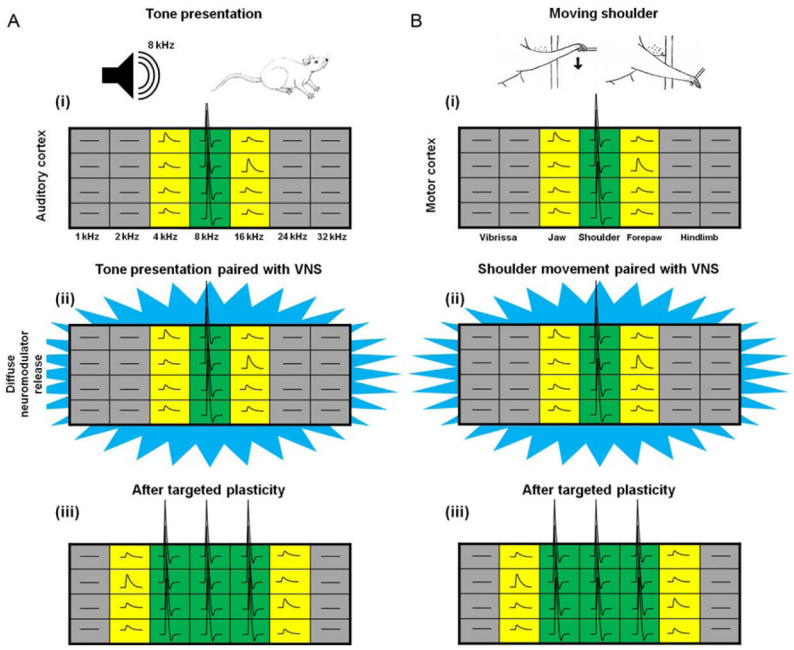

FIGURE 1.

Model of targeted plasticity therapy driving specific changes in neural circuits and not in other areas. (A) (i) Presentation of an 8 kHz tone drives circuit activity in the auditory cortex (green). (ii) Temporally precise release of neuromodulators (blue), such as that induced by VNS, paired with this activity drives plasticity. (iii) After targeted plasticity, the map reorganization results in an increase in representation of the paired tone (Engineer et al., 2011). Previously subthreshold inputs (yellow) drive activity (green) after pairing with VNS. (B) (i) Activity within neurons of the motor cortex results in movement of the shoulder. (ii) Diffuse release of neuromodulators paired with movement drives plasticity in the motor cortex. (iii) After targeted plasticity, the number of circuits representing the shoulder movement is increased (Porter et al., 2011). The large rectangles represent topographical organization of the auditory and motor cortices, and the activity of neurons is represented within each individual box. Green denotes suprathreshold action potential firing, yellow denotes subthreshold depolarization, and gray denotes no response.

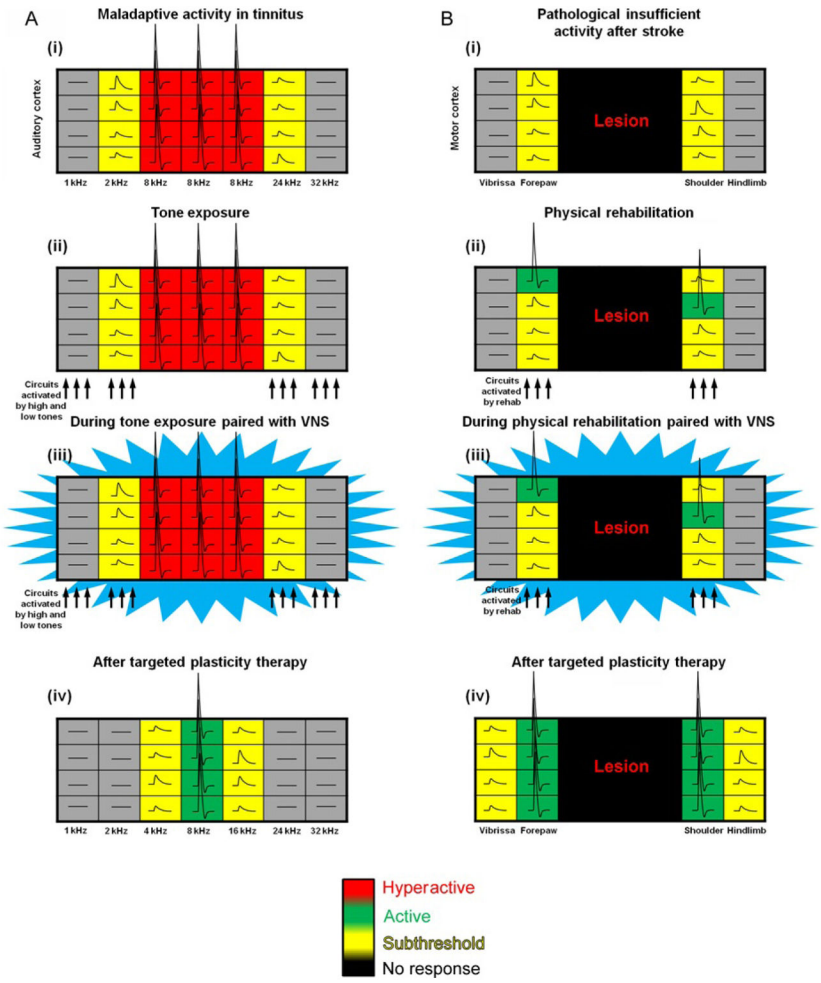

FIGURE 2.

Model of VNS paired with experience driving therapeutic plasticity in neural circuits. (A) (i) In tinnitus, the auditory neurons are hyperactive and the map of sound frequency is distorted. (ii) Presentation of high and low tones (black arrows) is insufficient to drive plasticity. (iii) However, high and low tones paired with VNS (blue) drive plasticity within the auditory system. (iv) After targeted plasticity therapy, activity within the auditory system is renormalized, demonstrating that VNS paired with experience can reverse maladaptive plasticity (Engineer et al., 2011). (B) (i) Following a stroke, circuits previously controlling the forelimb are destroyed (black), resulting in impaired function. (ii) Physical rehabilitation (black arrows) drives some reorganization and partially restores function. (iii) Physical rehabilitation paired with VNS drives robust and specific neural plasticity by increasing subthreshold activity (yellow). (iv) VNS paired with physical rehabilitation can drive robust and specific changes to enhance recovery limited by insufficient plasticity (Khodaparast et al., 2013; Khodaparast et al., submitted).

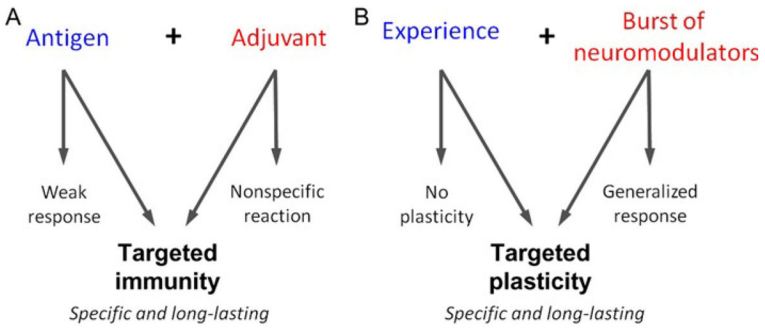

FIGURE 3.

Vaccination and targeted plasticity therapy are based on similar principles. (A) Injection of an antigen alone causes a generally weak immunologic response. Injection of an adjuvant alone causes a nonspecific inflammatory response. Many different compounds can act as adjuvants, including aluminum salts, virosomes, or saponins (Cox and Coulter, 1997). Concurrent presentation of the antigen and adjuvant results in a significantly enhanced immunologic response beyond that evoked by either element alone, resulting in specific and long-lasting immunity. (B) Targeted plasticity therapy is based on similar principles of synergism. Experience alone drives activity within circuitry but does not result in plasticity. Neuromodulators alone have generalized neuronal effects, but do not drive lasting changes. A variety of factors can cause release of neuromodulators, including attention, pain, or VNS. When bursts of neuromodulators correspond with experience, specific and long-lasting plasticity results.