Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke


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A B S T R A C T

Upper limb impairment is a common debilitating consequence of ischemic stroke. Physical rehabilitation after stroke enhances neuroplasticity and improves limb function, but does not typically restore normal movement. We have recently developed a novel method that uses vagus nerve stimulation (VNS) paired with forelimb movements to drive specific, long-lasting map plasticity in rat primary motor cortex. Here we report that VNS paired with rehabilitative training can enhance recovery of forelimb force generation following infarction of primary motor cortex in rats. Quantitative measures of forelimb function returned to pre-lesion levels when VNS was delivered during rehab training. Intensive rehab training without VNS failed to restore function back to pre-lesion levels. Animals that received VNS during rehab improved twice as much as rats that received the same rehabilitation without VNS. VNS delivered during physical rehabilitation represents a novel method that may provide long-lasting benefits towards stroke recovery.

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Introduction

Stroke is the second most common cause of disability worldwide (Leary and Saver, 2003). Ischemic stroke causes neural death due to inadequate blood flow, often resulting in movement impairments on the opposite side of the body (Deb et al., 2010; Lo et al., 2003). Seventy-five percent of patients who survive an ischemic stroke continue to have significant weakness in the upper extremities even after extensive rehabilitative therapy (Harvey and Nudo, 2007; Kwakkel, 2009; Levine and Greenwald, 2009). Impaired limb function reduces the ability to perform activities of daily living, reduces the quality of life, and increases medical costs (King, 1996; Whyte et al., 2004). The development of an effective therapy to restore motor function would fulfill a large unmet clinical need.

Physical rehabilitation after stroke drives plasticity in the form of reorganization of cortical circuitry in the motor system (Johansson, 2000; Nudo, 2003; Rossini and Forno, 2004; Schaechter, 2004; Ward and Cohen, 2004). One common rehabilitative intervention, constraint induced movement therapy (CIMT) causes reorganization of the motor cortex map of arm movement (Sawaki et al., 2008; Schaechter et al., 2002). Additionally, new methods using virtual reality and electrical stimulation of motor cortex may also promote increased synaptic plasticity and cortical reorganization within the motor cortex (Adkins-Muir and Jones, 2003; Lindenberg et al., 2012; You et al., 2005). The development of additional methods to increase neural plasticity may lead to improved recovery of motor function (Hallett, 2001; Nudo, 2003). We have recently developed a method to induce specific and long-lasting cortical map plasticity by pairing vagus nerve stimulation (VNS) with movements or sensory stimuli in intact rats (Engineer et al., 2011; Porter et al., 2011). Repeatedly delivering VNS with forelimb movements resulted in movement-specific map plasticity within the primary motor cortex beyond training without VNS (Porter et al., 2011). We hypothesized that this enhancement in reorganization within the motor cortex may improve recovery of function after stroke.

Upper limb strength is one of the best prognostic indicators for arm function and chronic disability following stroke (Harris and Eng, 2007; Mercier and Bourbonnais, 2004; Sunderland et al., 1989). Here, we evaluated whether the delivery of VNS during rehabilitative training can enhance recovery of forelimb strength in a model of ischemic stroke. Rats were trained to perform an isometric force task that quantitatively measured forelimb force generation (Hays et al., 2012). This task is fully automated, allowing the experimenter to test several animals simultaneously and avoid the possibility of experimenter bias. Unilateral injections of a peptide vasoconstrictor, endothelin-1, into primary motor cortex caused an ischemic infarct and impaired function of the trained forelimb (Fang et al., 2010; Gilmour et al., 2004; Hays et al., 2012). Rats underwent rehabilitative training for five weeks with or without the delivery of VNS. No VNS was delivered on week six to allow evaluation of persistent effects. VNS delivered during rehabilitative training restored pull force generation back to pre-lesion levels, whereas extensive rehabilitative training without VNS failed to restore function. These findings suggest that VNS paired with physical rehabilitation may hold promise for enhancing recovery of upper extremity function after stroke.
Materials and methods

Subjects

Nineteen adult female Sprague–Dawley rats, approximately 4 months old and weighing approximately 250 g when the experiment began, were used in this experiment. The rats were housed in a 12:12 h reversed light cycle environment so that behavioral testing took place during the dark cycle in order to increase daytime activity levels. Rats were food deprived to no less than 85% of their normal body weight during training as motivation for the food pellet rewards. This study was designed to take into consideration the rapid hormonal cycle of female rats. To ensure that the data for each rat was collected during every stage of the estrus cycle all analyses were based on the average of a week’s worth of behavioral data. All handling, housing, surgical procedures, and behavioral training of the rats were approved by the University of Texas at Dallas Institutional Animal Care and Use Committee.

Behavioral apparatus and software

The behavioral chamber consisted of an acrylic box (10 × 12 × 4.75 in.) with a slot (2.5 × 0.4 in.) located in the front right corner of the box through which the rats could access the pull handle. The slot location restricted access such that only the right forelimb could be used to perform the task. The aluminum pull handle was centered in the slot at a height of 2.5 in. from the floor and at lateral distances varying from 0.75 in. inside to 0.75 in. outside relative to the inner wall surface of the cage, depending on the training stage. The handle was affixed to a custom designed force transducer (Motor Pull Device, Vulintus LLC, Sachse, TX) located outside the cage. The maximum load capacity of the transducer was 2 kg, and the typical forces generated by the rats fell within the linear range of measurement. Forces readings were sampled at 20Hz and measured with ±1 g accuracy. Force measurements were calibrated with a force meter at least once per week.

Custom software was used to control the task and collect data. A motor controller board (Motor Controller, Vulintus LLC, Sachse, TX) sampled the force transducer every 50 ms and relayed information to a custom MATLAB software which analyzed, displayed, and stored the data. Force values and corresponding timestamps were collected as continuous traces for each trial to allow for the analysis of force profiles over the course of a session. If a trial was successful, the software triggered an automated pellet dispenser (Vulintus LLC, Sachse, TX) to deliver a sucrose pellet (45 mg dustless precision pellet, BioServ, Frenchtown, NJ) to a receptacle located in the front left corner of the cage.

Isometric force task training

The isometric force task was performed as previously described. Training sessions lasted 30 min and were conducted twice daily, five days a week, with sessions on the same day separated by at least 2 h. During early phases of training, experimenters manually shaped animals by using ground sucrose pellets to encourage interaction with the handle. Rats pulled the handle initially located 0.75 in. inside the training cage to receive a sucrose reward pellet. A trial was initiated when the rat generated a force of at least 10 g on the handle. After trial initiation, the force was sampled for 4 s. If the force threshold was broken within a 2 second window following the initial contact, the trial was recorded as a success and a reward pellet was delivered. If the force did not exceed threshold within the 2 second window, the trial was recorded as a failure and no reward was given. Hit rate was calculated based on the number of successful trials over the total number of initiated trials: Hit rate = [ (total successful trials / total trials) × 100]. Force on the pull handle was sampled for additional seconds following the 2 second trial window, regardless of the trial outcome, to capture any late attempts which were unrewarded. Following the 4 s of data collection there was a 50 millisecond pause before rats could initiate another trial. If rats did not receive 50 pellets in a single day, they were given 10 g of pellets after daily training sessions were complete. The task was made progressively more difficult as rats met the criterion for number of successful trials within a session and progressed to the next stage. As the training stages increased, the handle was gradually retracted to 0.75 in. outside the cage and the force threshold progressively increased up to 120 g. If an animal exceeded criteria for a proceeding stage, they were automatically advanced to the stage that matched their performance. The prescribed position and threshold values were strictly adhered to for pre- and post-lesion measurements.

Rats were held at the pre-lesion stage until they had 10 successive sessions averaging over 85% success rate. The pre-lesion data reported in this study is compiled from these 10 sessions. After this point, the rats were given an ischemic lesion followed by seven days of recovery, after which they returned for post-lesion behavioral testing with the same parameters as pre-lesion allowing for a direct comparison of performance. All rats were tested until they had 4 sessions with greater than 10 trials each during the post-lesion assessment. Rats then proceeded to the therapy stage where VNS was delivered on each successful trial for 25 days (Fig. S1). Following the therapy stage, all rats underwent an additional two days (week 6) of rehabilitative training only, to allow assessment of the persistent effects of VNS pairing.

Unilateral motor cortex ischemic lesion

Unilateral ischemic lesions of primary motor cortex were performed similar to a previously described method (Fang et al., 2010; Gilmour et al., 2004; Hays et al., 2012, 2013). See Supplementary Methods section for details.

Vagus nerve cuff implantation

Following ischemic lesion, all rats were implanted with a skull-mounted two-channel connector (headcap) and a bipolar stimulating nerve cuff constructed with platinum-iridium leads (5–6 kΩ impedance). Implantations were performed as previously described (Engineer et al., 2011; Porter et al., 2011). See Supplementary Methods sections for details.

Application of VNS

Behavioral training was identical for all rats. The VNS during Rehab group received approximately 9000 total stimulations over 25 days (i.e., fifty 30 min sessions). VNS was delivered within 50 ms of a successful pull attempt. VNS was delivered as a 500 ms train of 15 pulses at 30 Hz (Fig. S1). Each biphasic pulse was 0.8 mA in amplitude and 100 μs in phase duration. These parameters are identical to our earlier studies (Engineer et al., 2011; Porter et al., 2011). Previous studies using the same parameters employed in this study have demonstrated changes in electroencephalographic measures and neuronal spiking synchrony during VNS, indicating that the nerve is successfully stimulated (Engineer et al., 2011; Nichols et al., 2011). No stimulation was delivered during the post-lesion assessment stage. During the first day of post-lesion assessment, no rats had a stimulator cable connected to the headcap. For both the Rehab rats and the VNS + Rehab rats, the stimulator cable was first connected during the second day of post-lesion assessment and was connected every day until the end of the fifth week of therapy. The stimulation cable for the Rehab rats was not connected to a stimulator. During the sixth week, the stimulator cable was not utilized for either group. Rats were perfused and brains removed following the sixth week of training to quantify lesion size (see Supplementary Methods for details).
Statistics

All data are reported as the mean ± SEM. All comparisons were planned in the experimental design a priori, and significant differences were determined using one-way ANOVA, two-way ANOVA, and t-tests where appropriate. Statistical tests for each comparison are noted in the text. One-tailed t-tests comparing individual subject performance after therapy (week 6) to baseline performance (PRE) were used to determine which rats exhibited a significant impairment after therapy. All other t-tests were two-tailed. Paired t-tests were used to compare repeated measures over time within groups. Alpha level was set at 0.05 for all comparisons. Significant differences between the Rehab and VNS + Rehab groups are noted in the figures with an asterisk. See Table S1 for statistical values for t-test comparisons.

Results

Rats acquire skilled performance of the isometric force task

To assess forelimb function in the context of stroke, rats were trained to perform the isometric force task, a behavioral test that quantitatively assesses multiple parameters of forelimb function (Hays et al., 2012). The task requires rats to reach out and grasp a handle attached to a force transducer and apply 120 g of force to receive a food reward (Fig. 1). Rats became highly proficient at the task in 10.1 ± 0.6 days. Early in training, rats were able to generate forces up to 400 g. Highly trained rats did not generate higher forces (Fig. 1D). The majority of trials in highly trained were over 120 g. Early in training, pull force was often less than 80 g and varied substantially from trial to trial. A significant decrease in the variance was observed in highly trained rats compared to newly trained rats (F test for equal variance, P < 0.001). This demonstrates that the increase in task performance with training is unlikely to be due to strengthening of forelimb muscles, but rather is due to the acquisition of skilled forelimb use. Daily observations did not reveal any obvious differences in the reach or grasp strategy used to perform the pull task.

Unilateral ischemic lesion impairs task performance

Prior to the induction of ischemic damage, subjects were held until they achieved a pre-lesion baseline of five consecutive days exceeding 85% hit rate performance. Performance during the baseline did not differ significantly across days (Day 1: 84.6 ± 2.1%, Day 5: 87.2 ± 1.6%, n = 15, P = 0.36, paired t-test). Single trial examples matched to the bottom quartile of force show that pull force exceeded the 120 g threshold on the vast majority of trials (Figs. 2A,B, left panel). Both groups were...
Fig. 2. VNS paired with Rehab improves hit rate after ischemic lesion. (A, B) Single trial force profiles matched to the bottom quartile of force for each experimental group throughout the course of the experiment. The gray dashed line indicates the 120 g hit threshold. (C) Hit rate performance over the course of the experiment. VNS paired with Rehab improves recovery compared to Rehab on most weeks. The increase in hit rate is still present at week 6, after the cessation of VNS therapy. N refers to number of rats in each group. * indicates significant difference between Rehab and VNS + Rehab. (D) Correlation of individual subject performance prior to lesion and after the completion of therapy. Empty symbols denote a significant reduction after therapy compared to pre-lesion performance. Symbols on or above the line suggest recovery, while those below the line indicate impairment. Note the consistent recovery compared to Rehab on most weeks. The increase in hit rate is still present at week 6, after the cessation of VNS therapy.

Unilateral ischemic lesion reduces forelimb strength

In addition to assessing hit rate performance, we sought to evaluate forelimb strength. Before ischemic lesion, peak force generated by the
forelimb was similar in both groups. On the majority of trials, peak force exceeded 120 g (Figs. 3A,B, left panel). Averaged pre-lesion peak force was slightly, but significantly, higher in the VNS + Rehab group (Fig. 3C, PRE, Rehab: 144.1 ± 2.0 g; VNS + Rehab: 152.0 ± 2.2 g, unpaired t-test, P = 0.017). After ischemic lesion, peak force generation was significantly reduced in both groups compared to pre-lesion (Fig. 3C, POST, Rehab: 103.6 ± 4.2 g, paired t-test, P < 0.001; VNS + Rehab: 99.0 ± 7.9 g, P < 0.001). No difference in peak force was observed between groups (unpaired t-test, P = 0.57). The distribution of peak forces demonstrated a notable leftward shift with significantly fewer trials with peak forces above the 120 g threshold (Figs. 3A,B, center panel).

Rehabilitative training without VNS was insufficient to fully restore forelimb strength. The distribution of peak forces after therapy reveals substantial deficiencies compared to pre-lesion (Fig. 3B). Significant increases are observed in bins 80–120 g (paired t-test, P < 0.05 for each bin) and significant decreases are observed in bin 140–160 g (P < 0.05) after therapy. This increase in low force pulls and decrease in high force pulls is consistent with a deficit in forelimb strength. ANOVA on peak force revealed a significant effect of therapy for the Rehab group (F[6,56] = 2.98, P = 0.014). Rehab resulted in a small but significant improvement in peak force by week 2 (Fig. 3C, POST v. week 2, paired t-test, P < 0.05). However, peak force remained significantly reduced compared to pre-lesion levels throughout the course of therapy (Fig. 3C, PRE vs. weeks 1–6, paired t-test, all P < 0.05). On week 6, peak force had recovered 56.8 ± 16.6% of the deficit relative to pre-lesion levels. 7 of 9 rats (78%) demonstrated significant impairment of force generation after the completion of therapy (Fig. 3D, also see Fig. 5B).

VNS paired with physical rehabilitation resulted in notable recovery of forelimb strength. After five weeks of therapy, the distribution of peak forces is highly similar to that observed pre-lesion, with no differences observed between any bins (Fig. 3A, paired t-test, all P > 0.15). This indicates a complete restoration of forelimb strength. ANOVA on peak force revealed a significant effect of therapy for the VNS group (F[6,35] = 8.88, P < 0.001). Examination of group averages over the course of therapy demonstrates that peak force increased significantly compared to the post-lesion baseline during the first week of therapy (Fig. 3C, POST vs. week 1, paired t-test, P < 0.05) at the completion of therapy, peak force had recovered 104.3 ± 15.3% relative to the deficit and was indistinguishable from pre-lesion levels. The restoration of peak force remained after the cessation of VNS therapy at week 6, indicating that the recovery of forelimb

![Fig. 3](https://example.com/fig3.png)

**Fig. 3.** VNS paired with Rehab improves recovery of forelimb strength. (A, B) Peak force distributions for both groups at each time point. The gray dashed box indicates trials which exceed the 120 g threshold. The numerical value indicates the cumulative percentage (± SE) of trials exceeding the 120 g threshold. (C) Maximal force over the course of the experiment. VNS paired with rehabilitative training significantly improves maximal force compared to rehabilitative training alone by the second week of therapy. The increase in force is still present at week 6 after the cessation of VNS. N refers to number of rats in each group. * indicates significant difference between Rehab and VNS + Rehab. (D) Correlation of individual subject maximal force prior to lesion and after the completion of therapy. Empty symbols denote a significant reduction after therapy compared to pre-lesion performance. All subjects (6 of 6) in the VNS + Rehab group demonstrate complete recovery, while only 2 of 9 subjects in the Rehab group recover.


**Discussion**

This study tested whether delivering VNS during rehabilitative training could improve recovery of forelimb motor function following cortical ischemic damage compared to rehabilitative training alone. Forelimb function was assessed using the automated isometric pull task with approximately 50,000 pull attempts collected per rat, resulting in unbiased data collection and high statistical power (Hays et al., 2012). Rats received rehabilitative training on an isometric force task (Hays et al., 2012) for five weeks with or without the delivery of VNS. Weeks of daily intensive rehabilitative training without VNS failed to restore pre-lesion function. Forelimb function recovered completely when brief bursts of VNS were delivered during rehabilitative training. VNS paired with rehabilitative training doubled recovery of hit rate performance and forelimb strength compared to rehabilitative training without VNS. VNS did not alter the size of the lesion or increase the intensity of rehabilitative training. The enhanced recovery facilitated by the delivery of VNS during rehabilitative training may present an opportunity for reducing motor impairments in stroke patients.

Stroke often results in deficits of skilled movement which persist in spite of extensive rehabilitation (Segura et al., 2006; Van Peppen et al., 2004). Rehabilitative training is focused on improving motor function after stroke, which is thought to be supported by reorganization of the motor cortex (Hallett, 2001; Kleim, 2011; Nudo, 2003). Rehabilitation-induced cortical plasticity is associated with the degree of recovery in animal models (Castro-Alamancos and Borrell, 1995; Dijkstra et al., 2001; Frost et al., 2003; Ramanathan et al., 2006) and in stroke patients (Calautti and Baron, 2003; Lindenberg et al., 2012). A variety of factors that limit neural plasticity include recovery following brain damage (Boyeson et al., 1992; Conner et al., 2005; Goldstein et al., 1991; McHughen et al., 2010; Siironen et al., 2007; Sweetnam et al., 2012). Because of the association of plasticity and recovery, it was reasonable to expect that enhancement of plasticity would lead to gains in functional recovery after stroke. Vagus nerve stimulation paired with motor training in unlesioned animals induced robust plasticity in the motor cortex, while similar amounts of motor training without VNS did not drive observable plasticity (Porter et al., 2011). The improvement of recovery observed in this study in subjects that received VNS during rehabilitative training is likely due to the VNS-dependent enhancement of plasticity within motor cortex. However, the cellular and molecular mechanisms that underlie VNS-dependent recovery remain unclear.

Stimulation of the vagus nerve engages multiple neuromodulatory systems and results in the release of acetylcholine, noradrenergic, and brain-derived neurotrophic factor (Dorr and Debonnel, 2006; Follesa et al., 2007; Groves and Brown, 2005; Hassert et al., 2004; Nicholas et al., 2011; Roosevelt et al., 2006). Individually, each of these neuromodulators is known to enhance cortical plasticity and facilitate recovery after brain damage (Boyeson et al., 1992; Conner et al., 2005; Goldstein et al., 1991; Ramanathan et al., 2009; Schäbitz et al., 2004, 2007). There is considerable evidence that these neuromodulators, particularly acetylcholine and noradrenergic, operate synergistically to promote plasticity (Bear and Singer, 1986; Salgado et al., 2012; Seol et al., 2007).

The ability of vagus nerve stimulation to engage these neuromodulatory systems arises from its unique anatomy. Eighty percent of the vagus nerve is comprised of afferent sensory fibers that project into the medulla (Foley and DuBois, 1937; George et al., 2000). These fibers synapse bilaterally on neurons within the nucleus of the tractus solitarius, which then project to the noradrenergic locus coeruleus (LC) and the cholinergic basal forebrain (BF) (Berntson et al., 1998; George et al., 2000; Henry, 2002; Semba et al., 1988). Stimulation of the vagus nerve drives activity within both the LC and BF regions and consequently induces release of acetylcholine and norepinephrine throughout the cortex (Follesa et al., 2007; Nicholas et al., 2011; Roosevelt et al., 2006). Both of these regions are required for the effects of VNS in the central nervous system (Krahl et al., 1998; Nicholas et al., 2011). It is not yet known whether the release of these neuromodulators is required for the robust enhancement of recovery driven by VNS.

Our results provide a proof of concept demonstration that VNS during rehabilitative training holds promise for improving recovery of motor function after stroke. However, translating pre-clinical stroke research into effective therapies for patients has proven to be difficult (Lyden and Lapchak, 2012; O’Collins et al., 2006). Many therapies require delivery soon after the onset of ischemic damage, either to inhibit neuronal death or to bolster the innate transient increase in plasticity after damage (Adams et al., 1994; Savitz, 2007). As a result, many strategies are less effective once chronic deficits are in place. The discrepancy between the timing of delivery of a treatment in animal studies and human trials is thought to be a contributing factor the failure of many promising preclinical therapies (Cheng et al., 2004; Gladstone et al., 2002; Kahle and Bix, 2012). In this study, VNS paired with rehabilitative training was effective when initiated nine days after the stroke. The ability of VNS to confer a beneficial outcome when delivered at this time scale is an improvement over interventions that must be delivered shortly after (i.e., typically within six hours of) stroke to be effective (Ay et al., 2009; Hiraki et al., 2012; Yenari and Hemmen, 2010; Zivin, 1998).
However, it is possible that VNS paired with rehabilitative training may not be ineffective when delivered long after stroke. Later delivery of rehabilitation is associated with worse functional outcomes in animal models and patients (Biernaskie et al., 2004; Cifu and Stewart, 1999), potentially because the rehabilitation occurs after the transient upregulation of plasticity and growth-promoting factors induced by brain damage (Carmichael et al., 2005; Murphy and Corbett, 2009; Wieloch and Nikolich, 2006).

In spite of this, two factors suggest that a delay of weeks or months might not occlude the beneficial effects of VNS paired with rehabilitative training. First, VNS paired with physical training can generate motor cortical plasticity independent of brain damage (Porter et al., 2011). This suggests that VNS-dependent plasticity does not rely on the transient period of enhanced growth and plasticity after injury; therefore VNS may be successful when delivered later. Second, VNS drives a precisely-timed release of neuromodulators that are normally increased during natural motor learning (Izaki et al., 1998; Orsetti et al., 1996). It has been predicted that the ability to achieve supranormal levels of these neuromodulators during rehabilitative training may improve functional gains (Nadeau et al., 2004). Pharmacological interventions that alter the levels of acetylcholine and norepinephrine during rehabilitative training improve motor outcomes in some studies (Adkins and Jones, 2005; Gilmour et al., 2005; Kessler et al., 2000; Nadeau et al., 2004; Walker-Batson et al., 1995). If VNS improves rehabilitation by triggering a consistent trial-by-trial burst of neuromodulators, then it is reasonable to expect that VNS might continue to improve rehabilitation that begins long after stroke onset. However, since the current experiments do not test this possibility, the potential utility of VNS during the chronic stage is speculative and needs to be tested.

There is considerable preclinical and clinical evidence that VNS could be safely delivered in stroke patients. VNS has been used to treat a wide range of conditions, including refractory epilepsy (Benn-Menachem, 2002; Morris and Mueller, 1999), treatment-resistant depression (Rush et al., 2005; Sackeim et al., 2001), Alzheimer’s disease (Sjogren et al., 2002), fibromyalgia (Lange et al., 2011), and bipolar disorder (Marangell et al., 2008). Over 60,000 patients have received VNS over the past twenty-five years (Englot et al., 2011). The clinically approved therapy, which is typically delivers 100 times more daily current than our therapy, is well-tolerated and usually continues for many years (Morris and Mueller, 1999). Few patients report side effects, the most common of which are cough and hoarseness (Sackeim et al., 2001). Even at these high currents, no significant changes in heart rate or oxygen saturation are observed (Binks et al., 2001; Handforth et al., 1998). Additional studies will be needed to determine whether delivery of VNS during physical therapy would be safe in stroke patients.

This is the first study to show that VNS paired with rehabilitative training promotes recovery of strength in a model of stroke. However, the ability for VNS to enhance event-specific plasticity applies in other brain regions and may have therapeutic implications for other diseases (Kilgard, 2012; Lozano, 2011). VNS paired with tones drives tone-specific plasticity within auditory cortex (Engineer et al., 2011). A therapy based on specifically targeting plasticity employed VNS pairing with tones and successfully reversed pathological plasticity and eliminated the behavioral correlate of tinnitus in a rat model (Engineer et al., 2011). This same therapy is now undergoing clinical trials in chronic tinnitus patients, with promising preliminary results (Arns and De Ridder, 2011). The benefits of therapy for tinnitus appear to be long-lasting and seem to be blocked by medications that interfere...
with acetylcholine and norepinephrine, providing further mechanistic support of a neuromodulatory basis of VNS-directed plasticity. In addition to tinnitus and stroke, targeted plasticity represents a potential tool for other neurological disorders, including aphasia, apraxia, dystonia, and pain (Lozano, 2011).

Conclusions/implications

This study provides a proof of concept demonstration that stimulation of the vagus nerve paired with rehabilitative training can improve recovery of forelimb function in a rat model of stroke. VNS delivered during rehabilitative training fully restored forelimb force generation to pre-injury levels. A similar amount of rehabilitative training without VNS was insufficient to restore performance. These results suggest that VNS paired with physical rehabilitation is a potentially viable new therapy for enhancing recovery of motor function after stroke.

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Author contributions

N.K., S.A.H., and M.P.K. wrote the manuscript. N.K., M.P.K., R.L.R., and A.M.S. designed the study. N.K., S.A.H., D.R.H., A.R., and M.P. performed behavioral testing. N.K., S.A.H., and A.M.S. analyzed the data. A.M.S. and R.L.R. provided software and hardware support. All authors discussed the results and provided comments on the manuscript.

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