At-Home Delivery of Vagus Nerve Stimulation Paired With Task-Specific Training Improves Performance of High-Priority Activities in Persons With Chronic Spinal Cord Injury or Stroke

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Objective: Vagus nerve stimulation during rehabilitative training can improve motor function years after stroke or spinal cord injury. This open-label study examined whether vagus nerve stimulation paired with participant-selected activities of daily living in a home environment can improve task performance in participants with chronic stroke or incomplete cervical spinal cord injury.

Design: Fourteen participants were recruited from our previous randomized studies involving months of vagus nerve stimulation delivered during in-clinic therapy. Seven participants with chronic stroke and seven with chronic incomplete spinal cord injury completed 36 additional sessions of vagus nerve stimulation paired with training on a set of self-selected, high-priority activities of daily living at home. Each participant trained on 5–10 tasks. Performance was measured before and after vagus nerve stimulation + ADL therapy.

Results: Vagus nerve stimulation + activity of daily living therapy reduced time to complete trained activities of daily living by 19.8 ± 5.2% for participants with stroke and 33.8 ± 4.9% for participants with spinal cord injury.

Conclusions: The observed gains are clinically meaningful and suggest a reduction in the functional burden of injury, which has the potential to improve independence and reduce reliance on caregivers. These initial results are sufficient to justify a randomized, sham-controlled study to evaluate whether vagus nerve stimulation during task-specific training can improve task performance and independence.

Key Words: Ischemic Stroke, Cervical Spinal Cord Injury, Neuromodulation, Vagal Nerve Stimulation

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What Is Known

Task-specific training, including activities of daily living (ADL), can improve motor function and task performance after stroke or spinal cord injury, but progress is limited in chronic phases. Vagus nerve stimulation (VNS) enhances synaptic plasticity and improves motor function when paired with rehabilitative training. Previous studies show VNS during in-clinic therapy yields meaningful improvements in recovery.

What Is New

This is the first study to pair VNS with at-home ADL therapy focused on participant-prioritized tasks and compare task performance across therapy. Findings suggest that this approach improves performance on high-priority, real-life tasks with potential to reduce the functional burden of injury and promote independence.

Stroke and cervical spinal cord injury (SCI) often produce profound, chronic motor dysfunction of the arm and hand leading to persistent functional deficits and impaired ability to complete common activities of daily living (ADLs).[1] Task-oriented therapy, including ADL training, is a typical component of rehabilitation for these populations, but chronic functional deficits can persist despite intervention.[2] Vagus nerve stimulation (VNS) enhances the benefits of therapist-supervised rehabilitative training in persons with chronic stroke and incomplete SCI[3] (NCT04288245, NCT04534556). The addition of VNS to 18 sessions of upper extremity therapy in persons with stroke produces an additional 2.6 point improvement in the Fugl-Meyer upper extremity assessment (UEFM) over equivalent therapy without VNS.[3] This observation led the United States Food and Drug Administration (FDA) to approve VNS during upper-limb motor therapy to treat moderate to severe motor deficits associated with chronic ischemic stroke.[3] Similarly, the addition of VNS to 18 sessions of upper extremity therapy in persons with chronic incomplete cervical SCI produces an additional 4.1 point improvement in the Graded and Redefined Assessment of Strength, Sensibility, and Prehension score over equivalent therapy without VNS (NCT04288245). This is consistent with extensive preclinical studies in multiple animal models showing that VNS promotes recovery by enhancing the synaptic plasticity produced by rehabilitative training.[4–12]

These findings show that VNS, when paired with supervised rehabilitation in a controlled clinical setting, is effective.

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Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Additionally, emerging evidence suggests that extending VNS therapy to self-directed, at-home use can lead to further, long-term gains. For example, 2 yrs of VNS delivered during unsupervised, open-loop, home-based rehabilitation produced an additional 4.7-point improvement on UEFM.[13] In this same study, significant improvements were also observed on the Wolf Motor Function Test, the Motor Activity Log, and the hand section of the Stroke Impact Scale. However, while these improvements indicate enhanced function, there is no direct evidence that participants translated these gains into meaningful improvements in their self-selected, high-priority ADLs. The extent to which long-term, home-based rehabilitation with VNS influences real-world task performance remains unclear. The observation of cumulative progress occurring over years long after injury suggests that VNS may help mitigate the plateau effect typically seen in persons with chronic neurological injury, but further investigation is needed to determine its effect on personally relevant ADLs.

The aim of the current open-label study was to quantify whether VNS combined with practice of self-selected, high priority ADLs performed at home can improve the performance on these tasks in participants with chronic stroke or incomplete cervical SCI. All participants were implanted with VNS devices as part of earlier randomized studies and had received many months of previous VNS delivered during in-clinic therapy. For the present study, each participant selected a set of tasks that they most wanted to perform. The time to complete a set of trained and untrained ADLs was recorded before and after 36 sessions of VNS delivered during ADL training. Results indicate VNS paired with ADL practice at home produced a significant improvement in performance of the trained and untrained ADLs and justify a randomized, sham-controlled study to demonstrate that VNS during task-specific training can improve task performance.

METHODS

Subjects and Exclusion Criteria

All procedures were approved by the institutional review board at the University of Texas at Dallas (UTD IRB: 22-563, 023-267). Written informed consent as obtained for all trial participants. Participants for this study were recruited from the participants in an earlier randomized controlled trial (NCT04288245 or NCT04534556), where participants with upper limb motor impairments due to either stroke or SCI were previously implanted with a miniature externally powered stimulator (MEPS).[14] The MEPS device is not yet FDA-approved and was used under an investigational device exemption. Seven participants with chronic stroke ages 27–78 yrs were enrolled in this study. The mean time since stroke was 42.2 ± 2.4 months. Seven chronic SCI participants' ages 29–62 yrs were enrolled in this study. The mean time since SCI was 135.5 ± 72.0 mos (Table 1).

TABLE 1. Demographic and clinical characteristics by injury type. SCI participants grouped by ASIA Impairment Scale (AIS) Score.

	Stroke	SCI
Classification	Ischemic *n* = 5 Hemorrhagic *n* = 2	AIS-D *n* = 5 AIS-B *n* = 2
Sex	86% male	57% male
Age (yr)	58 ± 6.4	45 ± 5.3
Months since injury	42.2 ± 2.4	135.5 ± 72.0

Activities of Daily Living Therapy

Study participants used the MEPS system only during rehabilitative exercises.[14] Participants completed 36 one-hour sessions of VNS paired with training on 5–10 selected ADLs. Participants completed the first two to four sessions in-clinic with trial staff to become familiarized with rehabilitation software, hardware, and therapy materials and instructions. The remaining sessions were completed at the participants' homes. One stroke participant completed all 36 sessions

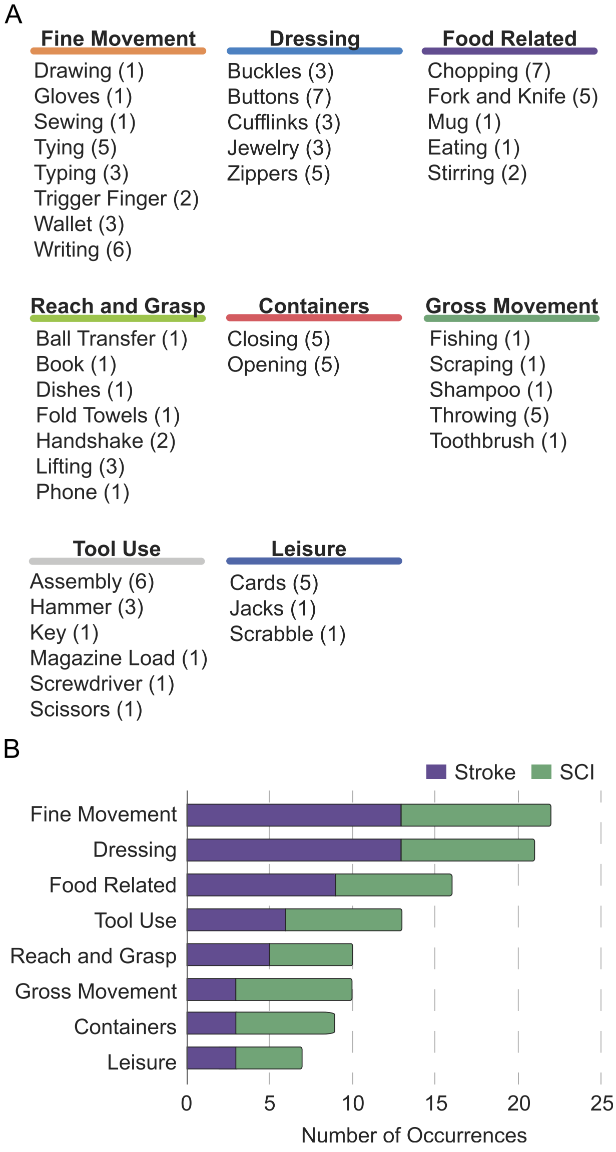

FIGURE 1. VNS was delivered during a wide variety of ADLs. A, VNS was delivered during 41 unique ADLs. These 41 ADLs were grouped into 8 categories. The number of occurrences of each ADL is included in parentheses. B, The occurrence frequency of each ADL category.

in-clinic by request. Study staff supervised home sessions at-home by video call once per week. All assessments were conducted in-clinic.

At enrollment, each participant self-selected a unique set of ADLs, which they felt would most improve their independence and quality of life. Each set consisted of 5 to 10 ADLs. Task difficulty was graded based on each participant's individual abilities and progressed based on criteria established by study staff to ensure an appropriate level of challenge. Examples of increasing task difficulty included extending the reaching distance, increasing the weight or size of objects, and altering the participant's position (e.g., sitting to standing). Participants were instructed to complete as many repetitions as possible of each ADL within a prescribed amount of time, typically 5–10 mins. Participants could take rest breaks. Forty-one unique ADLs were delivered during therapy (Fig. 1A).

Vagus Nerve Stimulation

The MEPS system, previously described,[14] triggered short bursts of VNS only while participants were engaged with ADL practice. Stimulation was only delivered during active rehabilitation and was paused during breaks or transitions between ADLs. Participants received 0.5-sec trains of 30 Hz stimulation (100-μsec biphasic pulses) every 10 secs during active ADL training. Stimulation intensity was individualized for each person and ranged from 0.4 mA to 1.2 mA. The most common intensity was 0.8 mA delivered to 10 of the participants.

Study Outcomes

The primary outcome for this study was the change in time to complete trained and untrained ADLs. Performance assessments measured the amount of time taken to complete a set of instructions specific to each ADL. Time to complete each ADL was recorded in-person before and after 36 sessions of therapy using a digital stopwatch. Each assessment was video recorded. Participants had up to 2 mins to complete the instructions for each ADL. Instruction completion time and the number of successfully completed repetitions were recorded. Instruction difficulty was individualized to each participant, and participants were reassessed at the same instruction difficulty at every assessment.

For participants with SCI, the untrained ADL tasks consisted of each of the Jebsen-Taylor Hand Function test components, except for writing since some individuals trained on writing. These tasks were performed using the dominant hand and the nondominant hand. For participants with stroke, the untrained ADL tasks consisted of the 9 functional tasks from the Wolf Motor Function Task, including stacking checkers, flipping cards, turning a key in a lock, folding a towel, reaching and retrieving, and lifting a can, pencil, paper clip, and basket. These tasks were performed using the hemiparetic hand. All untrained ADLs were assessed on-site by a licensed physical therapist.

Statistics

Within-subject changes in time to complete the trained ADLs and the between-subject median percent reduction in time to complete trained and untrained tasks were analyzed in MATLAB R2023a using Wilcoxon signed-rank tests. Data are presented as mean ± standard error of the mean across study participants.

RESULTS

This open-label study was designed to determine whether VNS delivered during ADLs can improve performance in participants with chronic stroke or incomplete cervical SCI. Seven persons with stroke and seven persons with spinal cord injury were recruited after completion of previous studies in which they received VNS therapy (NCT04288245 or NCT04534556). Each participant selected the 5–10 ADLs that they most wanted to improve on. The 14 study participants selected 41 unique ADLs which were paired with VNS primarily in an at-home setting (Fig. 1A). The ADLs fell into 8 broad categories, including fine movement, gross movement, reach and grasp, dressing, tool use, container opening, food-related, and leisure tasks (Fig. 1B).

Successful VNS Delivery and High Levels of Compliance Support Intervention Feasibility

Participants were instructed to complete 60 mins of VNS + ADL therapy and were allowed to take breaks. The average active time engaged in practice paired with VNS was 58.3 ± 4.3 mins per session. The average number of successful stimulation events per session was 245 ± 18 (Table 2). All participants completed all 36 sessions of training, which were self-paced with a mean frequency of 2.0 ± 0.2 sessions per week. The average total time to complete 36 sessions was 21.9 ± 3.2 wks. These findings indicate that VNS can be feasibly combined with a self-directed, structured exercises program of ADLs at home.

VNS + ADL Therapy Can Improve Performance on Trained ADLs

The time to complete each task was recorded before and after the completion of 36 sessions of VNS therapy. Despite considerable variability in the time to complete each task and in the degree to which speed improved, there was clear evidence in favor of improvement (Figs. 2A, B; Supplementary Movies 1-6 [http://links.lww.com/PHM/C902, http://links.lww.com/PHM/C903, http://links.lww.com/PHM/C904, http://links.lww.com/PHM/C905, http://links.lww.com/PHM/C906, http://links.lww.com/PHM/C918]; pretherapy vs. posttherapy P1–P14; Wilcoxon signed-rank tests results in Table 3). VNS + ADL therapy reduced the time to complete trained ADLs by 19.8 ± 5.2% for participants with stroke (Fig. 3A; stroke trained tasks; Wilcoxon signed-rank test, $P = 0.016$) and by 33.8 ± 4.9%

TABLE 2. Therapy and stimulation characteristics by injury type

	Stroke	SCI
Number of ADLs	6.6 ± 0.4	7.7 ± 0.6
Sessions per week	2.0 ± 0.2	2.0 ± 0.4
% of sessions completed	100	100
Total successful stimulations per session	251 ± 31	239 ± 20
Active minutes per session	62.5 ± 8.5	54.2 ± 1.8

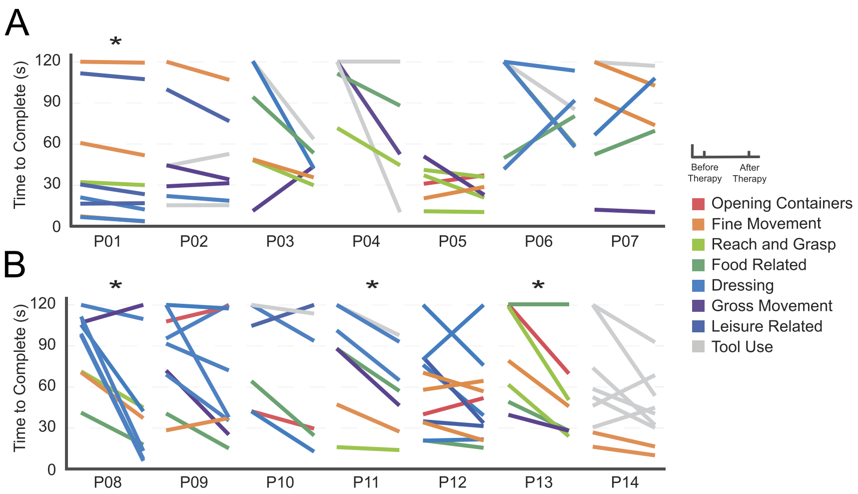

FIGURE 2. VNS + ADL therapy reduced time to complete tasks in stroke and SCI participants. A, Individual data for participants with chronic stroke reduced their time to complete most trained ADLs. Each participant completed a unique set of ADLs that was well-distributed across different movement categories. (B) Individual data for participants with chronic incomplete cervical SCI reduced their time to complete most trained ADLs. * indicates $P < 0.05$.

for participants with SCI (Fig. 3B; SCI trained tasks; Wilcoxon signed-rank test, $P = 0.016$) after 36 sessions of therapy. Qualitative records, including handwriting samples, reveal the improvement in speed was not due to compromised movement quality (Fig. 4; Supplementary Movies 1-6 [http://links.lww.com/PHM/C902, http://links.lww.com/PHM/C903, http://links.lww.com/PHM/C904, http://links.lww.com/PHM/C905, http://links.lww.com/PHM/C906, http://links.lww.com/PHM/C918]). These data indicate that VNS + ADL therapy can improve function on high-priority ADLs in both chronic stroke and chronic SCI populations.

Benefits From VNS + ADL Therapy Have Potential to Generalize to Untrained ADLs

Study participants were also tested on a set of untrained ADLs to determine whether VNS + ADL therapy could improve function in a manner that might generalize to other tasks. VNS + ADL therapy significantly reduced the time to complete untrained ADLs by 8.1 ± 2.9% (stroke and SCI untrained tasks; Wilcoxon signed-rank test, $P = 0.01$). Participants with SCI showed a 10.2 ± 3.8% reduction (Fig. 3B; SCI untrained tasks; Wilcoxon signed-rank test, $P = 0.047$) while those with stroke had a 6.0 ± 4.6% reduction, which failed to reach significance (Fig. 3A; stroke untrained tasks; Wilcoxon signed-rank test, $P = 0.25$). These findings suggest that VNS + ADL therapy has the potential to promote generalized functional improvements, corroborating previous evidence that this therapy can be effective even when delivered in an at-home setting with limited supervision.[13]

TABLE 3. Wilcoxon-signed rank test results for participants 01 through 14. * indicated P < 0.05.

Participant ID	**P01**	**P02**	**P03**	**P04**	**P05**	**P06**	**P07**
P-Value	0.015*	0.297	0.156	0.125	0.563	0.438	1
Participant ID	**P08**	**P09**	**P10**	**P11**	**P12**	**P13**	**P14**
P-Value	0.012*	0.109	0.156	0.016*	0.078	0.031*	0.240

DISCUSSION

This open-label follow-on study was designed to determine whether VNS paired with ADLs can improve task performance in participants with chronic stroke or incomplete cervical SCI. VNS paired with ADL practice produced a meaningful improvement in performance of the trained ADLs.[15] There was also a more modest but statistically significant improvement on related, but untrained, tasks. These results suggest that VNS paired with at-home practice of ADLs may reduce the functional burden of injury with the potential to improve independence and reduce reliance on caregivers. These initial results justify a randomized, sham-controlled study to demonstrate that VNS during task-specific training can improve task performance and independence long after injury.

Participants with stroke exhibited a notable improvement in trained ADLs, with an average reduction in time to complete of 19.8 ± 5.2%. Similarly, participants with SCI experienced an even more substantial improvement, with their time to complete ADLs reducing by 33.8 ± 4.9%. To put these results in

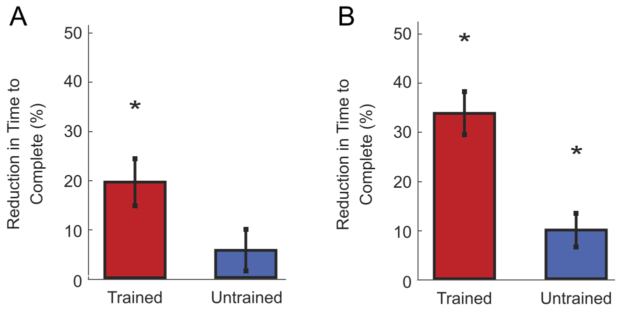

FIGURE 3. VNS + ADL therapy reduced time to complete trained and untrained ADLs. Participants with chronic stroke (A) and incomplete cervical SCI (B) reduced their time to complete trained ADLs (red). The reduction in the time to complete untrained tasks (blue) appears to be smaller. Stroke n = 7, SCI n = 7. * indicates $P < 0.05$.

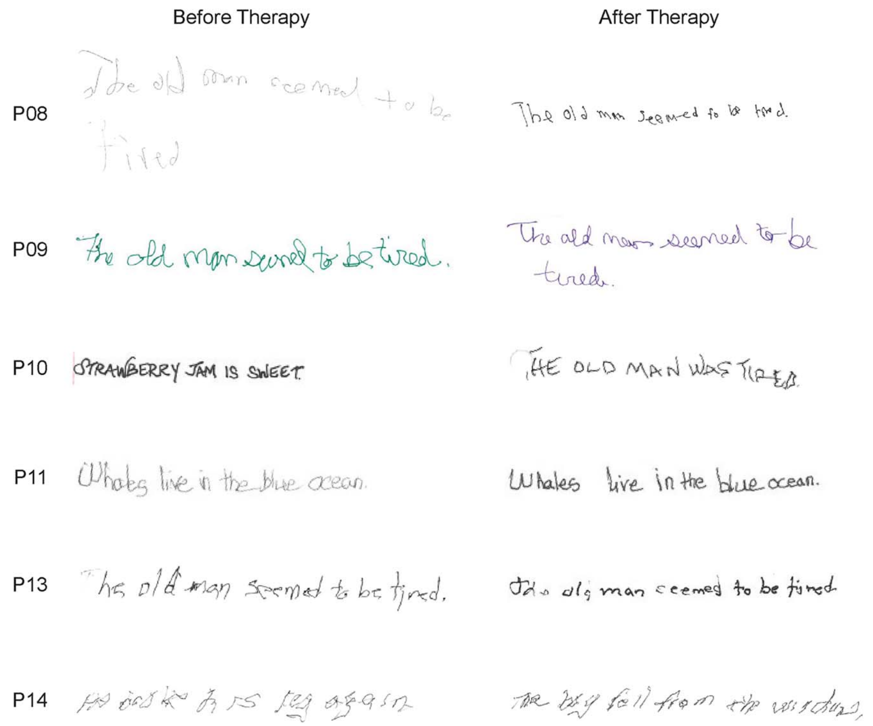

FIGURE 4. Handwriting samples suggest the improvement in speed was not due to compromised movement quality. Samples were collected before and after 36 sessions of therapy for participants whose trained ADLs included writing. Most participants improved their time to complete the writing prompt. Participants used their preferred hand to train writing and used the same hand for the entirety of the study.

perspective, the minimal detectable change on the Wolf Motor Function Test—a widely used standardized assessment of functional movement—is a 16% reduction in time to complete in the acute stage of the injury.[15] Given this benchmark, the observed improvements of 19.8% for participants with stroke and 33.8% for participants with SCI represent not only statistically significant, but also meaningful, progress. Importantly, exceeding the 16% threshold in the chronic stage of neurological injury, where functional gains are often harder to achieve, suggests that this intervention may be driving neuroplastic changes beyond what is traditionally expected at later stages of recovery. Notably, we observed no evidence that improvement in performance on either trained or untrained tasks was due to reduced precision or any form of undesirable compensation. These findings reinforce the potential of VNS + ADL therapy to deliver meaningful and lasting improvements, even in populations where progress is typically more limited. Further, these gains were achieved in ADLs that were individually selected by the participants themselves, highlighting that the therapy led to significant enhancements in activities that are directly relevant and impactful in their daily lives.[2] Most of the participants had received years of rehabilitation following their injuries and yet failed to make satisfactory progress on these high-priority tasks.

While VNS + ADL therapy did not eliminate impairments in ADLs, the extent of the improvement suggests a clinically meaningful reduction in the functional burden of injury. These improvements can lead to increased independence, potentially reducing the need for assistance from caregivers and enhancing the participants' quality of life. By targeting tasks that matter most to the individuals, the therapy fosters practical benefits in everyday functioning and overall autonomy.[16]

We observed that the magnitude of improvements was greater in trained than untrained ADLs. Given that repeatedly pairing VNS with a movement is known to specifically strengthen the engaged motor circuits in animals,[4,17] it is perhaps not surprising that we would observe greater gains in trained versus untrained tasks. Despite the specificity of VNS-enhanced plasticity, generalization to untrained tasks has been observed in animal models. When the trained and untrained tasks were somewhat similar, generalization was observed to be high.[8] For example, in a study where rats with stroke received VNS paired with a task involving reaching through a slot to turn a knob, their ability to reach through a slot and pull a handle—an untrained task—also improved despite never pairing this task with VNS, suggesting VNS-enhanced plasticity can extend to related movements. However, the tasks in this study were more distinct from each other compared to the rat study, making the possibility of generalization less likely. Consequently, it is somewhat surprising to observe a statistically significant improvement in this set of untrained tasks.

Based on earlier animal studies, the observed improvements are likely a result of synaptic changes in motor and sensory networks.[6–8,11,18–21] While VNS-induced changes in the human auditory system have been reported,[22] no study to date has documented VNS-induced changes in the human motor pathway. VNS-enhanced rehabilitation was approved by the FDA in 2021 and studies to identify plastic changes in the human motor system are underway[23] (NCT06716112, NCT03945851). Documentation of VNS-induced neural plasticity could prove difficult given the significant heterogeneity produced by stroke and SCI.[24] Within-subject controls comparing trained and untrained tasks provide one method to potentially improve statistical power and identify the biological basis for VNS-enhanced recovery. The generalization of task improvement observed in this study suggests that a future imaging study should select distinctly different tasks engaging different musculatures to increase the probability of observing training-induced neural plasticity in the human motor system.

Animal studies have demonstrated that appropriate timing of VNS in relation to movement onset is critical for producing therapeutic effects.[11,25,26] In the earlier double-blind, sham-controlled trials[3] (NCT04288245, NCT04534556), therapist-supervised or automated, software-controlled systems were used to ensure that VNS was delivered during movement. In the current study, VNS was delivered once every 10 secs during active ADL training. This method of delivery facilitated at-home therapy and allowed the participants to complete sessions unsupervised. Either real-time video monitoring or sensor-based methods could be used to deliver closed-loop VNS in an at-home setting.[27] Animal studies suggest that a closed-loop VNS could produce even greater gains than the open-loop VNS used in this study and in earlier studies of at-home VNS during motor rehabilitation.[3,13,26,28]

Historically, when implanted study participants received VNS during at home ADL training, participants swipe a magnet over their device which begins a fixed program of 0.5 sec VNS bursts every 10 secs for 30 mins regardless of duration or type of activities the participant engaged in.[3,13,28] This FDA-approved method for at-home stimulation is currently used in clinical practice for persons implanted with a VNS device to treat upper extremity motor deficits associated with chronic ischemic stroke.[23] In the current study, participants initiated VNS and terminated VNS at the beginning and end of each exercise. As a result, this study collected data about the precise number of minutes each subject was actively engaged in ADL training paired with VNS. Thus, while the system was open-loop in terms of individual movement onsets, VNS was delivered during at-home ADL training with greater precision than in previous studies. Future studies will be needed to determine if at-home VNS systems with closed-loop delivery capable of precise timing to movement onset and selection of above average movement precise, speed, or strength can produce greater gains than open-loop systems.

Despite the encouraging finding that participants with stroke and SCI can make meaningful improvements on high priority tasks even many years after injury, there are considerable limitations inherent to the design of this open-label, follow-on study from the earlier randomized controlled trials. Importantly, data collection for this study was limited due to a small number of participants. The study was designed based on a convenience sample drawn from participants who were willing to engage in an additional follow-on study of VNS-enhanced rehabilitation after the completion of a double-blind, sham-controlled trial (NCT04288245 or NCT04534556). The current study is underpowered to demonstrate that VNS can improve performance after injury more than identical practice without VNS. It is possible that the improvements in speed documented in this study could be attributed to practice alone. However, in the previous clinical trial, rehabilitation alone did not drive recovery (NCT04288245), and the self-selected ADLs are tasks that have been practiced for years before VNS delivery without observed improvements. In the future, a randomized, controlled study design will be needed to demonstrate that VNS can improve performance after injury more than identical practice without VNS. Collectively, these results provide preliminary evidence that VNS delivered during unsupervised, at-home ADL practice can improve performance even many years after stroke or SCI. By targeting participant-selected, high-priority tasks, this approach demonstrates the potential to reduce the functional burden of injury and enhance independence. The observed generalization to untrained tasks further supports its broader applicability. Future studies should include improved performance of high priority ADLs to assist people in deciding what therapy options are best suited to promote their recovery goals.

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REFERENCES

1. Feigin VL, Vos T, Nichols E, et al: The global burden of neurological disorders: translating evidence into policy. *Lancet Neurol* 2020;19:255–65
2. Waddell KJ, Birkenmeier RL, Moore JL, et al: Feasibility of high-repetition, task-specific training for individuals with upper-extremity paresis. *Am J Occup Ther* 2014;68:444–53
3. Dawson J, Liu CY, Francisco GE, et al: Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet* 2021;397:1545–53
4. Porter BA, Khodaparast N, Fayyaz T, et al: Repeatedly pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. *Cerebral cortex* (New York, NY : 1991*)*. 2012; 22:2365–74
5. Khodaparast N, Hays SA, Sloan AM, et al: Vagus nerve stimulation delivered during motor rehabilitation improves recovery in a rat model of stroke. *Neurorehabil Neural Repair* 2014; 28:698–706
6. Darrow MJ, Torres M, Sosa MJ, et al: Vagus nerve stimulation paired with rehabilitative training enhances motor recovery after bilateral spinal cord injury to cervical forelimb motor pools. *Neurorehabil Neural Repair* 2020;34:200–9
7. Pruitt DT, Danaphongse TT, Lutchman M, et al: Optimizing dosing of vagus nerve stimulation for stroke recovery. *Transl Stroke Res* 2021;12:65–71
8. Meyers EC, Solorzano BR, James J, et al: Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. *Stroke* 2018;49:710–7
9. Khodaparast N, Hays SA, Sloan AM, et al: Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke. *Neurobiol Dis* 2013;60:80–8
10. Meyers EC, Kasliwal N, Solorzano BR, et al: Enhancing plasticity in central networks improves motor and sensory recovery after nerve damage. *Nat Commun* 2019;10:1–14
11. Ganzer PD, Darrow MJ, Meyers EC, et al: Closed-loop neuromodulation restores network connectivity and motor control after spinal cord injury. *Elife* 2018;7:7
12. Hays SA, Khodaparast N, Hulsey DR, et al: Training improves functional recovery after intracerebral hemorrhage. *Stroke* 2014;45:97–100
13. Francisco GE, Engineer ND, Dawson J, et al: Vagus nerve stimulation paired with upper-limb rehabilitation after stroke: 2- and 3-year follow-up from the pilot study. *Arch Phys Med Rehabil* 2023;104:1180–7
14. Sivaji V, Grasse DW, Hays SA, et al: ReStore: a wireless peripheral nerve stimulation system. *J Neurosci Methods* 2019;320:26–36
15. Lang CE, Edwards DF, Birkenmeier RL, et al: Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehabil* 2008;89: 1693–700
16. Birkenmeier RL, Prager EM, Lang CE: Translating animal doses of task-specific training to people with chronic stroke in one hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair* 2010;24:620–35
17. Darrow MJ, Mian TM, Torres M, et al: The tactile experience paired with vagus nerve stimulation determines the degree of sensory recovery after chronic nerve damage. *Behav Brain Res* 2021;396:396

18. Morrison RA, Danaphongse TT, Pruitt DT, et al: A limited range of vagus nerve stimulation intensities produce motor cortex reorganization when delivered during training. *Behav Brain Res* 2020;391:112705
19. Morrison RA, Hulsey DR, Adcock KS, et al: Vagus nerve stimulation intensity influences motor cortex plasticity. *Brain Stimul* 2019;12:256–62
20. Hulsey DR, Hays SA, Khodaparast N, et al: Reorganization of motor cortex by vagus nerve stimulation requires cholinergic innervation. *Brain Stimul* 2016;9:174–81
21. Khodaparast N, Kilgard MP, Casavant R, et al: Vagus nerve stimulation during rehabilitative training improves forelimb recovery after chronic ischemic stroke in rats. *Neurorehabil Neural Repair* 2016;30:676–84
22. Vanneste S, Martin J, Rennaker RL, et al: Pairing sound with vagus nerve stimulation modulates cortical synchrony and phase coherence in tinnitus: an exploratory retrospective study. *Sci Rep* 2017;7:17345
23. Commissioner O of the: FDA approves first-of-its-kind stroke rehabilitation system. *FDA* August 31, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-stroke-rehabilitation-system. Accessed January 21, 2025
24. Schwarz A, Feldman M, Le V, et al: Association that neuroimaging and clinical measures have with change in arm impairment in a phase 3 stroke recovery trial. *Ann Neurol* 2024709–19. doi:10.1002/ana.27156
25. Ruiz AD, Malley KM, Danaphongse TT, et al: Vagus nerve stimulation must occur during tactile rehabilitation to enhance somatosensory recovery. *Neuroscience* 2023;532:79–86
26. Hays SA, Khodaparast N, Ruiz A, et al: The timing and amount of vagus nerve stimulation during rehabilitative training affect post-stroke recovery of forelimb strength. *Neuroreport* 2014;25:676–82
27. Epperson JD, Meyers EC, Pruitt DT, et al: Characterization of an algorithm for autonomous, closed-loop neuromodulation during motor rehabilitation. *Neurorehabil Neural Repair* 2024;38:493–505
28. Dawson J, Engineer ND, Prudente CN, et al: Vagus nerve stimulation paired with upper-limb rehabilitation after stroke: one-year follow-up. *Neurorehabil Neural Repair* 2020;34:609–15