Letters to the Editor
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Closed-Loop Fully Automated Wireless Vagus Nerve Stimulation: Heralding a New Paradigm in Bioelectronic Medicine- Brief Review

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ABSTRACT:

Closed-loop vagus nerve stimulation (VNS) represents a transformative advancement in bioelectronic medicine, offering real-time, adaptive neuromodulation for conditions such as epilepsy, heart failure, inflammatory diseases, and neurorehabilitation. Unlike traditional open-loop systems that rely on fixed parameters and surgical battery-based devices, closed-loop VNS dynamically adjusts stimulation based on physiological feedback, enhancing therapeutic precision and safety. Recent innovations, such as the wireless, fully automated VNS system developed by Mathews et al. (2025), integrate heart rate-driven feedback loops for personalized modulation. Clinical studies further validate its promise: microburst-pattern VNS reduced seizure frequency in 68% of drug-resistant epilepsy patients (Nichol et al., 2024), while closed-loop taVNS improved motor recovery post-stroke (Xie et al., 2024). Functional MRI data show enhanced cortical engagement with optimized VNS protocols (Verner et al., 2024), and real-time motor-triggered stimulation significantly improved outcomes in spinal cord injury rehabilitation (Rennaker et al., 2025). Despite these advances, limitations persist, including variability in patient responses, lack of standardized biomarkers, and insufficient large-scale trials. Future directions must focus on AI-driven algorithms, robust biophysical modeling, and wearable-compatible miniaturization to enable broader clinical translation. With these innovations, closed-loop VNS may redefine the standard of care in precision neuromodulation.

KEYWORDS: *Closed-loop VNS, Bioelectronic medicine, Adaptive neuromodulation*

INTRODUCTION:

Vagus nerve stimulation (VNS) has emerged as a promising neuromodulatory therapy for a variety of conditions, including epilepsy, heart failure, inflammatory diseases, and treatment-resistant depression. Traditional VNS systems, however, suffer from key limitations such as fixed stimulation parameters, lack of physiological feedback, and the need for surgical implantation with battery-powered devices, limiting real-time adaptability and increasing complication risks.(Eskandari et al., 2025) Recent innovations have focused on transitioning VNS toward closed-loop systems, wherein stimulation is automatically adjusted in response to physiological signals. Shinohara et al. (2025) introduced a video-based system that dynamically activates transcutaneous VNS (tVNS) in synchrony with motor activity, aiming to enhance motor learning in rehabilitation settings.(Shinohara et al., 2025)

More recently, Mathews et al. (2025) developed a fully automated, wireless, implantable VNS system

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that uses real-time heart rate as a feedback loop to modulate stimulation dynamically. Their work, published in Scientific Reports, represents one of the first practical implementations of an autonomous bioelectronic loop capable of long-term, real-world deployment. Closed-loop neuromodulation refers to stimulation systems that automatically adjust therapy parameters in real time based on feedback from physiologic or behavioral signals. By continuously sensing and responding to patient-specific changes, these systems aim to optimize efficacy while minimizing side effects. (Mathews et al., 2025) These systems reflect a growing convergence between bioelectronics, signal processing, and physiological sensing, collectively defining the future of adaptive neuromodulation.

ADVANCES IN CLOSED-LOOP VAGUS NERVE STIMULATION:

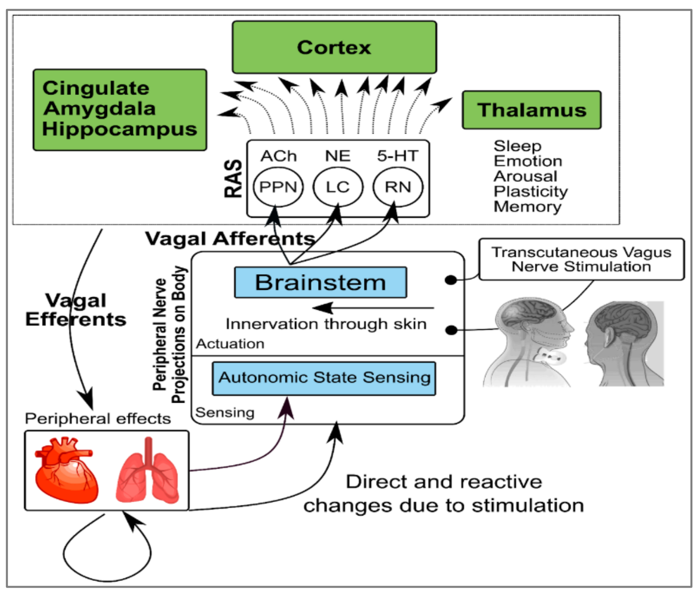
Clinical Applications and Efficacy

The following examples highlight recent representative studies demonstrating closed-loop VNS approaches across diverse clinical indications, illustrating both clinical potential and current developmental limitations. In the study by Nichol et al. (2024), 25 patients with drug-resistant focal or generalized epilepsy were assessed using microburst-pattern VNS. Over a follow-up period of 12 weeks, 68% of participants experienced a ≥50% reduction in seizure frequency, with no serious adverse events reported. The therapy was well-tolerated, and preliminary data supported its safety and potential efficacy in both seizure types.(Drees et al., 2024) In the randomized controlled protocol by Xie et al. (2024), 60 post-stroke patients were enrolled to assess closed-loop transcutaneous auricular VNS combined with upper-limb rehabilitation. Although results are pending, preliminary pilot data showed enhanced motor response timing and improved arm function when stimulation was paired with movement intent. The study aims to validate closed-loop taVNS as an adjunct to neurorehabilitation.(Xiao et al., 2024)

Neurophysiological Mechanisms of VNS

Figure 2 depicts the neuroanatomical and functional pathways engaged during VNS, showing how afferent vagal inputs reach the brainstem, activate reticular activating system (RAS) nuclei, including the pedunculopontine nucleus (PPN), locus coeruleus (LC), and raphe nuclei (RN)and modulate cortical and thalamic circuits governing arousal, emotion, memory, and plasticity (Engineer et al., 2011; Hulsey et al., 2017). Efferent vagal projections mediate peripheral autonomic effects on organs such as the heart and lungs. ("Issue Information," 2018).

Figure 1: Neurophysiological pathways engaged during VNS. Afferent vagal inputs activate brainstem nuclei and reticular activating system pathways, influencing cortical and thalamic networks, while efferent fibers mediate autonomic effects on periphera



Closed-Loop vs Open-Loop Architectures

Figure 2 illustrates the operational framework and physiological basis of these closed-loop systems. In a closed-loop VNS architecture (Figure 2A), physiological signals are continuously monitored by sensors, processed to extract relevant features, and

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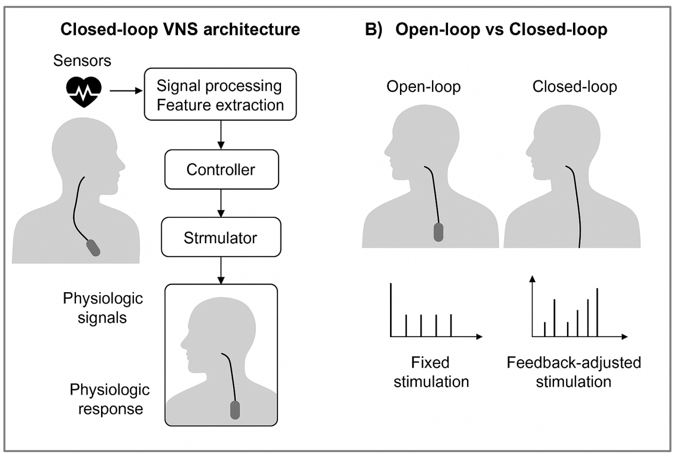
sent to a controller that dynamically adjusts stimulation parameters in real time. This feedback-based approach contrasts with traditional open-loop systems (Figure 2B), which deliver fixed-parameter stimulation without adapting to ongoing physiological changes.

Figure 2: Closed-loop VNS architecture and comparison with open-loop systems. (A) Sensors capture physiological signals, which are processed and used by a controller to adjust stimulation in real time (B). Open-loop delivers fixed stimulation, while closed-loop uses feedback-adjusted stimulation.



Comparative Outcomes with Novel Stimulation Parameters:

Similarly, Verner et al. (2024) evaluated 16 patients undergoing VNS for treatment-resistant epilepsy using optimized microburst parameters, compared against standard open-loop stimulation. Functional MRI results revealed that microburst VNS activated broader cortical and thalamocortical networks, suggesting enhanced neuromodulatory reach. Patients tolerated the modified waveform well with no increased side effects.(Szaflarski et al., 2024) Most recently, Rennaker et al. (2025) conducted a double-blinded controlled trial involving 20 participants with chronic incomplete spinal cord injury. Closed-loop VNS, delivered in real time with movement intent, led to a 67% greater improvement in motor function compared to rehabilitation alone, sustained over 12 weeks. No device-related complications occurred, and the system showed excellent tolerability and clinical impact. Recent advances in wireless communication, low-power electronics, and wearable sensors have accelerated the feasibility of fully automated VNS platforms. (Kilgard et al., 2025) These innovations enable real-time data processing, compact form factors, and integration with mobile health applications, creating opportunities for remote monitoring and personalized therapy.

Technical and Clinical Limitations of Closed-Loop VNS:

Despite its therapeutic promise, closed-loop vagus nerve stimulation (VNS) faces key limitations, including variability in individual neurophysiological responses and the absence of standardized biomarkers to guide feedback control. Current systems struggle with optimizing stimulation parameters in real time, often relying on generalized protocols that fail to capture patient-specific dynamics.(Kaniusas et al., 2019) Furthermore, Jiang and Akhtar (2023) highlighted the lack of large-scale, multicenter trials, noting that most adaptive VNS studies are limited to small sample sizes and short follow-up periods, particularly in cardiac and psychiatric applications.(Caballero-Florán et al., 2023) From a physiological standpoint, Leão et al. (2025) argued that the absence of interoceptive modeling, that is, closed-loop systems capable of detecting and interpreting internal bodily states, limits the therapy’s responsiveness to dynamic changes in autonomic tone. (LEÃO et al., 2025) To overcome these barriers, future innovations must focus on integrating adaptive algorithms, enhancing biophysical modeling, and miniaturizing wearable-compatible technologies. These improvements are essential for realizing personalized, precision-guided neuromodulation in routine clinical practice. (Kaniusas et al., 2019).

Regulatory Barriers

Regulatory pathways for advanced neuromodulation devices in LMICs are often underdeveloped, fragmented, or lack harmonization with international standards. This leads to prolonged approval timelines, inconsistent safety oversight, and difficulty in adopting rapidly evolving bioelectronic technologies. Moreover, the absence of established device-specific guidelines in many LMICs can delay clinical trials and inhibit local manufacturing or adaptation of imported systems. Capacity-building within national regulatory authorities, coupled with alignment to WHO prequalification frameworks, is critical to facilitate safe and timely adoption. (Haaksma et al., 2020; Reddy et al., 2011)

Ethical Barriers

There are particular ethical issues with the use of implantable and adaptive neuromodulation in LMICs. These include protecting patient autonomy in the context of algorithm-driven stimulation adjustments, preventing unequal access that favors urban over rural patients, and obtaining informed consent in populations with low health literacy. Furthermore, real-time physiological signal data governance is frequently unregulated, making it more susceptible to privacy violations. Sustainable integration requires a framework for responsible innovation that addresses cultural sensitivity, community involvement, and ethical oversight.(Belouin et al., 2022; Emanuel, 2000)

Cost-Related Barriers

In LMICs, where healthcare budgets are limited and out-of-pocket expenses are still high, the high upfront costs of closed-loop neuromodulation systems, which are caused by device complexity, surgical implantation, and the requirement for specialized follow-up, present severe difficulties. The affordability gap is made worse by maintenance expenses, a shortage of skilled biomedical engineers, and reliance on imported parts. Local manufacturing, tiered pricing structures, and incorporation into national health insurance programs may enhance accessibility.(Pipe et al., 2022; Todesco et al., 2022)

CONCLUSION:

In conclusion, closed-loop vagus nerve stimulation (VNS) represents a significant evolution in neuromodulatory therapy, offering dynamic, personalized intervention across neurological and systemic disorders. Emerging clinical evidence supports its safety, efficacy, and broader cortical activation compared to conventional approaches. However, technical limitations, variability in physiological responses, and a lack of standardized biomarkers currently hinder widespread clinical adoption. Future development must prioritize adaptive algorithms, miniaturized biocompatible hardware, and long-term human validation. With these advancements, closed-loop VNS holds the potential to redefine therapeutic standards in precision bioelectronic medicine.

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