Brain Stimulation 18 (2025) 1990–1992

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Longitudinal evaluation of laryngeal motor-evoked potentials following vagus nerve stimulation in patients with drug-refractory epilepsy

Dear Editor,

Epilepsy affects over 70 million individuals worldwide [1]. For patients who do not respond to antiseizure medications and are not candidates for resective surgery, vagus nerve stimulation (VNS) offers an alternative. VNS can be delivered in a programmed mode or manually with a magnet, but clinical response remains highly variable. One understudied source of this variability may be nerve function and recovery after implantation. Insufficient activation, possibly due to processes such as nerve injury, could limit efficacy [2].

The vagus nerve contains multiple fiber types; therapeutic effects are thought to depend primarily on larger myelinated fibers (Aβ, Aδ, B) [3], while VNS also co-activates the recurrent laryngeal nerve composed of motor Aα fibers [4]. Laryngeal motor evoked potentials (LMEPs), which reflect Aα-fiber recruitment, therefore provide an accessible marker of vagal function [5,6]. Preclinical studies in rats have shown that VNS-induced laryngeal motor responses can be readily recorded [2–4], and LMEPs have also been demonstrated in humans [5]. Although LMEPs have been recorded in both rats and humans within weeks of implantation [4,6], their longitudinal evolution and relationship to seizure outcomes remain unknown. Here, we examined how LMEP characteristics change over time and whether they may serve as a biomarker to optimize and individualize VNS therapy.

We prospectively enrolled patients undergoing newly VNS implantation between 2022 and 2024. Assessments were performed pre-implantation (baseline for VNS clinical response) and LMEPs were recorded at 2 weeks, 1, 3, and 6 months post-surgery (electrodes placement see Fig. 1A). At each visit, clinical response was evaluated using the Clinical Research-Response Scale (CRRS) [7], which captures both acute and chronic VNS effects (Supplementary S1). LMEPs can be characterized by latency (time from stimulation onset to motor peak) and amplitude (peak-to-baseline difference) [6]. Acquisition and processing protocols are detailed in Supplementary S2, example of LMEPs can be seen in Fig. 1B. Linear mixed-effects models (LMM) were applied to examine longitudinal changes in latency and amplitude and their association with VNS response over time and at 6 months. A probability density function (PDF) of latency at clinical intensity was generated for the 6-month time point, and the standard deviation was calculated to quantify the dispersion.

Using this approach, data from 12 patients (mean age: 38.5 ± 12 years; 5 males, 7 females) were analyzed. One patient was excluded due to a postoperative laryngeal nerve lesion (demographic details provided in Supplementary Table S3). At the 6-month follow-up, five patients were classified as responders (>50 % seizure reduction; mean CRRS 12.8 ± 2.5) and six as non-responders (mean CRRS 6.0 ± 5.0). For detailed information on exclusions and missed visits, see Supplementary S4; CRRS scores across visits are reported in Supplementary S5, and all extracted latency and amplitude values along with the number of patients contributing data for each intensity and the intensities included in the LMM analysis in Supplementary S6.

At routine clinical stimulation, average LMEPs latency was 9.6 ± 0.9 ms (Fig. 1C). LMMs showed that latency decreased significantly over time, plateauing between 3 and 6 months (Supplementary S7). Importantly, greater within-subject latency reductions were associated with better clinical response, particularly at 0.875 mA (CI [0.17 to 0.65], $b = 0.41$ at 3 months; CI [0.15 to 0.62], $b = 0.35$ at 6 months; $p = 0.02$; Fig. 1D). Amplitude averaged 133.2 ± 50.2 mV at 6 months and did not change significantly overall. However, higher amplitudes at 0.875 mA were linked to better response (CI [7.36 to 43.9], $b = 25.5$; $p = 0.03$*) (Fig. 1E), with similar non-significant trends at other intensities (Supplementary S8). Collectively, these findings suggest that progressive reductions in latency and increases in amplitude over time may indicate enhanced vagal activation, with a stabilization observed between 3 and 6 months post-implantation. These electrophysiological changes appear to correlate with therapeutic efficacy.

Latency and amplitude of LMEPs are established markers of nerve injury and recovery [8]. In our cohort, patients with better VNS response exhibited shorter latencies and higher amplitudes over time, suggesting more robust vagal recovery in the early postoperative phase. Because vagal fibers are intrinsically interconnected [9], LMEP features at stabilization may help guide optimal VNS settings [9,10]. Specifically, the LMEP saturation intensity may serve as a surrogate marker for the threshold necessary to recruit low-threshold fibers, thereby providing indirect insight into the activation state of therapeutically relevant fibers and informing the optimization of stimulation parameters.

These findings raise the possibility that LMEP monitoring could identify peripheral contributors to poor response. Abnormal latency or amplitude values may reflect nerve damage or incomplete fiber recruitment, whereas stable LMEPs without clinical benefit may instead indicate central mechanisms of non-response. Distinguishing these scenarios could support clinicians in earlier decisions regarding stimulation adjustments, modify medications, or consider alternative therapies.

Several limitations warrant consideration. First, the relatively small sample size limits statistical power, and some missed visits may have introduced bias despite standardized acquisition protocols. Second, amplitude values can be affected by skin conductivity or small differences in electrode positioning, although prior work suggests these effects are minimal [5]. Despite these limitations, our prospective design and systematic recordings provide important proof of concept for the use

https://doi.org/10.1016/j.brs.2025.10.014
Received 3 October 2025; Accepted 19 October 2025
Available online 21 October 2025

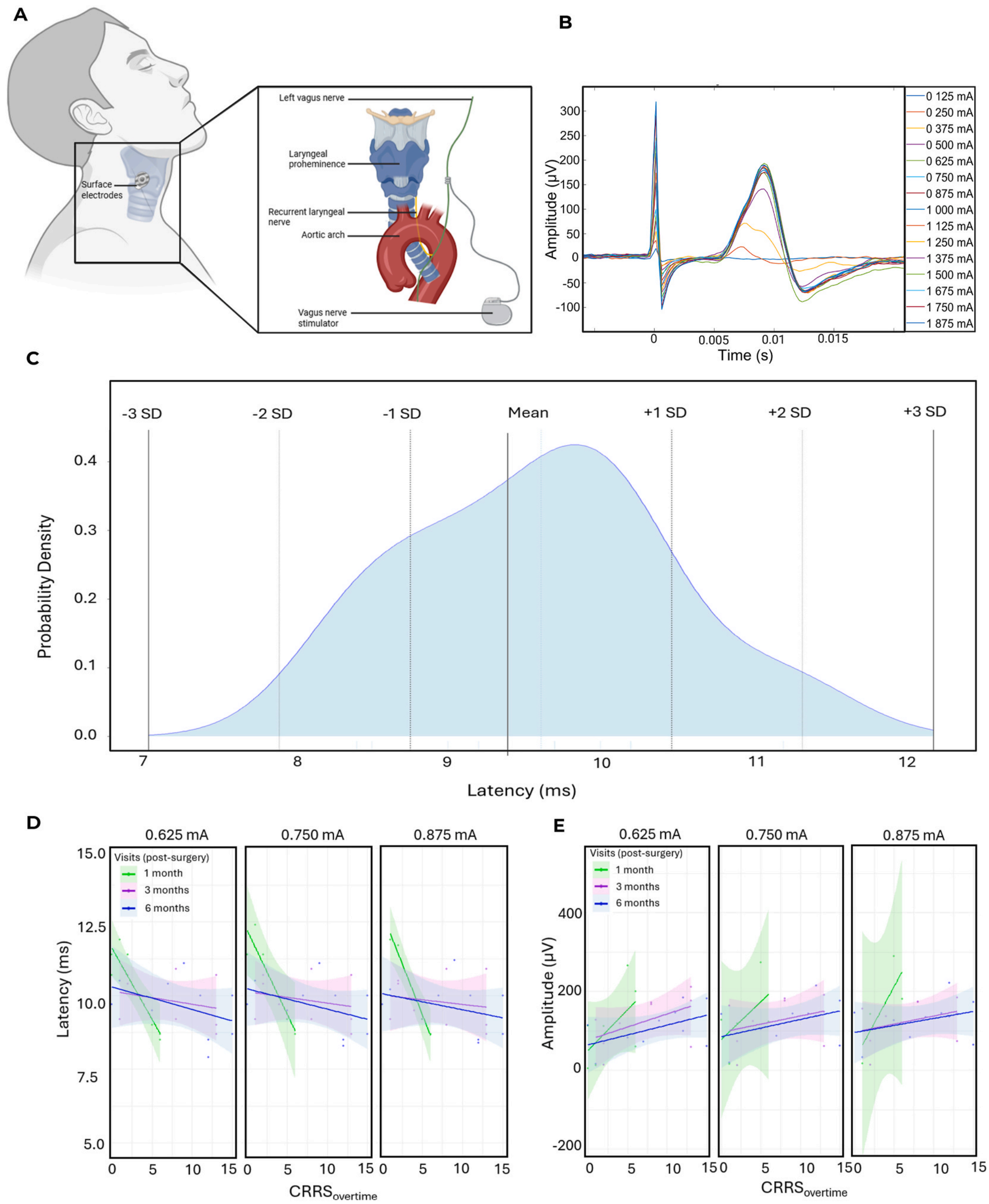

Fig. 1. Regression Lines for LMEPs Latencies and Amplitudes by Intensities and visits timing after implantation

Legend: Evaluation of LMEPs characteristics across patients. A) Skin surface electrodes placement (lateral view) and anatomy of the left vagus nerve and recurrent laryngeal nerve. B) Average of stimulation artifact and LMEPs following the different intensity used. C) Probability Density Function of latency for all patients at 6 months showing the mean and standard deviation (SD). D) Regression lines illustrating the relationship between latency and the different CRRS values over time at different intensities, demonstrating that latency variation correlates with patient response. Notably, patients with a stronger response to VNS exhibited lower latencies than less responsive patients. E) Regression lines illustrating the relationship between amplitude and the different CRRS values over time at different intensities, indicate that amplitude variation correlates longitudinally with patient response. Notably, patients with a stronger response to VNS exhibited higher amplitudes compared to less responsive patients.

of LMEPs in guiding VNS therapy.

Overall, longitudinal LMEP assessment may provide a practical biomarker of vagal recovery and treatment responsiveness. Incorporating LMEPs into clinical practice may support more individualized and timely management of VNS therapy, including optimized dosing and earlier identification of non-responders.

CRediT authorship contribution statement

Venethia Danthine: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft. **Enrique Ignacio Germany Morrison:** Formal analysis, Methodology, Software, Validation, Writing – original draft. **Inci Cakiroglu:** Conceptualization, Methodology, Writing – review & editing. **Najoua Boughaba:** Conceptualization, Methodology, Writing – review & editing. **Jean Delbeke:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Antoine Nonclercq:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Riëm El Tahry:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing – original draft.

Funding sources

This work is supported by a Fond de la Recherche Scientifique (F.R.S.-FNRS) with a FRIA grant. RET is funded by the Walloon Excellence in Life Sciences and Biotechnology (WELBIO) department of the WEL Research Institute (X.2001.22).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research has benefited from a statistical consultancy service with the Statistical Methodology and Computing Service, technical platform at UCLouvain – SMCS/LIDAM, UCLouvain.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.10.014.

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