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Role of vagus nerve stimulation in epilepsy

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ABSTRACT

Introduction and purpose:

Epilepsy affects 1% globally, with 2.6 to 6 million cases in Europe. 30-40% of the 50 million epilepsy patients globally don't respond to drugs. For those ineligible for surgery, Vagus Nerve Stimulation (VNS) therapy offers an alternative for drug-resistant epilepsy and major depression.

A brief description of the state of knowledge:

Vagus Nerve Stimulation (VNS) is a modern therapy using implanted or non-invasive devices to regulate nerve activity with controlled electrical impulses. Vagus Nerve Stimulation (VNS) is effective for focal seizures, including simple partial seizures and auras. It also shows promise in reducing seizures in generalized tonic-clonic seizures and benefits patients with epileptic encephalopathies like Lennox-Gastaut syndrome. VNS effectively decreases both the frequency and duration of seizures in individuals contending with intractable epilepsy. The use of vagus nerve stimulation is generally a safe and well-tolerated form of treatment. VNS therapy improves psychomotor functions in patients with severe drug-resistant epilepsy, showing positive effects on cognitive aspects. The precise mechanism through which VNS affects the body is not fully understood, but it has demonstrated effectiveness, especially in cases of drug-resistant epilepsy.

Conclusions:

Extensive research backs Vagus Nerve Stimulation (VNS) as an effective palliative for intractable epilepsy, reducing seizures. Yet, identifying specific patients who would benefit most from VNS treatment lacks clear criteria. Neuromodulation remains crucial for healthcare professionals handling drug-resistant epilepsy.

Keywords: epilepsy, vagus nerve, VNS, seizures

Introduction

One percent of the population experiences epilepsy and seizures, making it one of the most common neurological disorders. In Europe, between 2.6 and 6 million individuals suffer from epilepsy. Approximately 30% to 40% of the 50 million people worldwide with epilepsy do not respond effectively to antiepileptic drugs. Surgical removal or ablation may be an option, but not every patient qualifies for these procedures. For individuals whose seizures remain inadequately controlled, considering interventions based on neuromodulation can be beneficial. The limitations of antiepileptic drugs, dietary therapy, and epilepsy surgery in improving overall outcomes underscore the need for alternative treatments, including device therapy such as vagus nerve stimulation (VNS). Vagus nerve stimulation (VNS) therapy is a treatment method that provides an alternative for cases where surgery, diet, and pharmacotherapy prove ineffective. VNS is primarily used in the treatment of drug-resistant epilepsy and depression. The goals of epilepsy treatment include effectively controlling seizures while minimizing the side effects of medications and enabling normal daily functioning. Individualizing therapy is crucial, and regular collaboration with a doctor helps monitor progress, adjust treatment, and effectively manage epilepsy. [1,2,3,4,5,6]

Evolution and Components of Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) was developed in 1987, and a year later, in 1988, it was first implanted by Bell at Wake Forest University. The VNS system, resembling a cardiac pacemaker in appearance, is an advanced device powered by a battery. Currently, there are five models of therapeutic VNS generators available. The Vagus Nerve Stimulation (VNS) device comprises a sophisticated system featuring a pulse generator encased in durable titanium, accompanied by a lithium carbon monofluoride battery. Additionally, the ensemble includes a 43 cm lead wire equipped with two platinum/iridium helical electrodes, which wraps around the left vagus nerve within the carotid sheath. Moreover, it incorporates a heart rate detection feature, a noteworthy advancement that contributes to the device's effectiveness by identifying the onset of seizures. The estimated lifespan of the battery is an impressive 6–8 years, marking a testament to the device's longevity in the realm of VNS therapy. [7,8] It is strongly recommended to introduce the vagus nerve stimulator on the left side due to the potential risks associated with stimulating the right vagus nerve. The right vagus nerve innervates the sinoatrial node, and its stimulation may lead to adverse cardiac effects, such as bradycardia or asystole. In contrast, the left vagus nerve primarily innervates the atrioventricular node and cardiac branches leading to the recurrent laryngeal nerve, which seems to be safer in terms of cardiac influence. It is worth noting that although the implantation of the stimulator on the right vagus nerve has been performed in several cases, demonstrating similar effectiveness to left-sided implantation, there is noticeable risk of respiratory symptoms in children. [9,10,11,12,13,14]

Mechanisms and Immunomodulatory Effects of VNS

Vagus Nerve Stimulation (VNS) is a modern therapy method that employs implanted or non-invasive devices to regulate nerve activity through precisely controlled electrical impulses. In the case of implanted devices, VNS initiates signals to the brainstem via the vagus nerve, subsequently modulating the functions of various brain areas. VNS therapy has gained approval for treating epilepsy, depression, and stroke rehabilitation, particularly when conventional treatments have proven ineffective. Studies have demonstrated a significant reduction in seizure frequency with VNS, marking a notable advancement in therapy, although the precise mechanism through which VNS affects the body remains unclear.The vagus nerve stimulation (VNS) has shown increased activity in the TGF-beta signaling pathway, identified as a significant defensive element against inflammation according to research findings. There has also been noted a decrease in the activity level of the tumor necrosis factor (TNF) pathway, crucial in regulating immune responses in both healthy and diseased organisms. The role of TNF is immensely important in controlling cellular life processes within the immune system. In the context of vagus nerve stimulation, it appears that this therapy not only affects the nervous system but also regulates immune processes. This, in turn, holds potentially significant implications for patients with treatment-resistant epilepsy. It provides hope for a new perspective on the impact of VNS on the neuro-immune axis and the potential therapeutic benefits in regulating immune responses and alleviating symptoms of treatment-resistant epilepsy. [15,16]

The specific mechanism by which vagus nerve stimulation (VNS) functions as an antiepileptic treatment for idiopathic generalized epilepsy remains not entirely clear. Research suggests that VNS causes a disruption in nerve synchronization through various pathways, effectively reducing interictal epileptic activity in individuals who respond to the treatment. Studies utilizing positron emission tomography have indicated that VNS changes the flow of blood in the brain, enhancing synaptic activity across diverse brain regions, including the thalamus and connections between the thalamus and cortex. Additionally, functional MRI studies have detected increased activity in the thalamus and improved connectivity between the thalamus and cortex.Research findings pointed to the significant influence of stimulating the vagus nerve on cortical function, elucidating the intricate pathways from the nucleus tractus solitarii to a spectrum of brainstem nuclei, encompassing influential regions like the locus coeruleus and raphe magnus, which in turn exerted a diffuse impact on the cortex. These comprehensive investigations and their outcomes posed a compelling proposition suggesting that VNS could potentially serve as an effective avenue for antiepileptic therapy. They postulated that this therapy might manifest by effectively mitigating interictal events, those periods between seizures, and orchestrating a more synchronized cortical activity, potentially contributing to seizure control. Moreover, the groundbreaking work of Zabara shed light on an intriguing aspect: the enduring effects of VNS in preventing seizures persisted for a duration notably exceeding the actual period of stimulation, showcasing its sustained therapeutic influence long after the treatment was administered. [9,17,18,19]

Clinical Responses and Considerations in Vagus Nerve Stimulation Therapy

Patients predominantly experiencing focal seizures, particularly simple partial seizures and auras, showed the highest rates of clinical response. Despite VNS initially being indicated solely for partial epilepsy syndromes, the likelihood of reducing seizures by over 45% in patients with generalized tonic-clonic seizures might make VNS an attractive option for selected patients with these seizure types, considering the significant health impact associated with them. Additionally, patients with other epileptic encephalopathies, such as Lennox-Gastaut syndrome, displayed significant benefits from VNS therapy. [1, 20]

Individuals diagnosed with epilepsy, refractory to treatment despite trials with at least two different antiepileptic medications, are classified as having drug-resistant epilepsy. For these cases, it is recommended to seek assessment and evaluation at a specialized epilepsy center to determine the suitability for surgical intervention. Although resection surgery typically offers a higher likelihood of achieving complete seizure freedom compared to neuromodulation techniques like VNS therapy, there are specific patient profiles that may not meet the criteria for resection surgery. As a result, the consideration of neuromodulation becomes a potential alternative for these individuals in such circumstances. After over two years of VNS therapy, approximately 8% of patients achieve complete seizure freedom, marking a significant milestone in their treatment. Furthermore, in about half of the cases, approximately 50% of patients experience a reduction in seizure frequency by at least 50%. Despite the proven benefits of VNS in the treatment of medically intractable epilepsy, not all patients experience improvement after undergoing this therapy. Approximately 25% of patients receiving VNS therapy ultimately do not achieve therapeutic benefits, and fewer than 5% attain complete seizure freedom.

Ambulatory VNS implantation should not exclude individuals with developmental disabilities or multiple associated handicaps. The advancement of this outpatient procedure allows a wider range of patients in this specific group, including those whose families may be hesitant about traditional hospitalization in the neurosurgery department, to benefit from VNS surgery. This substantial decrease in seizure frequency can significantly improve the quality of life for individuals with epilepsy, which is an essential therapeutic aspect.The effectiveness of VNS as a palliative measure is substantiated by comprehensive research, indicating its positive outcomes. VNS significantly diminishes the frequency and duration of seizures in individuals grappling with intractable epilepsy.The duration of epilepsy independently predicts the response to Vagus Nerve Stimulation (VNS). It's worth noting that while achieving complete seizure freedom through VNS therapy remains a rarity, the merit of this approach lies in its potential to not only reduce the frequency of seizures but also to contribute significantly to enhancing the overall quality of life for those undergoing this form of treatment. This innovative neuromodulation technique showcases promise in offering a better semblance of control and management for individuals grappling with epilepsy, albeit not ensuring a complete cessation of seizures. [9,21,22,23,24,25,26]

Efficacy and Applicability of Vagus Nerve Stimulation in Pediatric and Adult Patients

The utilization of vagus nerve stimulation (VNS) treatment stands as an efficacious surgical intervention tailored for individuals aged 4 years and older who contend with pharmacoresistant epilepsy. The VNS therapy is equally effective in both children and adults, challenging the view that age limits its application. Its effectiveness in reducing seizure frequency, especially in patients with focal epilepsy and certain etiological factors like the presence of tumors, is of significant importance. This therapeutic approach becomes particularly relevant for those individuals who are ineligible for or have experienced unsuccessful outcomes with resective surgery. This form of treatment involves the implantation of a device to stimulate the vagus nerve, aiming to alleviate seizures and improve the quality of life for patients grappling with this challenging condition. Pediatric patients grappling with drug-resistant epilepsy, when subjected to interventions such as cranial epilepsy surgery or Vagus Nerve Stimulation (VNS), demonstrated a significantly elevated survival rate as opposed to their counterparts who exclusively underwent medical treatments. This underscores the potential benefits and improved outcomes associated with surgical or neuromodulatory approaches in the management of drug-resistant epilepsy among children, emphasizing the importance of exploring alternative therapeutic avenues beyond conventional medical interventions.[9,27,28,29,30,31,42]

Due to the rarity of patients achieving complete seizure cessation with VNS therapy, its widespread acknowledgment as the primary treatment approach is limited, despite endorsements by national health technology assessment bodies. Some perceive VNS therapy predominantly in a palliative light. However, this therapeutic effect appears to notably enhance the cost-effectiveness ratio, retaining its robustness even under conservative estimates related to device expenses, projected battery longevity, and the frequency of necessary treatments. This nuanced evaluation prompts the need for deeper discussions and extensive research to comprehend the broader adoption and perception of VNS therapy within the medical community. [32]

Pharmacological treatment and vagus nerve stimulation (VNS)

Combining VNS with synaptic vesicle glycoprotein 2A (SV2A) modulators or slow sodium channel inhibitors could offer advantages in enhancing seizure management. The underlying explanation for the potential synergistic effects between VNS and SV2A modulators is not entirely understood. At the cellular level, VNS has been observed to influence GABAergic, serotonergic, and noradrenergic transmission. High doses or combinations of sodium channel blockers are known to cause side effects like dizziness, drowsiness, vomiting, and double vision. Understanding the positive interactions of sodium channel blockers when used alongside VNS allows epilepsy specialists to steer clear of excessive doses or irrational combinations, optimizing the treatment approach.VNS stands out as a safe and effective method for the palliative treatment of both focal and generalized forms of treatment-resistant epilepsy in adults and children. When integrated into a comprehensive treatment plan, which includes intensified antiepileptic drug regimens and, where appropriate, epilepsy surgery, promising results are achieved. It has been observed that over 60% of individuals struggling with treatment-resistant epilepsy experience a significant, at least 50%, reduction in the frequency of seizures. This emphasizes the importance of a multidisciplinary and multimodal approach in epilepsy management, ensuring a more comprehensive and tailored therapeutic intervention to enhance outcomes for patients. [17,33]

Complications and benefits of VNS

Vagus nerve stimulation is typically a safe and well-tolerated treatment. Rare surgical complications, such as leaks or fluid buildup in the generator region, may occur. Side effects during pulse delivery include alterations in voice, cough, breathlessness, tingling sensations, headache, and local discomfort. Hoarseness, cough, and throat discomfort during pulse delivery are common, and adjustments may be needed to enhance patient comfort.[34,35,36]

Patients with severe drug-resistant epilepsy (DRE) undergoing VNS therapy experience significant improvements in overall psychomotor functions. Studies have demonstrated positive effects of VNS therapy on various aspects of cognitive and psychomotor functions. Perceptual organization, visual-spatial memory,concentration and visual scanning show substantial enhancements following VNS therapy in patients with severe DRE. These findings suggest that VNS may represent a promising therapeutic option for improving cognitive and psychomotor functions in patients with treatment-resistant epilepsy. [37,38.39,40,41]

Conclusions

The use of VNS as a palliative procedure has been supported by extensive research, validating its effectiveness. VNS significantly reduces the occurrence of seizures and shortens their duration in individuals dealing with intractable epilepsy. However, there is still a lack of clear criteria to identify which patients with treatment-resistant epilepsy would derive greater benefits from VNS treatment. Neuromodulation stands as a crucial therapeutic approach for healthcare professionals handling individuals with epilepsy resistant to conventional drug treatments.

Author's contribution:

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Methodology: Bożena Kmak
Software, validation, formal analysis, investigation, resources, writing original draft preparation: Bożena Kmak
Writing review editing and visualization: Bożena Kmak
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References:

1. Behr C., Goltzene M.A., Kosmalski G., et. al.: Epidemiology of epilepsy. Rev Neurol (Pa*Behr C, Goltzene MA, Kosmalski G, Hirsch E, Ryvlin P. Epidemiology of epilepsy. Rev Neurol (Paris). 2016;172(1):27-36. doi:10.1016/j.neurol.2015.11.003.*
2. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010 [published correction appears in Eur Neuropsychopharmacol. 2012 Mar;22(3):237-8. den Bergh, Peter Van [corrected to Van den Bergh, Peter]]. *Eur Neuropsychopharmacol*. 2011;21(10):718-779. doi:10.1016/j.euroneuro.2011.08.008
3. Engel J Jr. What can we do for people with drug-resistant epilepsy? The 2016 Wartenberg Lecture. *Neurology*. 2016;87(23):2483-2489. doi:10.1212/WNL.0000000000003407
4. Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. *Nat Rev Neurol*. 2012;8(12):669-677. doi:10.1038/nrneurol.2012.181
5. Lulic D, Ahmadian A, Baaj AA, Benbadis SR, Vale FL. Vagus nerve stimulation. *Neurosurg Focus*. 2009;27(3):E5. doi:10.3171/2009.6.FOCUS09126
6. Liporace J, Hucko D, Morrow R, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. *Neurology*. 2001;57(5):885-886. doi:10.1212/wnl.57.5.885
7. Kaur S, Selden NR, Aballay A. Anti-inflammatory effects of vagus nerve stimulation in pediatric patients with epilepsy. *Front Immunol*. 2023;14:1093574. Published 2023 Feb 10. doi:10.3389/fimmu.2023.1093574
8. Wang W, Huang XR, Li AG, et al. Signaling mechanism of TGF-beta1 in prevention of renal inflammation: role of Smad7. *J Am Soc Nephrol*. 2005;16(5):1371-1383. doi:10.1681/ASN.2004121070
9. González HFJ, Yengo-Kahn A, Englot DJ. Vagus Nerve Stimulation for the Treatment of Epilepsy. *Neurosurg Clin N Am*. 2019;30(2):219-230. doi:10.1016/j.nec.2018.12.005

10. Baltuch GH, Villemure JG. Operative Techniques in Epilepsy Surgery. *AJNR Am J Neuroradiol*. 2009;30(9):E133. doi:10.3174/ajnr.A1689
11. Boluk C, Ozkara C, Isler C, Uzan M. Vagus Nerve Stimulation in Intractable Epilepsy. *Turk Neurosurg*. 2022;32(1):97-102. doi:10.5137/1019-5149.JTN.33775-21.2
12. Suller Marti A, Mirsattari SM, MacDougall K, et al. Vagus nerve stimulation in patients with therapy-resistant generalized epilepsy. *Epilepsy Behav*. 2020;111:107253. doi:10.1016/j.yebeh.2020.107253
13. Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. *Epilepsy Behav*. 2018;88S:2-10. doi:10.1016/j.yebeh.2018.06.032
14. Sourbron J, Klinkenberg S, Kessels A, Schelhaas HJ, Lagae L, Majoie M. Vagus Nerve Stimulation in children: A focus on intellectual disability. *Eur J Paediatr Neurol*. 2017;21(3):427-440. doi:10.1016/j.ejpn.2017.01.011
15. Wang W, Huang XR, Li AG, et al. Signaling mechanism of TGF-beta1 in prevention of renal inflammation: role of Smad7. *J Am Soc Nephrol*. 2005;16(5):1371-1383. doi:10.1681/ASN.2004121070
16. Peña-Ceballos J, Moloney PB, Valentin A, et al. Vagus nerve stimulation in refractory idiopathic generalised epilepsy: An Irish retrospective observational study. *Seizure*. 2023;112:98-105. doi:10.1016/j.seizure.2023.09.019
17. Weissinger F, Losch F, Winter Y, Brecht S, Lendemans D, Kockelmann E. Effectiveness of eslicarbazepine acetate in dependency of baseline anticonvulsant therapy: Results from a German prospective multicenter clinical practice study. *Epilepsy Behav*. 2019;101(Pt A):106574. doi:10.1016/j.yebeh.2019.106574
18. Lulic D, Ahmadian A, Baaj AA, Benbadis SR, Vale FL. Vagus nerve stimulation. *Neurosurg Focus*. 2009;27(3):E5. doi:10.3171/2009.6.FOCUS09126
19. Zabara J. Peripheral control of hypersynchronous discharge in epilepsy. *Electroencephalography.* 1985;61:S162.
20. Xie H, Ma J, Ji T, Liu Q, Cai L, Wu Y. Efficacy of vagus nerve stimulation in 95 children of drug-resistant epilepsy with structural etiology. *Epilepsy Behav*. 2023;140:109107. doi:10.1016/j.yebeh.2023.109107
21. Englot DJ, Chang EF, Auguste KI. Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. *Neurosurg Clin N Am*. 2011;22(4):443-v. doi:10.1016/j.nec.2011.07.002
22. Lim MJR, Fong KY, Zheng Y, et al. Vagus nerve stimulation for treatment of drug-resistant epilepsy: a systematic review and meta-analysis. *Neurosurg Rev*. 2022;45(3):2361-2373. doi:10.1007/s10143-022-01757-9
23. Cramer SW, McGovern RA, Chen CC, Park MC. Clinical Benefit of Vagus Nerve Stimulation for Epilepsy: Assessment of Randomized Controlled Trials and Prospective Non-Randomized Studies. *J Cent Nerv Syst Dis*. 2023;15:11795735231151830. Published 2023 Jan 11. doi:10.1177/11795735231151830
24. Dibué M, Greco T, Spoor JKH, Senft C, Kamp MA. Does response to vagus nerve stimulation for drug-resistant epilepsy differ in patients with and without Lennox-Gastaut syndrome?. *Brain Behav*. 2023;13(8):e3025. doi:10.1002/brb3.3025

25. Navas M, Navarrete EG, Pascual JM, et al. Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. *Epilepsy Res*. 2010;90(1-2):1-7. doi:10.1016/j.eplepsyres.2010.04.007
26. Sourbron J, Klinkenberg S, Kessels A, Schelhaas HJ, Lagae L, Majoie M. Vagus Nerve Stimulation in children: A focus on intellectual disability. *Eur J Paediatr Neurol*. 2017;21(3):427-440. doi:10.1016/j.ejpn.2017.01.011
27. Pires do Prado HJ, Pinto LF, Bezerra DF, et al. Predictive factors for successful vagus nerve stimulation in patients with refractory epilepsy: real-life insights from a multicenter study. *Front Neurosci*. 2023;17:1210221. Published 2023 Jul 27. doi:10.3389/fnins.2023.1210221
28. Zhang L, Hall M, Lam SK. Comparison of long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients with drug-resistant epilepsy in the USA: an observational cohort study. *Lancet Child Adolesc Health*. 2023;7(7):455-462. doi:10.1016/S2352-4642(23)00082-2
29. Giordano F, Zicca A, Barba C, Guerrini R, Genitori L. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. *Epilepsia*. 2017;58 Suppl 1:85-90. doi:10.1111/epi.13678
30. Liporace J, Hucko D, Morrow R, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. *Neurology*. 2001;57(5):885-886. doi:10.1212/wnl.57.5.885
31. Klinkenberg S, van den Bosch CN, Majoie HJ, et al. Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy - a randomized controlled trial. *Eur J Paediatr Neurol*. 2013;17(1):82-90. doi:10.1016/j.ejpn.2012.07.003
32. Kaur S, Selden NR, Aballay A. Anti-inflammatory effects of vagus nerve stimulation in pediatric patients with epilepsy. *Front Immunol*. 2023;14:1093574. Published 2023 Feb 10. doi:10.3389/fimmu.2023.1093574
33. Lyu J, Wang JB, Quan Y, et al. Effectiveness of vagus nerve stimulation for drug-resistant generalized epilepsy in children aged six and younger. *Neurochirurgie*. 2023;69(6):101500. doi:10.1016/j.neuchi.2023.101500
34. Fernando DA, Lord RS. The blood supply of vagus nerve in the human: its implication in carotid endarterectomy, thyroidectomy and carotid arch aneurectomy. *Ann Anat*. 1994;176(4):333-337. doi:10.1016/s0940-9602(11)80511-x
35. Zhu J, Xu C, Zhang X, et al. Epilepsy duration as an independent predictor of response to vagus nerve stimulation. *Epilepsy Res*. 2020;167:106432. doi:10.1016/j.eplepsyres.2020.106432
36. Wheless JW. Intractable epilepsy: A survey of patients and caregivers. *Epilepsy Behav*. 2006;8(4):756-764. doi:10.1016/j.yebeh.2006.03.010
37. Colzato LS, Ritter SM, Steenbergen L. Transcutaneous vagus nerve stimulation (tVNS) enhances divergent thinking. *Neuropsychologia*. 2018;111:72-76. doi:10.1016/j.neuropsychologia.2018.01.003
38. Martin CO, Denburg NL, Tranel D, Granner MA, Bechara A. The effects of vagus nerve stimulation on decision-making. *Cortex*. 2004;40(4-5):605-612. doi:10.1016/s0010-9452(08)70156-4

39. Mezjan I, Gourfinkel-An I, Degos V, et al. Outpatient vagus nerve stimulation surgery in patients with drug-resistant epilepsy with severe intellectual disability. *Epilepsy Behav*. 2021;118:107931. doi:10.1016/j.yebeh.2021.107931
40. Sun L, Peräkylä J, Holm K, et al. Vagus nerve stimulation improves working memory performance. *J Clin Exp Neuropsychol*. 2017;39(10):954-964. doi:10.1080/13803395.2017.1285869
41. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg*. 2011;115(6):1248-1255. doi:10.3171/2011.7.JNS11977
42. Bordes A, El Bendary Y, Goudard G, Masson V, Gourfinkel-An I, Mathon B. Benefits of vagus nerve stimulation on psychomotor functions in patients with severe drug-resistant epilepsy. *Epilepsy Res*. 2023;198:107260. doi:10.1016/j.eplepsyres.2023.107260