Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in Scienze Biomediche Integrate e Bioetica
XXXVIII ciclo a.a. 2022-2023

EEG functional connectivity is modulated by vagus nerve stimulation in drug-resistant epilepsy

Marilisa Boscarino

Coordinatore
Prof. Raffaele Antonelli Incalzi

Tutor
Dott. Giovanni Assenza

22/04/2026

Index

1. Introduction – Drug-resistant epilepsy

1.1 Epidemiology, definition and health-care implications

Epilepsy is a neurological condition affecting approximately 70 million people worldwide, accounting for almost the 0.5% of the 'global burden of disease'[1]. Currently, more than thirty antiseizure medications (ASM)s are commercialized and effective in treating seizures, with almost a 60-70% of people with epilepsy that will achieve prolonged seizure control[2].

However, it is estimated that approximately 30% of people with epilepsy exhibit a form of disorder that is refractory to commonly prescribed antiseizure medications, a condition referred to as drug-resistant epilepsy or DRE[3,4], which is defined, according to the International League Against Epilepsy (ILAE), as 'the failure of adequate trials of two tolerated, appropriately selected, and properly used antiseizure medications - whether administered as monotherapy or in combination - to achieve sustained seizure freedom'[5].

The incidence of DRE ranges from 0.06 to 0.51, and the prevalence from 0.11 to 0.58[5]. However, prevalence and incidence of DRE may substantially change across studies for different reasons. One of these is the lack of a standardized terminology before the 2010 ILAE consensus proposal. In their systematic review and metanalysis, Kalilani et al.[4] evidenced that only few studies (the 10% of their cohort) referred to the ILAE's criteria terminology for the definition of DRE, thus resulting in a false estimation of the real prevalence. Moreover, the duration of epilepsy itself may affect the epidemiological studies, since for DRE diagnosis the failure of at least two antiseizure drugs is required; consequently, patients with newly diagnosed epilepsy tend to show a lower proportion of drug-resistance compared to those with a longer history of disease. Additionally, as some authors suggested, drug responsiveness should be considered as a dynamic rather than a fixed state[6] as most types of epilepsy behave as 'relapsing-remitting' diseases, where periods of seizure recurrence are alternated with seizure-free periods[7,8], with the consequences that a real estimation of DRE prevalence and incidence at a time is difficult to extrapolate.

The burden of drug-resistance epilepsy is high for the patients, their caregivers and the health-care system.

A significantly increased risk of injury and SUDEP (sudden unexpected death in epilepsy) has been observed in DRE patients compared to general population[9,10]. Drug-resistant epilepsy increases the probability of unfavourable evolution into a status epilepticus, a neurological emergency that often requires hospitalization in intensive care units and may necessitate invasive interventions, such as sedation, endotracheal intubation, and artificial nutritional support; conversely, status epilepticus itself is a negative predictor for subsequent drug-unresponsiveness[11]. Psychiatric comorbidities -

particularly depression (30%), anxiety disorders (10-25%), psychoses (2-7%) and personality disorders - are also frequent and contribute to worse patients' quality of life[12]. In newborns and children, certain epileptic syndromes are typically associated with drug resistance with catastrophic consequences in terms of neurocognitive outcome[13].

1.2 Predictors of risk

Early identification of individuals at risk for developing DRE is crucial for guiding clinicians in management of epilepsy and estimating prognosis.

The major clinical predictors of DRE identified from systematic reviews and metanalyses are the following: a younger age at onset, 'symptomatic' epilepsy (an old terminology referring to epilepsy due to an acquired cause), the presence of neurologic deficits and abnormal EEG, seizure types and poor response to the first antiepileptic drug[3,14,15].

Younger age at epilepsy onset: In newborns and children, drug resistance is strictly connected to the aetiology. The group of the self-limited epileptic syndromes is typically associated with a good prognosis and pharmaco-responsiveness is one of the key features for diagnosis. On the contrary, children affected by certain epileptic syndromes - such as the group of the developmental and epileptic encephalopathies - usually become drug-resistant in the early stages of disease[13].

'Symptomatic' epilepsy – an old terminology referring to infectious, metabolic, immune-mediated, structural disorders, as well as other acquired conditions underlying the aetiology of epilepsy - are frequently accompanied by ***neurological impairments*** and ***EEG abnormalities*** which are strong predictors of a poor prognosis in terms of seizure relapse. It has been estimated that delaying a pre-surgical evaluation in children with early pharmaco-resistance and an abnormal neuroimaging study is the strongest prognostic factor for a poor prognosis[15,16].

Among ***seizure types***, complex febrile seizures and focal to bilateral tonic-clonic seizures have been linked to a major risk of developing DRE[17]. In adults with focal epilepsy, complex partial seizures (an old terminology referring to focal seizures with loss of awareness) are the strongest predictors of DRE[18], as well as focal onset seizures or multiple seizure types are in children[15,19].

Patients with epilepsy ***failing the initial AED trial*** are at increased risk of poor outcomes for the first years after diagnosis, including future pharmaco-resistance[20]. It is well-known from literature that the rate of responsiveness after multiple ASMs trial decreases proportionally (with an estimation of 11%, 4% and 2% for the second, third and subsequent ASMs regimens, respectively)[21], thus the responsiveness to the first or second ASM is crucial to determine the 'clinical trajectory' of that patient.

1.3 Pathogenetic mechanisms

Various theories have been advanced to explain the biological mechanisms of drug resistance[6]:

- The **transporter hypothesis** suggests that chronic seizures – or genetic determinants - might induce the expression of drug efflux transporters or multidrug resistance proteins at the blood-brain barrier, resulting in a lower concentration of the antiseizure medication at its site of action[22].
- The **target hypothesis** points out that drug-resistant populations, for acquired or genetic factors, carry an 'intrinsic' modification in antiseizure medication target proteins that may contribute to a reduction in drug response[23].
- The **intrinsic severity hypothesis** supports the theory that drug resistance is intrinsically a more complex phenomenon, and its underlying molecular abnormalities are so 'strong' or so extensive that they cannot be adequately suppressed by antiseizure medications[22]. The therapeutic failure results in recurrent seizures which chronically induce neuronal degeneration, axonal sprouting, gliosis remodelling which overall alter the neural network by further worsening seizure recurrence and reducing the effect of drugs at their target.
- The **neuroinflammation hypothesis** is a recent concept according to whom seizure unresponsiveness is chronically responsible for a serious of inflammatory cascade reactions at the brain level resulting in a remodelling of the neural network and a reduction of ASMs effects. These novel findings have provided the basis for trials where inflammatory molecules are the targets to treat or prevent drug-resistant epilepsy, yet research in this field is currently at a very early stage[24].

According to this evidence, drug resistance should be viewed as a heterogeneous and multifactorial phenomenon where each of these mechanisms may exert its effects at various levels in a more interconnected way.

1.4 Management

Epilepsy surgery is a valid option for managing DRE and the treatment of choice, when practicable, for its high rate of success in terms of seizure remission. Nevertheless, most people with DRE would be addressed to a first surgical-evaluation only after 15-20 years from diagnosis, thus delaying the access to a potential life-changing treatment[25]. The aim of epilepsy surgery is to remove the focal epileptogenic zone – the area of cortex that is indispensable for the generation of epileptic seizures, and whose removal (or complete disconnection) is necessary for complete abolition of seizures[26] – and this is the case where surgery might be potentially curative; however, when pre-surgical evaluation is not able to define a clear seizure-onset zone, surgery may be a palliative intervention (i.e. corpus callosotomy) to reduce the burden of seizures and improve

patients' quality of life[27,28]. The seizure-free rate of epilepsy surgery ranges from approximately 75-80% in hippocampal sclerosis and 70%–75% for other temporal lobe lesions[29], to 40% for extra-temporal lobe resection and 64% for hemispherectomy[30]. Patients affected by Rasmussen's encephalitis and focal infarcts seem to have the best prognosis after hemispherectomy with a seizure-free rate of 75%–85%, while hemi-megalocephaly has the worst prognosis[31].

Among non-pharmacological approaches for DRE, **ketogenic diet** is one of the most efficacious in seizure control, especially for children and adolescents. It consists in an extremely low-carbohydrate, high fat and adequate (or low) protein-diet which induces the production of ketone bodies. Its mechanism is not still fully understood although various hypotheses have been proposed (increased levels of neurotransmitters involved in seizure reduction, decreased glutamatergic synaptic transmission, increased GABA concentrations in the brain, and neuronal hyperpolarization by activation of potassium channels)[32]. In a cohort of 63 children and infants receiving ketogenic diet for at least 3 months, the responder rate (≥50% reduction in seizure frequency) ranged from 52% at 3 years to 30% at more than 3 years of follow-up, while the seizure-free rate was 14%-17%[33]. Similarly, other meta-analyses have found seizure free rates of 15%–20%[34]. In particular, the highest success rate was achieved by those patients remaining on the diet for the prescribed period[35].

Over the past decade, novel antiseizure medications have emerged in the therapeutic landscape of drug-resistant epilepsy. Among these, **Cenobamate** is a recently approved, third-generation ASM, licensed for use as add-on treatment for focal epilepsy in patients aged 18 years or older. It reduces neuronal excitability by inhibiting the persistent component of the sodium channel current and acting as a positive allosteric modulator of high-affinity GABA-A receptors at a non-benzodiazepine site[36,37]. Efficacy and safety of cenobamate have been evaluated in two randomized, double-blind, placebo-controlled adjunctive therapy trials in adults with focal seizures[38,39] and in a large, phase 3, multicentre, open-label safety study[40]. In the first trial, median percentage changes in seizure frequency were -35.5% for the 100 mg dose group, -55% for the 200 mg dose group, and -55% for the 400 mg dose group (compared to -24% for the placebo group); responder rates during the maintenance phase were 40%, 56% and 64% for the 100 mg, 200 mg and 400 mg dose group, respectively (compared to 25% for the placebo group); most of treatment-related side effects were recorded at increasing doses (65%, 76% and 90% in the 100 mg, 200 mg and 400 mg group, respectively)[38]. In the second trial, the responder rate was 50.4% for the 200 mg group compared to 22.2% of placebo, while seizure freedom rate was 28.3% for cenobamate-treated versus 8.8% of placebo; treatment-emergent adverse events were reported in >10% of either group[39]. The most frequent treatment-related adverse effects - emerged from a large, phase 3, multicenter, open-label

safety study - were somnolence (28.1%), dizziness (23.6%), and fatigue (16.6%); however, the retention rate was high (with >80% of patients continuing cenobamate for ≥6 months), thus long-term treatment with cenobamate as adjunctive therapy could be considered safe and well tolerated[40]. No cases of severe idiosyncratic adverse events were reported in this trial by adopting a slow titration rate which is currently a standard for clinical practise: a starting dose of 12.5 mg with subsequent increase at 2-week intervals to 25, 50, 100, 150, and 200 mg/d are allowed, with eventually additional biweekly 50 mg/d increases to a maximum of 400 mg/d[40].

2. Neuromodulation for DRE treatment: an overview

Neurostimulation is an option for patients with DRE who are not eligible for resective surgery for several reasons, for example when the epileptic focus is within an eloquent cortex, or when no clear localization can be found on pre-surgical assessment (invasive or not).

Three neurostimulation techniques have been approved by the Food and Drug Administration (FDA) for treatment of drug-resistant epilepsy: vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS)[41]. All these neurostimulation techniques are based on open-loop or closed-loop stimulation paradigms that deliver stimulation when specific physiological parameters are detected[42].

2.1 Deep brain stimulation

Deep brain stimulation or DBS consists into the implantation of deep electrodes targeting specifical brain regions, which are connected to a subclavicular implantable pulse generator. The most promising DBS targets for the treatment of DRE include the anterior (ANT) and centromedian (CM) nuclei of the thalamus. In the SANTE (the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) trial, median seizure frequency percent reduction from baseline was 75% at seven years from implantation and the most severe seizure type, i.e. focal to bilateral tonic–clonic seizures, was reduced by 71%[43]. Concomitantly, CM-DBS is the primary choice for treatment of primary generalized DRE for its well demonstrated effectiveness in treating generalized epilepsies and patients with Lennox-Gastaut syndrome (LGS)[44]. The ESTEL (DBS of the Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome) trial – a prospective, double-blind, randomized study of continuous, cycling stimulation of CM-DBS in patients with LGS – demonstrated a median seizure reduction of 46.7% for diary-recorded seizures and 53.8% for electrographic seizures after three months of stimulation[45]. The therapeutic mechanisms of DBS are not yet fully elucidated. Principal hypotheses suggest that ANT stimulation would modulate limbic and thalamocortical networks and reduced functional connectivity between the ANT and hippocampus, thus explaining its efficacy in treating especially focal (limbic and temporal lobe)

epilepsies[46]. CNT-DBS may explicate its anti-seizure effects by desynchronizing thalamocortical circuits and modulating reticular formation and somatomotor cortices, brain regions typically associated with the spread of epileptic seizures in LGS patients[47,48].

2.2 Responsive neurostimulation

Responsive neurostimulation (RNS) consists of a pulse generator, an external programmer and depth or subdural strip leads targeting the ictal onset zone and, consequently, the area to be stimulated to stop the seizure or to prevent its initiation. RNS system is based on a closed-loop paradigm, an algorithm capable of detecting specific patterns of epileptogenic activity and triggering focal stimulation to interrupt the seizure[49]. Data of RNS efficacy are extrapolated mainly from the Randomized multicenter double-blinded controlled trial of responsive focal cortical stimulation (RNS System): at a four-months follow-up period, seizure reduction was of 37.8% with stimulation vs 17.3% in the sham group[50]; rates of responsiveness increased over time, with a 44% seizure reduction after 1 year to a 66% after 6 years from implantation[51,52].

Safety for neurostimulators is acceptable with a rate of severe adverse effects inferior to 10%, principally surgically related (implant site infection and neurostimulator explantation)[52].

3. Vagus Nerve Stimulation (VNS)

3.1 Definition and functioning

Among the above mentioned neurostimulation techniques, implantable Vagus Nerve Stimulation (VNS) is the most advantageous for being less invasive. It has been approved by the FDA in 1997 for the treatment of people with DRE with focal or generalized epilepsy who are not eligible for surgery (or where epilepsy surgery failed)[53]. The VNS device consists of a pulse generator that is subcutaneously implanted under the left clavicle (or in the axilla if preferred by the patient for cosmetic reasons) and connected to a lead wire with two helicoidal stimulating electrodes placed around the left vagus nerve, distal to the recurrent laryngeal nerve[54]. Stimulation of the left vagus nerve, rather than the right, is preferred to reduce cardiovascular effects (bradycardia, asystole)[55].

There are three main paradigms of VNS stimulation, that may be resumed as follows[56]:

- VNS **baseline stimulation** is usually started 2 weeks after implantation, with recommended settings of stimulation (1.0–2.0 mA; 500 μs pulse width; 20–30 Hz; 30 s ON, 5 min OFF) that must be gradually reached with 0.25 mA increases per week. The recent VNS models are provided with an auto-titration schedule previously set to reach automatically the desired output current, generally higher than 1.3 mA (1.25–2.0 mA), which is defined as therapeutic[57].

- A **magnet-induced stimulation** which may deliver a single extra-stimulation when passed over the battery to arrest seizures at their onset.
- The recent VNS models (AspireSR® Model 106 and SenTiva™ Model 1000 (VNS Therapy®, LivaNova)) are provided with a novel modality of stimulation known as '**AutoStim**', a cardiac-based seizure detection automatic stimulation. This algorithm recognizes tachycardia as a surrogate marker to predict the onset of seizure, and the battery delivers a closed-loop electrical current which provides an extra-stimulation in addition to the baseline stimulation[58].

Baseline stimulation is not continuous but intermitting, with 'on' time of activation cyclically alternated with 'off' time where the stimulation is not provided. This 'duty cycle' (calculated as the "ratio (on time+4s)/(on time+off time)" - where the 4s included in the calculation is 2s of ramp-up plus 2s of ramp-down) is usually set to 10% in the classical modality of stimulation, which corresponds to a 30-seconds 'on' period cyclically alternated with a 300 seconds (5 minutes) 'off' period[56].

3.2 Safety

Current literature supports the relative safety of VNS in epilepsy treatment. Side effects may be divided into early and late-onset[54]. Early-onset adverse effects can be reconducted to the surgical procedure and are relatively rare, with an average incidence of less than 5%: minor postoperative superficial infection, cough, neck pain, vocal cord paresis and lower facial paresis are the most reported, although advances in surgical techniques have significantly lowered their incidence[59]. Late-onset side effects are usually limited to the stimulation phases: mild voice hoarseness (38.8%), dysphonia (<5%), cervical pain (<5%), exertional dyspnea (<5%), cough (≈ 5%), snoring (<5%), hypersialorrhea (<5%). Laryngopharyngeal side effects (hoarseness, dyspnea, and coughing) are usually transitory due to the stimulation of the inferior (recurrent) laryngeal nerve and may be managed by reducing VNS intensity of stimulation[60]. Obstructive sleep apnoea syndrome can be worsened by VNS; therefore, patients should be evaluated for sleeping disorders before implantation[61,62].

3.3 Efficacy: seizure reduction and improvement of quality of life (QoL)

In most published studies, response rates (expressed as more than 50% reduction in seizure frequency) for implantable VNS vary from 45 to 65%[60]. The therapeutic effects of VNS compared to placebo in DRE have been evaluated in two pivotal randomized clinical trials[63,64]. In the first study (EO3), 114 patients were randomly assigned in a double-blind fashion to receive either high- or low-intensity stimulation; after 14 weeks of therapy, patients in the high-stimulation group

exhibited a mean seizure frequency reduction of 24.5% compared to 6.1% in the low-stimulation group[63]. The second randomized trial (EO5), which enrolled 196 patients, reported a seizure frequency reduction of 28% in the active treatment group versus 15% in controls after three months of follow-up[64]. As concern the other modalities of stimulation, magnet stimulation proved to be a useful tool to stop seizures in more than 50% of patients[65], and similarly AutoStim function seems to further reduce seizures in both adults[66] and children[67].

Growing evidence indicates that the therapeutic efficacy of vagus nerve stimulation in epilepsy increases progressively with long-term treatment. Data from pivotal trials, long-term observational studies, and patient registries consistently show that seizure reduction improves over time, suggesting a cumulative neuromodulatory effect. For instance, Morris et al. reported median seizure reductions of 35%, 44.3%, and 44.1% at one, two, and three years following VNS implantation, respectively[68]. Similarly, a large prospective study conducted in Japan by Kawai and colleagues showed progressive improvement over time, with median seizure reductions reaching more than 60% after two years of therapy[69]. Evidence from the VNS Therapy Patient Outcome Registry further supports this time-dependent effect, with increasing responder rates observed over prolonged follow-up[70,71]. The mechanisms underlying this delayed and cumulative efficacy may be searched in neural plasticity, synaptic reorganization and long-term modulation of epileptic networks induced by chronic vagal afferent stimulation.

The role of VNS in epilepsy management should not be considered solely in terms of seizure reduction, as beneficial effects on cognitive function and mood disorders have also been reported. In numerous cases, enhancing patients' quality of life and alleviating the burden on caregivers may be even more clinically relevant than achieving optimal seizure control. Although long-term studies have yielded contrasting results[72], VNS seems to improve some cognitive domains such as cognition tasks, short-term visual memory and working memory[73,74]. Conversely, VNS efficacy in treating mood disorders is well-demonstrated, with FDA approval also for treatment-resistant depression[75]. In a prospective longitudinal observational study including 41 patients with drug-resistant epilepsy undergoing VNS therapy, the authors observed reductions in anxiety, tension, and depressive symptoms at six-month follow-up; notably, these improvements appeared to occur independently of seizure control[76]. Overall, these effects have a clear repercussion on quality of life of epileptic individuals. In the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial, Ryvlin and colleagues demonstrated that VNS improved the overall quality of life - assessed with specific scale: the Quality of Life in Epilepsy Inventory-89 total score (QOLI-89) and the Clinical Global Impression-Improvement scale (CGI-I) - compared to best medical practise alone[77]. An analysis of over 5,000 patients included in the VNS Therapy Patient Outcome Registry

demonstrated that VNS therapy was associated with significant improvements across multiple quality-of-life domains, including alertness, postictal recovery, seizure clustering, mood, verbal communication, academic or professional performance, and memory, particularly among responders[78]. In conclusion, VNS efficacy should be evaluated not only in terms of seizure reduction but also for its substantial impact on overall quality of life, which can profoundly influence the long-term outcomes of both patients and their caregivers.

3.4 Mechanisms of action

Over the past decades, numerous animal and human studies have investigated the mechanisms through which VNS may exert its effects in aborting seizures. Most vagus nerve afferent fibers terminate in the nucleus of tractus solitarius, which further projects to several key structures in the brainstem such as the noradrenergic locus coeruleus, serotoninergic raphe nucleus, cerebellum, periaqueductal gray matter, and parabrachial nuclei. The parabrachial nuclei seem to play a key role in epilepsy for their connections to structures such as insula, thalamus, hippocampus, and amygdala. The principal hypothesis to explain VNS functioning in epileptic individuals may be summarized as follows[79]:

- **Reduction in excitatory neurotransmitters**: VNS may modulate the release of some neurotransmitters such as noradrenaline, dopamine, serotonin, GABA at strategic brain levels which are involved in seizure onset and propagation[80].
- **Changes in cerebral blood flow**: this evidence comes mainly from functional imaging studies. Following VNS implantation, increased and sustained cerebral blood flow has been observed in the bilateral thalami, hypothalami, and inferior cerebellum, suggesting a potential role of VNS in long-term modulation of cortical network[81].
- **Reduction of cortical excitability**: GABA-mediated effects have been proposed as a possible mechanism underlying VNS reduction of cortical excitability, as demonstrated by transcranial magnetic stimulation paradigms[82,83].

3.5 Exploring EEG modifications in VNS epileptic patients

To assess the therapeutic effects of VNS in epileptic patients, several studies in the last years have focused on the EEG modifications induced by VNS.

After VNS implantation, a significant reduction in epileptiform abnormalities - both ictal and interictal – has been observed over both short- and long-term follow-up periods[84,85].

VNS stimulation may also contribute to EEG desynchronization for specific band frequencies thus contributing to lower the epileptic threshold and reduce the spread of epileptic abnormalities (EEG spatial synchronization is considered a measure of seizure propagation). Marrosu et al. reported

changes in spectral power in gamma bands for patients treated with VNS at one-year follow-up from implantation[86]; the same authors observed a significant decrease in synchronization in theta frequencies, as confirmed by Ernst and colleagues in patients implanted with dual (VNS and RNS) neurostimulators[87]. Brádzil et al. demonstrated significant differences in EEG reactivity between responders and nonresponders and found that the changes in the alpha and gamma bands were the most associated with VNS efficacy[88].

Among quantitative EEG (qEEG) parameters, EEG functional connectivity (EEG-Fc) has been also widely explored in the past decades to assess VNS mechanisms of action in epilepsy. EEG-Fc refers to the statistical relationships between electrical activities recorded from different regions of the brain using electroencephalography; essentially, it measures how different brain areas interact or communicate with each other, based on their synchronized activity, even if they are not directly anatomically connected.

EEG functional connectivity may be assessed with different measures[89]:

- **Linear measures (correlation/coherence)**: they quantify the degree of synchronous activity between two signals, with coherence additionally providing frequency-specific information about oscillatory coupling.
- **Phase-based approaches:** they include phase-locking value (PLV) and phase-lag index (PLI) and assess the consistency of phase relationships over time, thereby capturing non-amplitude-dependent interactions and mitigating the effects of volume conduction.
- **Causal or directed connectivity frameworks:** including Granger causality and dynamic causal modelling, which aim to infer the directionality of influence between brain regions, offering insights into effective connectivity.
- **Graph theory metrics:** represent the brain as a network and quantify connectivity strength, hubs, and network efficiency.

Current literature seems to suggest significant remodulation of Fc induced by VNS in epileptic patients. Fraschini et al. observed that functional connectivity in the gamma band – assessed with the PLI model – significantly decreased in the group of responders to VNS therapy, thus indicating a global signal desynchronization; notably, in the subjects who failed to respond to VNS therapy, no differences were detected in the global mean PLI for all frequency bands before and after VNS implantation[90]. Bodin et al. measured EEG-Fc in patients with chronic VNS and compared responders and non-responder patients during ON and OFF periods; the authors observed that Fc tended to decrease in the ON period, and that this effect was also maximal for responder patients[91]. Sangare and colleagues replicated the same protocol in a wider cohort (35 patients) and compared effects on Fc-EEG (measured with PLI) between VNS-stimulated ON and OFF periods and

between responder and nonresponders; they observed that, for responder patients, Fc-EEG during ON periods was significantly lower than that during OFF periods in delta, theta and beta frequency bands, while no significant differences between ON and OFF periods was observed for non-responders[92].

These above-mentioned studies assessed Fc from scalp-EEG recordings, however similar evidence has been reported from intracortical EEG. Bartolomei et al. recorded intracortical EEGs from five patients with epilepsy during ongoing VNS therapy. They observed significant modifications in EEG-Fc induced by VNS by comparing ON period with OFF periods and, interestingly, the only patient with a decreased connectivity during the ON period was a responder[93].

Taken together, this evidence suggests that the therapeutic effect of VNS may be mediated by a global reduction in Fc-EEG activity.

4. Objective of the study

The objective of this study was to investigate the neuromodulatory effects of VNS on large-scale brain network organization in individuals with drug-resistant epilepsy, using a longitudinal quantitative electroencephalography (qEEG) framework. Specifically, this work aimed to characterize changes in cortical functional connectivity derived from scalp EEG recordings acquired before VNS implantation and after 12 months of therapy.

Considering the conceptualization of epilepsy as a network disorder, rather than a condition confined to a single epileptogenic focus, the study was designed to evaluate VNS-related modulation of distributed neural activity under different physiological and pathological conditions. To this aim, functional connectivity was assessed during periods of background activity free of epileptiform discharges, during active stimulation (ON condition), and in association with interictal epileptiform events, thereby allowing a comprehensive evaluation of both baseline and pathological network dynamics.

Additionally, the study sought to determine whether VNS-induced changes in electrophysiological measures—specifically connectivity and spectral properties across conventional frequency bands—were associated with clinical outcomes, including seizure frequency reduction and global measures of patient improvement.

By integrating longitudinal neurophysiological data with clinical indices, this work aimed to explore the potential of qEEG-derived functional connectivity as a biomarker of treatment response and to provide further insight into the mechanisms through which VNS exerts its therapeutic effects on epileptic brain networks.

5. Materials and Methods

5.1 Subjects

Ten consecutive patients with drug-resistant epilepsy, including six women, who were deemed eligible for VNS therapy, were recruited for the study. EEG and clinical data were collected as part of routine clinical practice and analysed retrospectively for this specific study. The inclusion criteria were as follows: (a) age between 18 and 75 years; (b) completion of a comprehensive presurgical evaluation (in individuals with focal epilepsy) that ultimately ruled out resective surgical intervention; (c) suitability for VNS therapy. Patients presenting with additional neurological comorbidities—excluding mild mood disorders—or receiving high doses of antidepressant or antipsychotic medications potentially affecting EEG recordings were excluded. VNS implantation was performed using the VNS Therapy® SenTiva™ Model device. No perioperative complications or short-term adverse events related to the device were observed. The stimulator was activated approximately three-four weeks after implantation, and stimulation parameters (output current, frequency, pulse width, and duty cycle) were individually adjusted. In the study cohort, output current ranged from 1.25 to 2.25 mA, with a maximum of 2.25 mA, depending on clinical efficacy and tolerability. Further stimulation parameters were a pulse width set to 500 μs and a frequency set to 30 Hz. Duty cycle settings varied across patients: 10% (30 s ON / 5 min OFF) in three patients, 16% (30 s ON / 3 min OFF) in four patients, and 25% (30 s ON / 1.8 min OFF) in the remaining three patients. Throughout the follow-up period, antiepileptic drug regimens - including number of medications, dosages, and administration schedules - were kept constant to minimize confounding effects.

Clinical outcomes were assessed by evaluating seizure frequency reduction, based on seizure diaries maintained by patients and caregivers, as well as changes in ictal and post-ictal severity and overall quality of life. Two clinical scales were used to assess modification in quality of life: the McHugh classification and the Clinical Global Impression of Improvement (CGI-I) scale, respectively. Seizure freedom and seizure responsiveness, defined as a ≥50% reduction in seizure frequency during the observation period, were classified according to ILAE criteria[94].

In addition to quantitative seizure reduction, we introduced the qualitative concept of “global responder” to capture patients’ overall satisfaction with VNS therapy. This classification was based on a combination of two clinical scales: (a) the McHugh classification, a standardized five-class outcome measure for VNS efficacy (classes I–V)[95], and (b) the Clinical Global Impression of Improvement (CGI-I) scale, a four-point clinician-rated measure of treatment-related clinical change (1 = worsened; 2 = no change; 3 = improved; 4 = markedly improved)[96]. Outcomes were categorized as “good” when, at the final follow-up, patients met the following criteria: a seizure

frequency reduction of at least 50% and/or a McHugh score of ≥ IIIA (indicating ≤50% seizure reduction accompanied by improvement in ictal or post-ictal severity), together with a CGI-I score of ≥ 3. Patients who did not fulfil these criteria were classified as having a "poor" outcome.

5.2 Quantitative EEG analysis

High-density EEG recordings were obtained using a 64-channel system for a total duration of 35 minutes at two time points: prior to VNS implantation (T0) and twelve months post-implantation (T1). EEGs were recorded during quiet rest with eyes closed while patients remained awake. Electrodes were positioned using a prewired cap according to the international 10–10 system, in compliance with ACNS guidelines[97]. Recordings were acquired using a 64-channel Micromed system (SystemPlus software; Micromed, Mogliano Veneto, Italy), with electrode impedance maintained below 5 kΩ.

Following VNS implantation, an additional electrode was placed over the left anterior chest wall at the projection site of the stimulator, with the reference electrode positioned contralaterally. This configuration allowed identification of VNS activation periods through the detection of stimulation-related interference on the electrocardiographic trace during active stimulation trains [**Figure 1**].

EEG data were processed using the Brainstorm toolbox for Matlab™ (version R2018a)[98]. Preprocessing was conducted via a semi-automated pipeline implemented in Matlab™ within the Brainstorm environment. Signals were filtered using a 1–70 Hz band-pass filter and notch filters at 50, 100, and 150 Hz. Channels exhibiting poor signal quality were visually identified and excluded from further analysis.

Two primary event types were defined for each EEG recording based on VNS activity: OFF periods, corresponding to intervals of VNS inactivity ("background" or "BG_OFF" events), and ON periods, corresponding to active stimulation ("ON" events). Both BG_OFF and ON events were selected during EEG segments free from interictal epileptiform activity. Interictal epileptiform discharges (spikes) were independently marked during both OFF and ON conditions and analyzed separately ("Spikes_OFF" and "Spikes_ON"). Background and ON events were segmented into 2-second epochs, yielding 90 BG_OFF epochs and 30 ON epochs per recording. All EEG data were re-referenced to the average reference prior to analysis.

Quantitative EEG analyses focused on two main measures: power spectral density (PSD) and functional connectivity. PSD was computed using Welch's method (2-second window length, 1-second step size, 50% overlap), and relative power (band power divided by total power) was calculated for each channel across the following frequency bands: delta (1–4 Hz), theta (5–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), and broadband (1–70 Hz). Gamma-band activity was excluded due to the high susceptibility of this frequency range to muscle artifacts[99].

EEG-Fc was assessed using the Amplitude Envelope Correlation (AEC) NxN method implemented in the Brainstorm toolbox, applying orthogonalization of signal pairs prior to envelope computation within 2-second windows. Connectivity analyses were performed separately for each frequency band to evaluate VNS-induced network changes.

Mean values of PSD and functional connectivity, computed across all channels for each frequency bands, were obtained for each experimental condition ("BG_OFF", "ON", "Spikes_OFF", "Spikes_ON") and subsequently analysed using custom-developed MATLAB™ scripts.

For each paradigm, we measured the global connectivity obtained as follows: connectivity matrices computed for each frequency band (delta, theta, alpha, and beta) were averaged to obtain a single composite connectivity matrix for each condition and subject. This averaged matrix was then used for the statistical analyses to provide a global measure of functional connectivity while reducing band-specific variability.

5.3 Statistical analysis

Data were analysed and plotted with JASP, version 0.16.4.0. Levine's test was used to assess the homogeneity of variance and Shapiro-Wilk test to verify if our cohort was normally distributed. Comparison between times of observation (T0 and T1) was performed with the Wilcoxon signed-rank test (for non-parametric data) for both the spectral and connectivity data. Connectivity data were also compared with the two outcome groups (good and poor outcome) with a one-way analysis of variance (ANOVA). p-value was set at 0.05 for statistical significance; all p-values are presented after correction for multiple comparisons.

6. Results

6.1 Clinical data

Ten patients, six of whom were female, met the inclusion criteria and were enrolled in the study. The mean age of the cohort was 43.2 ± 13.9 years (standard deviation, SD), with a mean disease duration of 40.3 ± 13.2 years (SD). A defined epilepsy syndrome was identified in only two individuals (ring chromosome 20 syndrome and Sturge–Weber syndrome). Seven patients were diagnosed with focal epilepsy, predominantly characterized by multifocal seizure onset. The clinical presentation was heterogeneous, with seizure types including focal seizures, focal to bilateral tonic–clonic seizures, atonic, myoclonic, and absence seizures. All patients were receiving polytherapy with anti-seizure medications, with a median number of 2.8 drugs per patient. Magnet activation was employed by five patients; however, only three reported a perceived benefit in reducing or interrupting seizures. In the remaining patients, the brief duration of seizures represented the primary factor limiting effective magnet use.

Seizure frequency was quantified as the mean number of seizures occurring during the six months preceding the observation period and ranged from 5 to 163 seizures per month. In one patient, accurate seizure quantification was challenging due to institutionalization. At the final follow-up, none of the patients achieved seizure freedom, and only three individuals met the criteria for seizure responsiveness, defined as a reduction in seizure frequency greater than 50%. Specifically, one patient experienced an 85% reduction in seizure frequency, another achieved a 55% reduction, and a particularly robust and sustained response was observed in the patient with ring chromosome 20 syndrome, who reported a 65% reduction in seizure frequency within three months of treatment initiation. An additional patient reported a 40% reduction in seizure frequency following VNS therapy. Among the seven patients classified as non-responders based on seizure frequency reduction, four (28%) attained a McHugh classification score of IIIA (indicating a reduction in seizure frequency < 50% but with an improvement in ictal or post-ictal severity). These four patients were also rated as "minimally improved" or better on the CGI-I scale, receiving scores of 3 or 2, respectively. According to our classification of prognosis, the overall outcome assessment indicated that seven patients (70%) achieved a favourable outcome, comprising three responders and four global responders, whereas the remaining 30% of the cohort was classified as having a poor outcome.

Adverse events in our cohorts were reported by 50% of the patients and were predominantly device-related, including transient voice changes, hoarseness, cough, and throat discomfort. To improve tolerability, minor adjustments to VNS stimulation parameters were implemented when necessary. The main clinical and demographic characteristics of the study population are summarized in **Table 1**.

6.2 EEG connectivity and spectral modifications after VNS therapy

We investigated changes in EEG-Fc before and after VNS therapy by considering the following four variables: "BG_OFF" and "ON", referring to the connectivity of VNS OFF and ON-mode free of epileptiform activity and "Spikes_OFF" and "Spikes_ON", which corresponded to the connectivity of interictal spikes marked during the OFF and ON period, respectively.

For each paradigm, we measured the global connectivity obtained as follows: connectivity matrices computed for each frequency band (delta, theta, alpha, and beta) were averaged to obtain a single composite connectivity matrix for each condition and subject. This averaged matrix was then used for the statistical analyses to provide a global measure of functional connectivity while reducing band-specific variability. Subsequently, a comparison for outcomes (good vs. bad) was performed.

Our findings revealed a significant decrease in Fc during the 'BG_OFF' state over a period of approximately 12 months (p=0.001) [**Figure 2**]. In contrast, no significant changes were observed in functional connectivity during the ON state.

Notably, spike-related connectivity exhibited significant reductions in both the OFF and ON conditions over the same 12-month period (p=0.002 and p=0.001, respectively) [**Figure 3** and **Figure 4**, respectively].

Power spectrum analysis did not indicate significant changes across the variables examined ("BG_OFF," "ON," "Spikes_OFF," "Spikes_ON"). Although there was a trend towards increased theta frequency over time, statistical significance was not achieved.

Comparison of connectivity values for outcome showed no significant differences between the good and poor response groups for all the four paradigms.

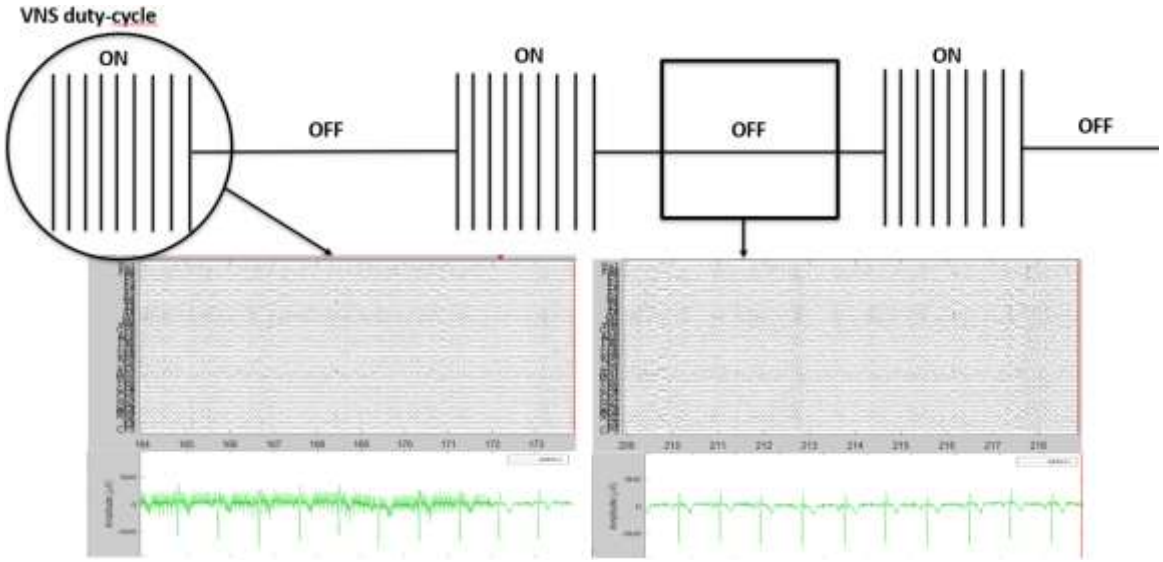

Figure 1. The figure shows the interferential signal on the electrocardiographic trace acquired during VNS trains of stimulation (obtained with the positioning of an adjunctive recording electrode placed over the projection of the VNS stimulator in the left anterior chest wall), which corresponds to the 'ON' modality of activation.

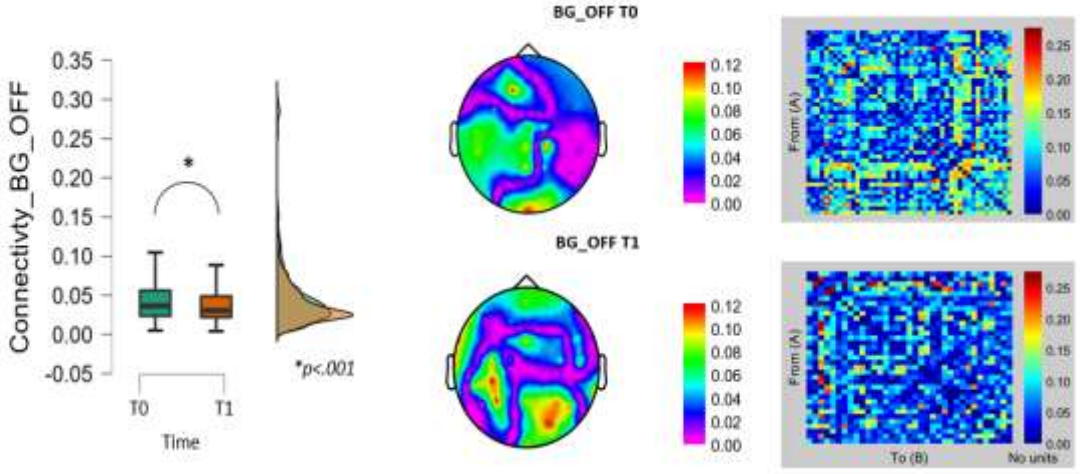

Figure 2. On the left, a raincloud plot representing a reduction in connectivity values for the background(BG)_OFF paradigm from T0 to T1 (p=0.001). On the right, an example of the average connectivity matrix for the BG_OFF paradigm (for all the band of frequencies) is provided, showing a reduction of connectivity power from T0 to T1.

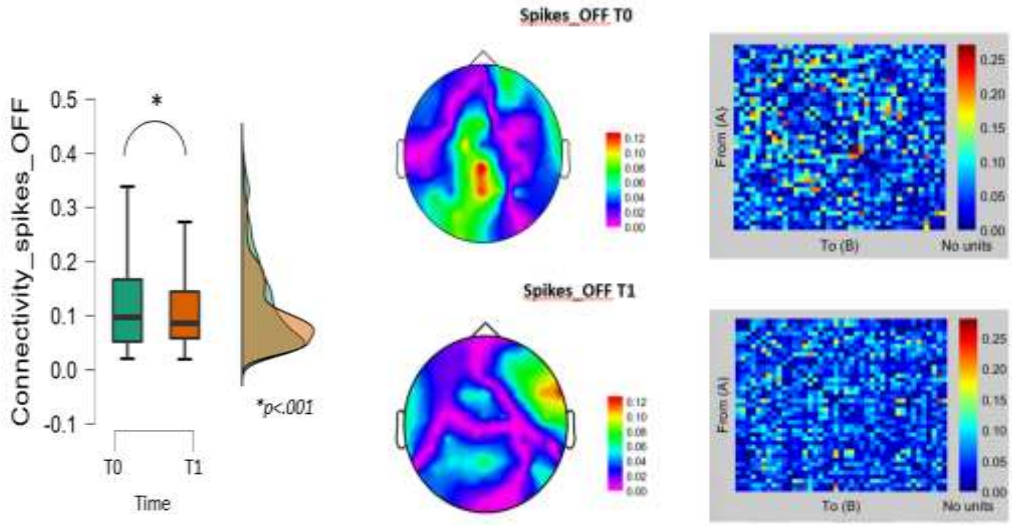

Figure 3. On the left, a raincloud plot representing a reduction in connectivity values for the Spikes_OFF paradigm from T0 to T1 (p=0.002). On the right, an example of the average connectivity matrix for the Spikes_OFF paradigm is provided, showing a reduction of connectivity power from T0 to T1.

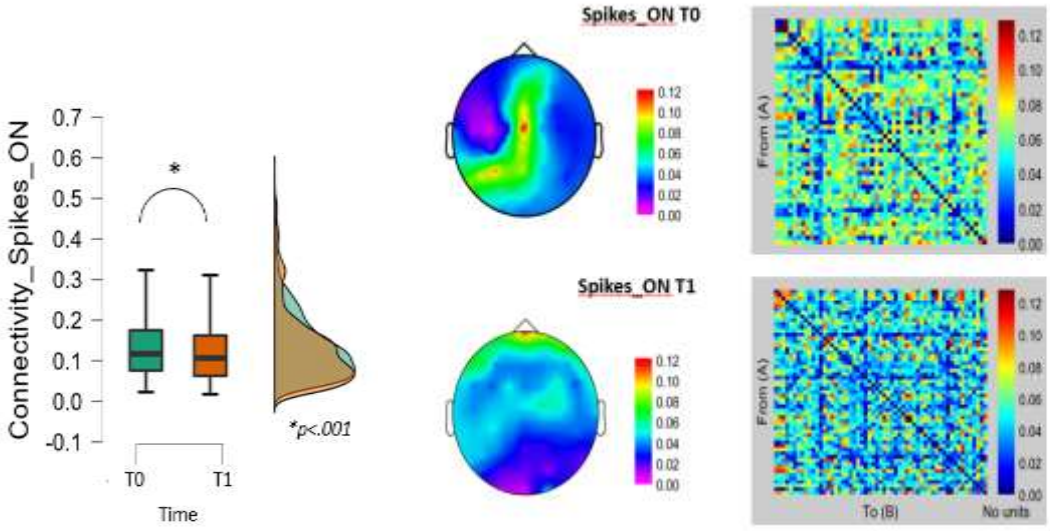

Figure 4. On the left, a raincloud plot representing a reduction in connectivity values for the Spikes_ON paradigm from T0 to T1 (p=0.001). On the right, an example of the average connectivity matrix for the Spikes_ON paradigm is provided, showing a reduction of connectivity power from T0 to T1.

7. Discussion

We examined the EEG-Fc changes induced by VNS over a 12-month period. As a first result, as expected from literature review, we observed that EEG-Fc in the 'background' – i.e. in periods free of epileptiform discharges - decreases over time. Recent evidence reinforces the idea that epilepsy is a network disorder rather than simply a dysfunction confined to a single brain region and this concept has surprisingly been demonstrated also in epilepsy syndromes characterized by a well-defined focal onset[100,101]. Most patients included in our cohort have epilepsy without a clear focal onset (that is one of the reasons of their exclusion from surgery). Our hypothesis is that in this specific population (patients with a long duration of disease) a high-powered 'dysfunctional' network is present even in the background (free of epileptiform discharges) activity. In this scenario, the reduction of a global (dys-)functional background connectivity may indicate a reduced connection among abnormal temporally related-brain areas, explaining how VNS may reduce the odds of seizure onset and propagation. Interestingly, we observed that also the interictal spike-related connectivity decreased significantly over time (in both the paradigms, ON and OFF). No seizures were recorded in our population therefore connectivity could not be analysed during periods of seizure activity. However, recent studies indicate that the epileptogenic network exhibits an altered dynamic not only during seizure onset, but also during the interictal period[102] and the spatiotemporal mapping of interictal spike propagation seems to be more valuable in predicting outcome after surgical resection than the seizure onset zone itself[103]. The observed decreased

connectivity in the interictal epileptiform network after VNS therapy may be expression of a reduced tendency to the propagation of the epileptiform activity. This is consistent with literature, which describes how VNS implantation leads to a progressive synchronization of epileptiform activity, resulting in longer spike-free intervals and a contextual reduction in both the duration and frequency of spikes and spike-and-wave activity over time. These effects are particularly evident in patients with more 'active' EEG patterns during a follow-up period of one year. Similar results were obtained by Kuba and colleagues who observed that VNS-induced reduction of epileptiform activity is higher in responder patients during the active mode[104].

A modulatory effect on subcortical structures involved in seizure-generation, such as thalamus, may explain the potentiality of VNS in reducing the spread of epileptiform activity to the overall cortex by reducing the risk of generalization. The long-lasting modifications induced by VNS on thalamus and cortical regions have been explored by neuroimaging functional studies[105].

Interestingly, our results suggest that VNS acts in both 'ON' that 'OFF' modality. As previously noted, the baseline activation of the VNS system employs a duty cycle that switches two activation modalities. However, the effects of VNS appear to extend beyond the brief duration of stimulation itself, maybe for long-lasting neuropathological effects induced by chronic vagal stimulation itself. Animal studies have documented significant anatomical changes in the stimulated cortex as a result of VNS therapy, highlighting its role in consistently altering synaptic transmission[106]. These modifications require time to manifest, which aligns with the observation that VNS efficacy tends to improve over time[64,69].

Spectral power analysis did not reveal significant changes induced by VNS, as already reported in our previous study[107].

As stated above, gamma frequencies were not included in the final analysis for the high susceptibility of this frequency range to muscle artifacts[99]. In literature, the most robust biomarker for VNS response, particularly in epilepsy, has been found into the reduction of theta band synchronization, often termed "desynchronization". Research suggests that VNS-induced theta desynchronization—especially during sleep—can accurately distinguish "responders" from "non-responders" with high sensitivity and specificity. Using measures like the Weighted Phase Lag Index (wPLI), researchers have found that responders exhibit a significant decrease in theta connectivity during stimulation periods[86]. Unfortunately, no differences between spectral frequency bands, nor clinical correlations with good or poor outcomes emerged from our analysis, although it should be noted that the study population was small and the percentage of effective responders after one year of therapy was low (only the 30%).

8. Conclusions

Our study is in line with literature review, providing evidence that VNS therapy, over time, modulates EEG connectivity. We observed how VNS therapy may reduce the global functional connectivity and the potentially pathological interictal network during spike activation, thus promoting a reduction in the spread of interictal epileptiform abnormalities. Our study has some obvious limitations: the small sample size is a significant limitation, but it is important to note that patients eligible for VNS therapy represents a minority of those observed in clinical settings; secondly, the overall response rate in these patients was too low (30% of our cohort) to allow detection of significant differences in these metrics; however, as previously reported, VNS efficacy in reducing seizure frequency is cumulative, with the best results obtained after almost one year from implantation. Therefore, an extended follow-up may provide additional insights into the real efficacy of VNS therapy.

Further and larger studies are mandatory to understand if these EEG modifications may be 'biomarkers' of a clinical response induced by neuromodulation techniques such as VNS.

Table 1. Clinical and neurophysiological data of our sample are shown. M = Male, F = Female, ASMs = Anti-Seizure Medications, AE = Adverse Events. CBZ = Carbamazepine, LCM = Lacosamide, LEV = Levetiracetam, LTG = Lamotrigine, PB = Phenobarbital, VPA = Valproic Acid, OXC = Oxcarbazepine, ESL = Eslicarbazepine, ZNS = Zonisamide.

	Sex	Age	Diagnosis	Epileptic focus	ASMs n°	ASMs dose (mg/day)	Responder	Mean seizure reduction (%)	Mc-Hugh	GCI-I	Outcome	AE
1	F	58	Focal symptomatic post-traumatic	Bilateral fronto-temporal	4	ESL 1600; LCS 200; ZNG 400; VPA 2000	Yes	55%	II A	2	Good	Cough, hoarseness
2	F	56	Focal of unknown origin	Left temporal	2	ZNG 400; LCS 500	No	-	III A	3	Good	Hoarseness, throat pain
3	M	57	Focal of unknown origin	Unknown	3	LCS 400; PER 8; OXC 1200	No	-	III A	2	Good	Hoarseness
4	M	47	Focal post-traumatic	Unknown	4	CBZ 800; TPM 700; LMT 400; PER 8	No	-	V	4	Bad	Hoarseness, cough, throat pain
5	M	45	Sturge-Weber syndrome	-	3	OXC 3600, ZNG 700, PB 200	No	-	III A	3	Good	Hoarseness
6	F	27	Focal of unknown origin	Unknown	2	VPA 900, P>ER 10	Yes	85%	I A	2	Good	None
7	M	31	Generalized epilepsy of unknown aetiology	-	3	Felbamate 1200, TPM 200, OXC 600	No	-	III B	4	Bad	None
8	F	57	Hypothalamic hamartoma, residual focal epilpesy post-surgery	Unknown	2	CBZ 1200, PB 100	No	-	V	4	Bad	None
9	F	24	Focal symptomatic	Right temporal	1	ESL 1600	No	40%	III A	3	Good	None
10	F	30	Ring 20 chromosome disease	-	3	LMT 400, TPM 300, PER 4	Yes	62.5%	II A	2	Good	None

9. Bibliography

[1] Epilepsy: a public health imperative. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

[2] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9. doi: 10.1056/NEJM200002033420503. PMID: 10660394.

[3] Sultana B, Panzini MA, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, Bauer PR, Kwon CS, Jetté N, Josephson CB, Keezer MR. Incidence and Prevalence of Drug-Resistant Epilepsy: A Systematic Review and Meta-analysis. Neurology. 2021 Apr 27;96(17):805-817. doi: 10.1212/WNL.0000000000011839. Epub 2021 Mar 15. PMID: 33722992.

[4] Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018 Dec;59(12):2179-2193. doi: 10.1111/epi.14596. Epub 2018 Nov 13. PMID: 30426482.

[5] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: Epilepsia. 2010 Sep;51(9):1922. PMID: 19889013.

[6] Perucca E, Perucca P, White HS, Wirrell EC. Drug resistance in epilepsy. Lancet Neurol. 2023 Aug;22(8):723-734. doi: 10.1016/S1474-4422(23)00151-5. Epub 2023 Jun 20. PMID: 37352888.

[7] Berg AT. Identification of pharmacoresistant epilepsy. Neurol Clin. 2009 Nov;27(4):1003-1013. doi: 10.1016/j.ncl.2009.06.001. PMID: 19853220; PMCID: PMC2827183.

[8] Beghi E, Beretta S, Carone D, Zanchi C, Bianchi E, Pirovano M, Trentini C, Padovano G, Colombo M, Cereda D, Scanziani S, Giussani G, Gasparini S, Bogliun G, Ferrarese C; PRO-LONG Study Group. Prognostic patterns and predictors in epilepsy: a multicentre study (PRO-LONG). J Neurol Neurosurg Psychiatry. 2019 Nov;90(11):1276-1285. doi: 10.1136/jnnp-2019-320883. Epub 2019 Jun 27. PMID: 31248935.

[9] Ficker DM. Sudden unexplained death and injury in epilepsy. Epilepsia. 2000;41 Suppl 2:S7-12. doi: 10.1111/j.1528-1157.2000.tb01519.x. PMID: 10885735.

[10] Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia. 2005;46 Suppl 11:54-61. doi: 10.1111/j.1528-1167.2005.00411.x. PMID: 16393182.

[11] Orlandi N, Giovannini G, Cioclu MC, Biagioli N, Madrassi L, Vaudano AE, Pugnaghi M, Lattanzi S, Meletti S. Remote seizures and drug-resistant epilepsy after a first status epilepticus in adults. Eur J Neurol. 2024 Apr;31(4):e16177. doi: 10.1111/ene.16177. Epub 2024 Jan 23. PMID: 38258477; PMCID: PMC11235869.

[12] Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand. 2004 Oct;110(4):207-20. doi: 10.1111/j.1600-0404.2004.00324.x. PMID: 15355484.

[13] Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, Guerreiro M, Gwer S, Zuberi SM, Wilmshurst JM, Yozawitz E, Pressler R, Hirsch E, Wiebe S, Cross HJ, Perucca E, Moshé SL, Tinuper P, Auvin S. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022 Jun;63(6):1398-1442. doi: 10.1111/epi.17241. Epub 2022 May 3. PMID: 35503717.

[14] Jiang T, Zhang X, Zhang M, Liu M, Zhu H, Sun Y. Drug-resistant idiopathic generalized epilepsy: A meta-analysis of prevalence and risk factors. Epilepsy Behav. 2023 Sep;146:109364. doi: 10.1016/j.yebeh.2023.109364. Epub 2023 Jul 29. PMID: 37523796.

[15] Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. Epilepsia. 2013 May;54 Suppl 2:19-22. doi: 10.1111/epi.12179. PMID: 23646966.

[16] Wirrell EC, Wong-Kisiel LC, Mandrekar J, Nickels KC. (2013) What predicts enduring intractability in children who appear medically intractable in the first two years after diagnosis. Epilepsia. doi: 10.1111/epi.12169

[17] Abokrysha NT, Taha N, Shamloul R, Elsayed S, Osama W, Hatem G. Clinical, radiological and electrophysiological predictors for drug-resistant epilepsy. Egypt J Neurol Psychiatr Neurosurg. 2023;59(1):44. doi: 10.1186/s41983-023-00647-1. Epub 2023 Mar 29. PMID: 37009468; PMCID: PMC10052302.

[18] Roy PL, Ronquillo LH, Ladino LD, Tellez-Zenteno JF. Risk factors associated with drug resistant focal epilepsy in adults: A case control study. Seizure. 2019 Dec;73:46-50. doi: 10.1016/j.seizure.2019.10.020. Epub 2019 Nov 5. PMID: 31734466.

[19] Arts WF, Geerts AT, Brouwer OF, Boudewyn Peters AC, Stroink H, van Donselaar CA. (1999) The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. Epilepsia 40:726–734

[20] Perucca P, Hesdorffer DC, Gilliam FG. Response to first antiepileptic drug trial predicts health outcome in epilepsy. Epilepsia. 2011 Dec;52(12):2209-15. doi: 10.1111/j.1528-1167.2011.03283.x. Epub 2011 Oct 5. PMID: 21973181.

[21] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol. 2018 Mar 1;75(3):279-286. doi: 10.1001/jamaneurol.2017.3949. Erratum in: JAMA Neurol. 2018 Mar 1;75(3):384. doi: 10.1001/jamaneurol.2018.0018. PMID: 29279892; PMCID: PMC5885858.

[22] Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020 Jul;72(3):606-638. doi: 10.1124/pr.120.019539. PMID: 32540959; PMCID: PMC7300324.

[23] Remy S, Gabriel S, Urban BW, Dietrich D, Lehmann TN, Elger CE, Heinemann U, Beck H. A novel mechanism underlying drug resistance in chronic epilepsy. Ann Neurol. 2003 Apr;53(4):469-79. doi: 10.1002/ana.10473. PMID: 12666114.

[24] Costagliola G, Depietri G, Michev A, Riva A, Foiadelli T, Savasta S, Bonuccelli A, Peroni D, Consolini R, Marseglia GL, Orsini A, Striano P. Targeting Inflammatory Mediators in Epilepsy: A Systematic Review of Its Molecular Basis and Clinical Applications. Front Neurol. 2022 Mar 11;13:741244. doi: 10.3389/fneur.2022.741244. PMID: 35359659; PMCID: PMC8961811.

[25] Vakharia VN, Duncan JS, Witt JA, Elger CE, Staba R, Engel J Jr. Getting the best outcomes from epilepsy surgery. Ann Neurol. 2018 Apr;83(4):676-690. doi: 10.1002/ana.25205. Epub 2018 Apr 10. Erratum in: Ann Neurol. 2018 Jun;83(6):1205. doi: 10.1002/ana.25259. PMID: 29534299; PMCID: PMC5947666.

[26] Luders HO, Engel J, Munari C. General principles. In: Surgical Treatment of the Epilepsies (2nd ed.). (Engel JJ, ed.) New York: Raven Press, 1993:137–153.

[27] Tanriverdi T, Olivier A, Poulin N, Andermann F, Dubeau F. Long-term seizure outcome after corpus callosotomy: a retrospective analysis of 95 patients. J Neurosurg. 2009 Feb;110(2):332-42. doi: 10.3171/2008.3.17570. PMID: 19245287.

[28] Rugg-Gunn F, Miserocchi A, McEvoy A. Epilepsy surgery. Pract Neurol. 2020 Feb;20(1):4-14. doi: 10.1136/practneurol-2019-002192. Epub 2019 Aug 16. PMID: 31420415.

[29] Paglioli E, Palmini A, Paglioli E, et al. Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. Epilepsia 2004; 45: 1383–91.

[30] de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, Duncan JS. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011 Oct 15;378(9800):1388-95. doi: 10.1016/S0140-6736(11)60890-8. PMID: 22000136.

[31] Schmeiser B, Zentner J, Steinhoff BJ, Schulze-Bonhage A, Kogias E, Wendling AS, Hammen T. Functional hemispherectomy is safe and effective in adult patients with epilepsy. Epilepsy Behav. 2017 Dec;77:19-25. doi: 10.1016/j.yebeh.2017.09.021. Epub 2017 Oct 23. PMID: 29073473.

[32] Borowicz-Reutt K, Krawczyk M, Czernia J. Ketogenic Diet in the Treatment of Epilepsy. Nutrients. 2024 Apr 24;16(9):1258. doi: 10.3390/nu16091258. PMID: 38732505; PMCID: PMC11085120.

[33] Lee HF, Chi CS, Liao JH. Use of cooking oils in a 2:1 ratio classical ketogenic diet for intractable pediatric epilepsy: Long-term effectiveness and tolerability. Epilepsy Res. 2018 Nov;147:75-79. doi: 10.1016/j.eplepsyres.2018.09.002. Epub 2018 Sep 12. PMID: 30273790.

[34] Lefevre F, Aronson N. Ketogenic diet for the treatment of refractory epilepsy in children: A systematic review of efficacy. Pediatrics. 2000 Apr;105(4):E46. doi: 10.1542/peds.105.4.e46. PMID: 10742367.

[35] Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. J Child Neurol. 2006 Mar;21(3):193-8. doi: 10.2310/7010.2006.00044. PMID: 16901419.

[36] Schmitz B, Lattanzi S, Vonck K, Kälviäinen R, Nashef L, Ben-Menachem E. Cenobamate in refractory epilepsy: Overview of treatment options and practical considerations. Epilepsia Open. 2023 Dec;8(4):1241-1255. doi: 10.1002/epi4.12830. Epub 2023 Oct 3. PMID: 37743544; PMCID: PMC10690671.

[37] Sharma R, Nakamura M, Neupane C, Jeon BH, Shin H, Melnick SM, et al. Positive allosteric modulation of GABA(a) receptors by a novel antiepileptic drug cenobamate. Eur J Pharmacol. 2020;879:173117.

[38] Krauss GL, Klein P, Brandt C, Lee SK, Milanov I, Milovanovic M, Steinhoff BJ, Kamin M. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020 Jan;19(1):38-48. doi: 10.1016/S1474-4422(19)30399-0. Epub 2019 Nov 14. Erratum in: Lancet Neurol. 2020 Mar;19(3):e3. doi: 10.1016/S1474-4422(20)30038-7. PMID: 31734103.

[39] Chung SS, French JA, Kowalski J, Krauss GL, Lee SK, Maciejowski M, Rosenfeld WE, Sperling MR, Mizne S, Kamin M. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2020 Jun 2;94(22):e2311-e2322. doi: 10.1212/WNL.0000000000009530. Epub 2020 May 14. PMID: 32409485; PMCID: PMC7357293.

[40] Sperling MR, Klein P, Aboumatar S, Gelfand M, Halford JJ, Krauss GL, Rosenfeld WE, Vossler DG, Wechsler R, Borchert L, Kamin M. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia. 2020 Jun;61(6):1099-1108. doi: 10.1111/epi.16525. Epub 2020 May 12. PMID: 32396252; PMCID: PMC7317552.

[41] Gouveia FV, Warsi NM, Suresh H, Matin R, Ibrahim GM. Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation. Neurotherapeutics. 2024 Apr;21(3):e00308. doi: 10.1016/j.neurot.2023.e00308. Epub 2024 Jan 4. PMID: 38177025; PMCID: PMC11103217.

[42] Ryvlin P, Rheims S, Hirsch LJ, Sokolov A, Jehi L. Neuromodulation in epilepsy: state-of-the-art approved therapies. Lancet Neurol. 2021 Dec;20(12):1038-1047. doi: 10.1016/S1474-4422(21)00300-8. Epub 2021 Oct 25. Erratum in: Lancet Neurol. 2021 Dec;20(12):e7. doi: 10.1016/S1474-4422(21)00390-2. PMID: 34710360.

[43] Salanova V, Sperling MR, Gross RE, Irwin CP, Vollhaber JA, Giftakis JE, Fisher RS; SANTÉ Study Group. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021 Jun;62(6):1306-1317. doi: 10.1111/epi.16895. Epub 2021 Apr 8. PMID: 33830503.

[44] Warsi NM, Yan H, Suresh H, Wong SM, Arski ON, Gorodetsky C, Zhang K, Gouveia FV, Ibrahim GM. The anterior and centromedian thalamus: Anatomy, function, and dysfunction in epilepsy. Epilepsy Res. 2022 May;182:106913. doi: 10.1016/j.eplepsyres.2022.106913. Epub 2022 Mar 25. PMID: 35395570.

[45] Dalic LJ, Warren AEL, Bulluss KJ, Thevathasan W, Roten A, Churilov L, Archer JS. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). Ann Neurol. 2022 Feb;91(2):253-267. doi: 10.1002/ana.26280. Epub 2021 Dec 28. Erratum in: Ann Neurol. 2022 Aug;92(2):347. doi: 10.1002/ana.26356. PMID: 34877694.

[46] Middlebrooks EH, Grewal SS, Stead M, Lundstrom BN, Worrell GA, Van Gompel JJ. Differences in functional connectivity profiles as a predictor of response to anterior thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes. Neurosurg Focus 2018 Aug;45(2):E7

[47] Dalic LJ, Warren AEL, Young JC, Thevathasan W, Roten A, Bulluss KJ, Archer JS. Cortex leads the thalamic centromedian nucleus in generalized epileptic discharges in Lennox-Gastaut syndrome. Epilepsia. 2020 Oct;61(10):2214-2223. doi: 10.1111/epi.16657. Epub 2020 Sep 18. PMID: 32944944.

[48] Torres Diaz CV, González-Escamilla G, Ciolac D, Navas García M, Pulido Rivas P, Sola RG, Barbosa A, Pastor J, Vega-Zelaya L, Groppa S. Network Substrates of Centromedian Nucleus Deep Brain Stimulation in Generalized Pharmacoresistant Epilepsy. Neurotherapeutics. 2021 Jul;18(3):1665-1677. doi: 10.1007/s13311-021-01057-y. Epub 2021 Apr 26. PMID: 33904113; PMCID: PMC8608991.

[49] Matias CM, Sharan A, Wu C. Responsive Neurostimulation for the Treatment of Epilepsy. Neurosurg Clin N Am. 2019 Apr;30(2):231-242. doi: 10.1016/j.nec.2018.12.006. Epub 2019 Feb 18. PMID: 30898274.

[50] Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011 Sep 27;77(13):1295-304. doi: 10.1212/WNL.0b013e3182302056. Epub 2011 Sep 14. PMID: 21917777.

[51] Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, Salanova V, Cole AJ, Smith MC, Gwinn RP, Skidmore C, Van Ness PC, Bergey GK, Park YD, Miller I, Geller E, Rutecki PA, Zimmerman R, Spencer DC, Goldman A, Edwards JC, Leiphart JW, Wharen RE, Fessler J, Fountain NB, Worrell GA, Gross RE, Eisenschenk S, Duckrow RB, Hirsch LJ, Bazil C, O'Donovan CA, Sun FT, Courtney TA, Seale CG, Morrell MJ. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014 Mar;55(3):432-41. doi: 10.1111/epi.12534. Epub 2014 Feb 22. PMID: 24621228; PMCID: PMC4233950.

[52] Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, Srinivasan S, Jobst B, Gross RE, Shields DC, Barkley G, Salanova V, Olejniczak P, Cole A, Cash SS, Noe K, Wharen R, Worrell G, Murro AM, Edwards J, Duchowny M, Spencer D, Smith M, Geller E, Gwinn R, Skidmore C, Eisenschenk S, Berg M, Heck C, Van Ness P, Fountain N, Rutecki P, Massey A, O'Donovan C, Labar D, Duckrow RB, Hirsch LJ, Courtney T, Sun FT, Seale CG. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015 Feb 24;84(8):810-7. doi: 10.1212/WNL.0000000000001280. Epub 2015 Jan 23. PMID: 25616485; PMCID: PMC4339127.

[53] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P970003

[54] Giordano F, Zicca A, Barba C, Guerrini R, Genitori L. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. Epilepsia. 2017 Apr;58 Suppl 1:85-90. doi: 10.1111/epi.13678. PMID: 28386925.

[55] Schachter SC, Saper CB. Vagus nerve stimulation. Epilepsia. 1998 Jul;39(7):677-86. doi: 10.1111/j.1528-1157.1998.tb01151.x. PMID: 9670894.

[56] Pérez-Carbonell L, Faulkner H, Higgins S, Koutroumanidis M, Leschziner G. Vagus nerve stimulation for drug-resistant epilepsy. Pract Neurol. 2020 May;20(3):189-198. doi: 10.1136/practneurol-2019-002210. Epub 2019 Dec 31. PMID: 31892545.

[57] Labiner DM, Ahern GL. Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings. Acta Neurol Scand. 2007;115(1):23-33. doi:10.1111/j.1600-0404.2006.00732.x

[58] FisherRS, AfraP, MackenM, BenbadisSR, MinecanDN, BagicA et al (2016) Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance—the U.S. E-37 Trial. Neuromodulation 19:188–195

[59] Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy: a review. Acta Neurol Belg. 2016 Sep;116(3):241-8. doi: 10.1007/s13760-016-0616-3. Epub 2016 Feb 24. PMID: 26908034.

[60] Toffa DH, Touma L, El Meskine T, Bouthillier A, Nguyen DK. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. Seizure. 2020 Dec;83:104-123. doi: 10.1016/j.seizure.2020.09.027. Epub 2020 Oct 10. PMID: 33120323.

[61] Gschliesser V, Högl B, Frauscher B, Brandauer E, Poewe W, Luef G. Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy. Seizure. 2009 Jun;18(5):339-42. doi: 10.1016/j.seizure.2008.12.003. Epub 2009 Jan 10. PMID: 19136281.

[62] Salvadé A, Ryvlin P, Rossetti AO. Impact of vagus nerve stimulation on sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav. 2018 Feb;79:126-129. doi: 10.1016/j.yebeh.2017.10.040. Epub 2017 Dec 26. PMID: 29287215.

[63] Ramsay RE, Uthman BM, Augustinsson LE, et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994;35(3):627-636. doi:10.1111/j.1528-1157.1994.tb02483.x

[64] DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 2000;41(9):1195-1200. doi:10.1111/j.1528-1157.2000.tb00325.x

[65] Fisher RS, Eggleston KS, Wright CW. Vagus nerve stimulation magnet activation for seizures: a critical review. Acta Neurol Scand. 2015 Jan;131(1):1-8. doi: 10.1111/ane.12288. Epub 2014 Aug 22. PMID: 25145652.

[66] HamiltonP, SoryalI, DhahriP, WimalachandraW, LeatA, Hughes D, Toghill N, Hodson J, Sawlani V, Hayton T, Samarasekera S, Bagary M, McCorryD,Chelvarajah R (2018). Clinical outcomes of VNS therapy with AspireSR(R) (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure 58:120–126

[67] Lo WB, Chevill B, Philip S, Agrawal S, Walsh AR. Seizure improvement following vagus nerve stimulator (VNS) battery change with cardiac-based seizure detection automatic stimulation (AutoStim): early experience in a regional paediatric unit. Childs Nerv Syst. 2021 Apr;37(4):1237-1241. doi: 10.1007/s00381-020-04962-3. Epub 2020 Nov 10. PMID: 33174154.

[68] Morris GL 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology. 1999 Nov 10;53(8):1731-5. doi: 10.1212/wnl.53.8.1731. Erratum in: Neurology 2000 Apr 25;54(8):1712. PMID: 10563620.

[69] Kawai K, Tanaka T, Baba H, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord. 2017;19(3):327-338. doi:10.1684/epd.2017.0929

[70] Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg. 2011 Dec;115(6):1248-55. doi: 10.3171/2011.7.JNS11977. Epub 2011 Aug 12. PMID: 21838505.

[71] Ryvlin P, So EL, Gordon CM, Hesdorffer DC, Sperling MR, Devinsky O, Bunker MT, Olin B, Friedman D. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia. 2018 Mar;59(3):562-572. doi: 10.1111/epi.14002. Epub 2018 Jan 16. PMID: 29336017.

[72] Boon P, Moors I, De Herdt V, Vonck K. Vagus nerve stimulation and cognition. Seizure. 2006 Jun;15(4):259-63. doi: 10.1016/j.seizure.2006.02.014. Epub 2006 May 2. PMID: 16651013.

[73] Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci. 1999 Jan;2(1):94-8. doi: 10.1038/4600. PMID: 10195186.

[74] Puteikis K, Jasionis A, Jasionytė G, Mameniškienė R. Long-term effects of vagus nerve stimulation therapy on cognitive functioning in patients with drug-resistant epilepsy. Neurol Sci. 2024 May;45(5):2245-2252. doi: 10.1007/s10072-023-07202-z. Epub 2023 Nov 20. PMID: 37981620.

[75] Chan AY, Rolston JD, Rao VR, Chang EF. Effect of neurostimulation on cognition and mood in refractory epilepsy. Epilepsia Open. 2018 Feb 13;3(1):18-29. doi: 10.1002/epi4.12100. PMID: 29588984; PMCID: PMC5839311.

[76] Klinkenberg S, Majoie HJ, van der Heijden MM, Rijkers K, Leenen L, Aldenkamp AP. Vagus nerve stimulation has a positive effect on mood in patients with refractory epilepsy. Clin Neurol Neurosurg. 2012 May;114(4):336-40. doi: 10.1016/j.clineuro.2011.11.016. Epub 2011 Nov 30. PMID: 22130047.

[77] Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P, Zamponi N, Aguglia U, Wagner L, Minotti L, Stefan H, Boon P, Sadler M, Benna P, Raman P, Perucca E. The long-term effect of vagus nerve stimulation on quality

of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014 Jun;55(6):893-900. doi: 10.1111/epi.12611. Epub 2014 Apr 22. Erratum in: Epilepsia. 2014 Sep;55(9):1476. Erratum in: Epilepsia. 2015 Jun;56(6):983. doi: 10.1111/epi.12949. PMID: 24754318; PMCID: PMC4283995.

[78] Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav. 2017;66:4-9. doi:10.1016/j.yebeh.2016.10.005

[79] Carron R, Roncon P, Lagarde S, Dibué M, Zanello M, Bartolomei F. Latest Views on the Mechanisms of Action of Surgically Implanted Cervical Vagal Nerve Stimulation in Epilepsy. Neuromodulation. 2023 Apr;26(3):498-506. doi: 10.1016/j.neurom.2022.08.447. Epub 2022 Sep 2. PMID: 36064522.

[80] Hammond EJ, Uthman BM, Wilder BJ, et al. Neurochemical effects of vagus nerve stimulation in humans. Brain Res. 1992;583:300–303. https://doi.org/10.1016/s0006-8993(10)80038-1

[81] Henry TR, Bakay RAE, Pennell PB, Epstein CM, Votaw JR. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. Prolonged effects at high and low levels of stimulation. Epilepsia. 2004;45:1064–1070. https://doi.org/10.1111/j.0013-9580.2004.03104.x

[82] Di Lazzaro V, Oliviero A, Pilato F, et al. Effects of vagus nerve stimulation on cortical excitability in epileptic patients. Neurology. 2004;62(12):2310-2312. doi:10.1212/01.wnl.0000131743.45131.ae

[83] Capone F, Assenza G, Di Pino G, et al. The effect of transcutaneous vagus nerve stimulation on cortical excitability. J Neural Transm (Vienna). 2015;122(5):679-685. doi:10.1007/s00702-014-1299-7

[84] Kuba R, Guzaninová M, Brázdil M, Novák Z, Chrastina J, Rektor I. Effect of vagal nerve stimulation on interictal epileptiform discharges: a scalp EEG study. Epilepsia. 2002 Oct;43(10):1181-8. doi: 10.1046/j.1528-1157.2002.08202.x. PMID: 12366734.

[85] Hallböök T, Lundgren J, Blennow G, Strömblad LG, Rosén I. Long term effects on epileptiform activity with vagus nerve stimulation in children. Seizure. 2005 Dec;14(8):527-33. doi: 10.1016/j.seizure.2005.07.004. Epub 2005 Aug 10. PMID: 16098769.

[86] Marrosu F, Santoni F, Puligheddu M, Barberini L, Maleci A, Ennas F, Mascia M, Zanetti G, Tuveri A, Biggio G. Increase in 20-50 Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. Clin Neurophysiol. 2005 Sep;116(9):2026-36. doi: 10.1016/j.clinph.2005.06.015. PMID: 16055378.

[87] Ernst LD, Steffan PJ, Srikanth P, Wiedrick J, Spencer DC, Datta P, Joseph NM, Wernovsky M, Becker DA. Electrocorticography Analysis in Patients With Dual Neurostimulators Supports Desynchronization as a Mechanism of Action for Acute Vagal Nerve Stimulator Stimulation. J Clin Neurophysiol. 2023 Jan 1;40(1):37-44. doi: 10.1097/WNP.0000000000000847. Epub 2021 Apr 7. PMID: 34009846.

[88] Brázdil M, Doležalová I, Koritáková E, Chládek J, Roman R, Pail M, Jurák P, Shaw DJ, Chrastina J. EEG Reactivity Predicts Individual Efficacy of Vagal Nerve Stimulation in Intractable Epileptics. Front Neurol. 2019 May 2;10:392. doi: 10.3389/fneur.2019.00392. PMID: 31118916; PMCID: PMC6507513.

[89] Bastos AM, Schoffelen JM. A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. Front Syst Neurosci. 2016 Jan 8;9:175. doi: 10.3389/fnsys.2015.00175. PMID: 26778976; PMCID: PMC4705224.

[90] Fraschini M, Puligheddu M, Demuru M, Polizzi L, Maleci A, Tamburini G, Congia S, Bortolato M, Marrosu F. VNS induced desynchronization in gamma bands correlates with positive clinical outcome in temporal lobe pharmacoresistant epilepsy. Neurosci Lett. 2013 Mar 1;536:14-8. doi: 10.1016/j.neulet.2012.12.044. Epub 2013 Jan 15. PMID: 23333601.

[91] Bodin C, Aubert S, Daquin G, Carron R, Scavarda D, McGonigal A, Bartolomei F. Responders to vagus nerve stimulation (VNS) in refractory epilepsy have reduced interictal cortical synchronicity on scalp EEG. Epilepsy Res. 2015 Jul;113:98-103. doi: 10.1016/j.eplepsyres.2015.03.018. Epub 2015 Apr 9. PMID: 25986196.

[92] Sangare A, Marchi A, Pruvost-Robieux E, Soufflet C, Crepon B, Ramdani C, Chassoux F, Turak B, Landre E, Gavaret M. The Effectiveness of Vagus Nerve Stimulation in Drug-Resistant Epilepsy Correlates with Vagus Nerve Stimulation-Induced Electroencephalography Desynchronization. Brain Connect. 2020 Dec;10(10):566-577. doi: 10.1089/brain.2020.0798. Epub 2020 Nov 18. PMID: 33073582; PMCID: PMC7757623.

[93] Bartolomei F, Bonini F, Vidal E, Trébuchon A, Lagarde S, Lambert I, McGonigal A, Scavarda D, Carron R, Benar CG. How does vagal nerve stimulation (VNS) change EEG brain functional connectivity? Epilepsy Res. 2016 Oct;126:141-6. doi: 10.1016/j.eplepsyres.2016.06.008. Epub 2016 Jul 29. PMID: 27497814.

[94] Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521. doi:10.1111/epi.13709

[95] McHugh JC, Singh HW, Phillips J, Murphy K, Doherty CP, Delanty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia. 2007;48(2):375-378. doi:10.1111/j.1528-1167.2006.00931.x

[96] Berk M, Ng F, Dodd S, et al. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. J Eval Clin Pract. 2008;14(6):979-983. doi:10.1111/j.1365-2753.2007.00921.x

[97] Sinha SR, Sullivan L, Sabau D, et al. American Clinical Neurophysiology Society Guideline 1: Minimum Technical Requirements for Performing Clinical Electroencephalography [published correction appears in J Clin Neurophysiol. 2021 May 1;38(3):e16]. J Clin Neurophysiol. 2016;33(4):303-307. doi:10.1097/WNP.0000000000000308

[98] Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci. 2011;2011:879716. doi:10.1155/2011/879716

[99] Whitham EM, Pope KJ, Fitzgibbon SP, et al. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. Clin Neurophysiol. 2007;118(8):1877-1888. doi:10.1016/j.clinph.2007.04.027

[100] Novitskaya Y, Dümpelmann M, Schulze-Bonhage A. Physiological and pathological neuronal connectivity in the living human brain based on intracranial EEG signals: the current state of research. Front Netw Physiol. 2023 Nov 30;3:1297345. doi: 10.3389/fnetp.2023.1297345. PMID: 38107334; PMCID: PMC10723837

[101] Khambhati, A. N., Davis, K. A., Lucas, T. H., Litt, B. & Bassett, D. S. Virtual cortical resection reveals push-pull network control preceding seizure evolution. Neuron 91, 1170–1182 (2016)

[102] Korzeniewska, A., Cervenka, M. C., Jouny, C. C., Perilla, J. R., Harezlak, J., Bergey, G. K., et al. (2014). Ictal propagation of high frequency activity is recapitulated in interictal recordings: effective connectivity of epileptogenic networks recorded with intracranial EEG. Neuroimage 101, 96–113. doi:10.1016/j.neuroimage.2014.06.07

[103] Matarrese MAG, Loppini A, Fabbri L, Tamilia E, Perry MS, Madsen JR, Bolton J, Stone SSD, Pearl PL, Filippi S, Papadelis C. Spike propagation mapping reveals effective connectivity and predicts surgical outcome in epilepsy. Brain. 2023 Sep 1;146(9):3898-3912. doi: 10.1093/brain/awad118. PMID: 37018068; PMCID: PMC10473571.

[103] Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol. 2001;18(5):434-441. doi:10.1097/00004691-200109000-00008

[104] Kuba R, Guzaninová M, Brázdil M, Novák Z, Chrastina J, Rektor I. Effect of vagal nerve stimulation on interictal epileptiform discharges: a scalp EEG study. Epilepsia. 2002;43(10):1181-1188. doi:10.1046/j.1528-1157.2002.08202.x

[105] Zhu J, Xu C, Zhang X, et al. The thalamus-precentral gyrus functional connectivity changes in epilepsy patients following vagal nerve stimulation. Neurosci Lett. 2021;751:135815. doi:10.1016/j.neulet.2021.135815

[106] Alexander GM, Huang YZ, Soderblom EJ, He XP, Moseley MA, McNamara JO. Vagal nerve stimulation modifies neuronal activity and the proteome of excitatory synapses of amygdala/piriform cortex. J Neurochem. 2017 Feb;140(4):629-644. doi: 10.1111/jnc.13931. Epub 2017 Feb 3. PMID: 27973753; PMCID: PMC6537100.

[107] Lanzone J, Boscarino M, Tufo T, Di Lorenzo G, Ricci L, Colicchio G, Di Lazzaro V, Tombini M, Assenza G. Vagal nerve stimulation cycles alter EEG connectivity in drug-resistant epileptic patients: A study with graph theory metrics. Clin Neurophysiol. 2022 Oct;142:59-67. doi: 10.1016/j.clinph.2022.07.503. Epub 2022 Aug 5. PMID: 35970060.