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Electrodiagnostic artifacts due to neurostimulation devices for drug resistant epilepsy

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ABSTRACT

Background: Neurostimulation devices including vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) are approved therapeutic options for drug resistant epilepsy (DRE). As these devices are increasingly used in clinical practice, it is of importance to recognize their artifacts in electrodiagnostic studies.

Methods: This is a retrospective study of all adult DRE patients treated with neuromodulation devices for epilepsy at our center between 2012 and 2021. Available EEGs were reviewed for neurostimulator-related artifacts.

Results: Fifty-two patients were included. 37% of patients had neurostimulation related electrophysiological artifacts (20% of VNS, 75% of DBS, all patients with dual VNS-DBS treatment, and in the single patient with RNS). Artifacts were intermittent, appearing most commonly simultaenously in the EEG and ECG. VNS artifacts were monomorphic appearing mostly in the lower temporal EEG electrodes, whereas DBS artifacts were with variable morphology, amplitude, and scalp distribution. At times, the artifacts resembled electrographic seizures in the EEG and mimicked extrasystole or asystole in the ECG.

Conclusions: With the increasing use of neurostimulation treatments for DRE, and the need for frequent electrodiagnostic studies in this patient population, it is important clinicians recognize these electrophysiological findings as artifacts, to avoid misdiagnosis and facilitate accurate interpretation.

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Introduction

Nearly-one-third of people with epilepsy do not respond adequately to anti-seizure medications (ASMs) and suffer from drug resistant epilepsy (DRE). In this patient population, surgical resection of the epileptogenic tissue is the most efficacious therapy, however, majority of DRE patients undergoing pre-surgical evaluation are not eventually found eligible for surgical resection. Patients with DRE who are inoperable, or have not achieved adequate seizure control following surgery, are being increasingly treated with approved palliative neuromodulatory treatments such as vagal nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) [1–3].

DRE patients need frequent and detailed neurodiagnostic studies such as short- and long-term EEG and ECG recordings.

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These tests are prone to artifacts which could arise from physiological sources such as eye or muscle movements, or from external electromagnetic sources [4,5]. Neurostimulation devices could introduce artifacts that originate from the electrical pulse generator, typically implanted in the chest, or from the electrical current passing through the stimulation electrodes. These artifacts are influenced by the polarity of electric impulses and stimulation parameters including pulse amplitude and width, and in the case of ECG, proximity, or orientation of electrical source relative to ECG leads [6]. There are reports of EEG and ECG artifacts originating from patients with movement disorders treated with DBS [7,8], however, there are only a few reports regarding the various neurostimulations artifacts in epilepsy patients [4,9–15].

As neuromodulatory devices are gaining more use in epilepsy practice, we aimed to systematically study the occurrence of these artifacts in a relatively large cohort of DRE patients, and to describe the various configuration of these artifacts appearing in EEG and ECG recordings.







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Table 1

Demographics and clinical characteristics for DRE patients with neurostimulation devices.

Characteristics	Values
VNS group, N = 39	
Gender	15 Female, 24 Male
Epilepsy syndrome	34 Focal, 5
	Generalized
Average age at seizure onset (years)	11
Average current number of ASMs	3.4
Brain MRI	18 Lesional, 21
	Normal
Prior resective surgery, N (%)	10 (25.6 %)
Average disease duration at VNS implantation (years)	31
Average reduction of disabling seizures 1 year post	24.5 %
implantation	
-	
DBS group, $N = 8$	
Gender	5 Female, 3 Male
Epilepsy syndrome	8 Focal, 0
	Generalized
Average age at seizure onset (years)	16.8
Average current number of ASMs	3
Brain MRI	7 Lesional, 1
	Normal
Prior resective surgery, N (%)	2 (25 %)
Prior VNS (N, %)	7 (87.5 %)
Average disease duration at DBS implantation (years)	18.4
Average reduction of disabling seizures 1 year post	34.6 %
implantation	
Dual (VNS-DBS) group, N = 4	
Gender	1 Female, 3 Male
Epilepsy syndrome (N)	4 Focal. 0
	Generalized
Average age at seizure onset (years)	5 5
Average current number of ASMs	4
Brain MRI	2 Lesional, 2
	Normal
Prior resective surgery, N (%)	1 (25 %)
Prior VNS (N. %)	4 (100 %)
Average disease duration at DBS implantation (years)	21
Average reduction of disabling seizures 1 year post	515%
implantation	51,5 /0

DRE: drug resistant epilepsy, VNS: vagal nerve stimulation, DBS: deep brain stimulation, ASMs: antiseizure medications, MRI: magnetic resonance imaging.

Methods

This single-center retrospective study of patients treated at Tel-Aviv Sourasky Medical Center (TLVMC), from January 2012 until August 2021 was approved by the ethics committee of TLVMC.

We included adult DRE patients treated with neuromodulatory devices for epilepsy (VNS, DBS or RNS), and whom had an available standard or prolonged EEG recording with ECG traces while being treated with neurostimulation. Prior to stimulator implantations, all patients underwent assessment by a multi-disciplinary epilepsy surgery team, consisting of neurologists, neurosurgeons, neuropsychologists, and neuroimaging specialists. Presurgical work-up included video–EEG monitoring, structural and functional neuroimaging, and neuropsychological assessment. Demographic and clinical data including clinical history, response to stimulation and stimulation parameters were collected from patient charts.

Neurostimulation devices were implanted according to accepted and widely used surgical techniques: VNS (Models: Demipulse 103/ Aspire SR 106/ SenTiva 1000; Livanova, Houston, TX, USA) implantation was done microsurgically, by applying a coil electrode around the left vagus nerve, connected to an internal pulse generator implanted subcutaneously in the left chest wall [16]. DBS (ActivaTM PC model 3389 and Percept PC Model B 35200: Medtronic, Minneapolis, MN, USA) electrodes were stereotactically implanted under general anesthesia in the anterior thalamic nuclei (ATN) bilaterally through a trans- or extra-ventricular trajectories and were connected to an internal pulse generator implanted subcutaneously in the right upper chest [17]. Electrode contacts localizations within the ATN were confirmed by post-op MRI. One DRE patient was implanted with RNS (Model RNS-300 M, NeuroPace, Mountain View, CA, USA) in the United States (RNS is not available in Israel), with two subdural strip electrodes targeting the left motor cortex.

VNS initial stimulation parameters were 0.25–0.5 mA output current, 30 Hz signal frequency, 250–500 µs pulse width and 10 % duty cycle. DBS initial parameters were 5 V monopolar stimulation potential, 145 Hz stimulation frequency, 90 µs pulse width, 1 min "on" and 5 min "off" cycling. RNS initial parameters were set to 1.5 mA output current, 140 Hz signal frequency, 160 µs pulse

Table 2

Neurostimulators parameters and distriburtion of electrodiagnostic artifacts, in the different neurostimulation modalities.

Neurostimulator device	Stimulation parameters		Electrodiagnostic artifacts distribution in EEG and/or ECG
VNS	output current	duty cycle	
	1.75 mA	10-25%	EEG and ECG (3 cases)
	1.875 mA	51%	ECG (1 case)
	2 mA	25-35%	EEG and ECG (3 cases)
	2.5 mA	35%	EEG (1 case)
DBS	stimulation potential	ON:OFF minutes cycling	
	5.6V	1:5	EEG and ECG (1 case)
	6.5V	1:3	EEG and ECG (2 cases)
	6.5V	1:5	ECG
	7V	1:3	ECG
	7V	1:3	EEG and ECG (1 case)
Dual (VNS-DBS)	VNS (output current, duty	DBS (stimulation potential, ON:OFF minutes	
. ,	cycle)	cycling)	
	1.75mA, 16%	5.5V, 1:3	VNS & DBS induced EEG and ECG artifacts(1 case)
	2.25mA, 35%	7V, 1:3	DBS alone induced EEG and ECG artifacts (1 case)
	1.75mA, 25%	6.5V, 1:5	VNS induce EEG artifact, DBS induced ECG artifact(1 case)
	1.75mA, 35%	7V, 1:3	VNS induced EEG artifact, DBS induced EEG and ECG artifacts (1 case)

DRE: drug resistant epilepsy, VNS: vagus nerve stimulation, EEG: electroencephalography, ECG: electrocardiography, DBS: deep brain stimulation, ASMs: antiseizure medications, MRI: magnetic resonance imaging.



Fig. 1. Vagal nerve stimulation induces EEG and ECG artifacts. Scalp EEG extended longitudinal bipolar montage, sensitivity 7 μV/mm, LF 1 Hz, HF 70 Hz, notch 50 Hz, paper speed 30 mm/s. **A.** A burst of 30 Hz low-voltage sharply contoured waves in the ECG channel, corresponding to the stimulating frequency of VNS. **B.** A burst of 30 Hz low-voltage sharply contoured waves in the right mid-posterior temporal electrodes, coinciding with an electro-clinical seizure.

width and 200 ms burst duration. These stimulation parameters were gradually increased according to the patient's clinical status in order to elicit the highest seizure control and minimal stimulation-related adverse effects. Stimulation parameters in the study cohort for VNS were 1.75–2.5 mA output current, 30 Hz signal frequency, 500 µs pulse width and 10 %–35 % duty cycle, for DBS were 5 V–7 V monopolar stimulation potential, 145 Hz stimulation frequency, 90 µs pulse width, 1 min "on" and 3–5 min "off" cycling, and for RNS were 4.5 mA output current, 200 Hz signal frequency, 160 µs pulse width and 100 ms burst duration.

Patients underwent standard EEG recordings (awake, sleep or both) and/or video-EEG monitoring all with a single bipolar ECG channel. EEGs were recorded according to standard technique, with application of 19–25 AgCl electrodes according to the 10–20 and 10–10 international electrode systems. Electrodes impedances were kept below 5K Ω . All EEG studies were recorded using modular EEG systems (Natus, Middleton, WI, USA), with a sampling rate of 265–512 Hz. Traces were reviewed in longitudinal bipolar montage, using 1 Hz low frequency (LF), 70 Hz high frequency (HF), and 50 Hz notch filters. By disabling the HF filter, high frequency artifacts could be verified.

Standard EEGs and Video-EEG recordings with ECG traces were independently visually reviewed by two Epileptologists (TA and

FF) for the occurrence of stimulation-related artifacts in the EEG and ECG channels. The artifacts were finally labeled only if consensus was reached between the reviewers, otherwise the artifacts were not scored.

Results

One hundred and twenty-nine adult patients were treated with neurostimulation devices during the study period. Of these, 52 patients had available EEGs and were finally included in the study: thirty-nine patients treated with VNS, eight patients treated with DBS, four patients with dual VNS-DBS treatment, and one patient with RNS. Patients' clinical characteristics are shown in Table 1. Nineteen patients (37 %) had neurostimulation related artifacts. These artifacts were intermittent, with a similar frequency or frequency-harmonics of the stimulating frequency and with a duration corresponding to the stimulation period (30 s in VNS, 60 s in DBS and 100 ms in RNS).

VNS treated patients: Eight of 39 patients (20.5 %) had artifacts including 6 patients with artifacts both on EEG and ECG, one patient had an artifact visible only on ECG (Fig. 1) and one patient had an artifact visible only on EEG. All VNS artifacts were seen as low amplitude monomorphic 30 Hz transients in all electrodiag-

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**Fig. 2. Deep Brain stimulation induces EEG and ECG artifacts.** Scalp EEG extended longitudinal bipolar montage, sensitivity 7 μV/mm, LF 1 Hz, HF 70 Hz, notch 50 Hz, paper speed 30 mm/s. **A.** DBS induces high-frequency and focal seizure-like artifacts and in the temporal EEG channels bilaterally (box and arrowhead) and asystole-like artifact at the ECG channel (arrow). **B.** DBS induces 145 Hz low voltage fast frequency artifact in P8 channel (box and arrowhead) at the EEG channels and large amplitude sharply contoured artifact at the ECG channel (arrow). **C.** DBS induces diffuse 145 Hz artifact (box and arrowhead) at the EEG channels and a burst of irregular extrasystole combined with low-amplitude high-frequency artifact at the ECG channel, combined with low amplitude QRS complexes (arrow).

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nostic recordings, and were not related to output current of the VNS. In all but one patient, the artifacts were maximal in the low temporal EEG electrodes, and in the remaining patient the artifact was diffuse. All three patients who underwent repeated EEGs had artifacts recurring in all studies and were not related to change of VNS stimulation parameters.

DBS treated patients: Six of 8 patients (75 %) had artifacts, in 4 patients appearing both on EEG and ECG (Fig. 2A–C), and in 2 patients on ECG trace only. All EEG artifacts were with frequency of 145 Hz, with variable morphology and spatial distribution. In three patients the artifacts were diffuse, and in one patient the artifact was isolated to the lower temporal regions. ECG artifacts were more variable: three patients demonstrating large amplitude sharply contoured artifact, one patient with asystole-like ECG artifact and in the last two patients it was seen as a burst of irregular extrasystoles combined with low-amplitude high-frequency artifact and low amplitude QRS complexes. Two DBS patients had recurrent standard EEGs, in one patient artifacts were consistent

after increasing the stimulation voltage from 6.5 V to 7 V. *Dual VNS-DBS treated patients*: All 4 patients had stimulation artifacts: three patients with differential VNS and DBS artifacts appearing both on EEG and/or ECG (Figs. 3 and 4), and in one patient, only DBS induced both EEG and ECG artifacts without evi-

across the studies, and in the other patient the artifact appeared

dence for VNS induced artifacts. DBS EEG artifacts were of 145 Hz and diffusely distributed, with variable ECG artifacts, whereas VNS artifacts were of 30 Hz, and were seen both on EEG and/ or ECG.

*RNS treated patient* had an artifact mimicking poly-sharp-wave complex maximal at centro-temporal regions bilaterally in EEG channels.

It is of clinical interest that in few cases, the artifacts in the EEG were thought at first to represent electrographic seizures leading to discussions and dilemmas among the medical team. Conversely, in 7 cases these EEG artifacts co-occured with real focal seizures further complicating the clinical interpretation (example in Fig. 1B). In two cases the artifacts in the ECG were initially misin-



**Fig. 3. Dual VNS-DBS treatment induces EEG and ECG artifacts.** Scalp EEG extended longitudinal bipolar montage, sensitivity 7 μV/mm, LF 1 Hz, HF 70 Hz, notch 50 Hz, paper speed 30 mm/s. DBS induces diffuse 145 Hz artifact (box and arrowhead) at the EEG channels and a burst of irregular extrasystole combined with low-amplitude high-frequency artifact at the ECG channel, combined with low amplitude QRS complexes (arrow).

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**Fig. 4. Dual VNS-DBS treatment induces EEG and ECG artifacts.** Scalp EEG extended longitudinal bipolar montage, sensitivity 7 μV/mm, LF 1 Hz, HF 70 Hz, notch 50 Hz, paper speed 30 mm/s. DBS induces 145 Hz large-amplitude high-frequency sharply contoured ECG artifact (arrow), and diffuse EEG artifact (arrowhead) corresponding to the DBS stimulating frequency in dual treatment.

terpreted as cardiac conduction abnormalities resulting in unnecessary cardiological consultations. Overall, there was no clear correlation between the stimulation parameters and the ocuurence of artifacts in the electrodiagnostic recordings (Table 2).

# Discussion

In this retrospective descriptive study cohort of adult DRE patients treated with neurostimulation devices, we found that over one-third of patients had artifacts on EEG and/or ECG recordings. These artifacts were stereotypical and intermittent, and at times mimicking seizure activity in the EEG or cardiac rhythm abnormalities such as arrhythmias or asystole in the ECG, further stressing out the clinical need to accurately identufynig these artifacts. The ECG findings are especially important considering that the differential diagnosis of loss of consciousness in epilepsy patients includes seizures as well as cardiac arrhythmias [18,19].

Previously reported VNS-related EEG artifacts include diffuse high-amplitude, sharp, periodic waveforms persisting during the phase of stimulation [9,20], and have been reported as mimicking ictal changes [11]. In our cohonrt, these artifacts appeared with monomorphic morphology, often localized to the temporal head regions, further mimicking pathological epileptiform activity.

DBS-related artifacts have also been previously reported in the EEGs of movement disorders and epilepsy patients [11–14,21–23], as well as in ECG recordings of movement disorders patients. Some of these artifacts mimicking ECG rhythm abnormalities, including a case of resuscitation performed on a Parkinson's patient with DBS due to artifact masquerading as ventricular fibrillation [24], a case of delayed diagnosis of acute myocardial event in a patient with dystonia [25], and artifacts mimicking heart rate abnormalities including atrial and ventricular fibrillation [6,22]. Our study of DRE patients, a patient group that requires frequent electrodiagnostic tests, as well as the intermittent nature of neurostimulation therapies for DRE, stresses out even more the importance of acknowledging these episodic transients as artifacts. Furthermore, the common use of monopolar stimulation for epilepsy rather than bipolar stimulation in DBS for movement disorders increase the chance for eliciting artifacts in the ECG [7,8,15,26].

Dual-device neurostmulation in epilepsy including VNS-DBS and VNS-RNS are becoming increasingly used in DRE patients in recent years [27], and a small group of 4 patients in our cohort were treated with VNS-DBS. The electrodiagnostic artifacts over the EEG and/ or ECG traces appeared with similar pattern and distribution to monomodular neurostimulation as described previously.

Stimulation artifacts in the ECG are of particular importance to the general medical practitioners, as these could potentially be reviewed, unlike in the setting of EEG, by healthcare personnel without EEG training. Incorrect analysis of heart rhythms due to external artifacts is a well-known issue that could result in unnecessary tests and interventions on the one hand, or to mask underlying ECG abnormalities causing a delay in diagnosis of acute cardiac events, on the other.

Our study's main limitation is that ECG artifacts were in single ECG channel of standard EEG, and not in full 12-lead ECG recordings. One the other hand, standard ECG recordings are significantly shorter than EEG recordings (>30mins), and therefore could miss the intermittent neurostimulator artifacts.

In conclusion, neurostimulator-induced artifacts appeared in over one-third of our DRE patients treated with devices. As neuromodulatory treatments becomes more prevalent in epilepsy practices, clinicians should be aware of neurostimulator-elicited EEG and ECG artifact in order to accurately interpret findings and avoid unnecessary diagnostics and treatments.

#### **Ethical statement**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

#### **Declaration of Competing Interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Fahoum has served on scientific advisory boards and received speaker honoraria from LivaNova, as well as speaker honoraria from Medtronic. Dr. Strauss has received speaker honoraria from Medtronic. Dr. Arafat and Dr. Miron have no conflicts of interest.

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