Published in final edited form as:

Epilepsy Behav. 2020 November ; 112: 107327. doi:10.1016/j.yebeh.2020.107327.

RNS modifications to eliminate stimulation-triggered signs or symptoms (STS): Case series and practical guide

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Abstract

Responsive neurostimulation (RNS) for intractable epilepsy involves placement of electrodes onto or into the brain that detect seizure activity and then deliver a current to abort a seizure before it spreads. Successful RNS treatment can deliver hundreds of stimulations per day, which are generally unnoticeable to patients. Uncommonly, RNS electrodes may result in stimulation of brain regions or peripheral structures that causes uncomfortable sensory or motor effects, a phenomenon we refer to as stimulation-triggered signs or symptoms (STS). Occurrence of STS may limit the ability to use RNS to full capacity to reduce seizures. In this case series, we describe STS in six out of 58 (10.3%) RNS patients at our institution. To eliminate or minimize STS, we developed a protocol for modification of RNS parameters. Modifying RNS stimulation was associated with reduced STS in all six patients, five had adjustment of stimulation settings, one of lead position. Five out of six patients were able to undergo further optimization of RNS for improved seizure control after reduction of symptoms. One patient had recurrent STS that prevented further increase of RNS stimulation current. This study may help other medical teams in identifying and reducing STS in patients with epilepsy receiving RNS devices.

Keywords

Responsive neurostimulation; RNS adverse effects; Stimulation-triggered signs or symptoms; RNS stimulation modification; Intractable epilepsy

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Declaration of competing interest

Authors do not have a conflict of interest.

1. Introduction

Neurostimulation devices can reduce or stop seizures in drug-resistant epilepsy. Responsive neurostimulation (RNS) treatment provides closed-loop seizure detection and resultant electrical brain stimulation with four-contact electrodes placed directly onto or into the brain with the goal of interrupting seizure activity before it spreads [1–5]. RNS implantation has been shown to produce a lasting reduction in seizure burden for about two-thirds of patients and may even result in seizure freedom for one year or longer in 13–15% of patients, with shorter periods of seizure freedom seen in 23–45% of patients [1–5]. Patients with epilepsy implanted with RNS devices also demonstrate improvements in neurocognitive function and report increased quality of life [3,6,7].

RNS placement is regarded as safe and effective with therapeutic charge densities of 2–6 $\mu\text{C}/\text{cm}^2$ [2,4]. Prior to RNS implantation, intracranial monitoring (ICM) is often performed to identify seizure foci. In previous trials, 46% of patients with mesial temporal epilepsy and 82% of those with neocortical epilepsy had undergone ICM [2,4]. At the time of ICM, bedside cortical mapping can be done to ensure that stimulation of seizure foci or neighboring cortex does not produce undesired effects. Reports of serious adverse events associated with RNS have focused on complications related to surgery, infections, hemorrhage, lead damage, and premature battery depletion [1–5,8–10]. Only rare instances when RNS implantation or stimulation produced adverse effects such as photopsia (4.7–14.4%), muscle twitch (3.1%), and dizziness (2.6%) have been reported [2–4]. Photopsia was explicitly associated with stimulation at occipital electrodes [2] or mesial temporal depth electrodes [4]; for other symptoms, duration and timing in relationship to stimulation was not detailed. All patients improved spontaneously or with – unspecified – modifications to stimulation parameters. Of note, RNS stimulation used for seizure foci located in motor and language cortex did not cause involuntary movement or dysphasia [2]. It has been concluded from these studies that RNS stimulation is generally not noticeable to patients — a desirable feature because successful RNS treatment is accompanied by several hundred stimulations per day [2].

As increasing numbers of patients are treated with RNS, additional complications might be recognized. We identified six patients at our institution who had sensory or motor effects directly related to RNS stimulation pulses, phenomena we refer to as stimulation-triggered signs or symptoms (STS). Here, we aim to document the patient experience, location of leads, and the successful modification of lead position, stimulation settings, and montages to eliminate STS. We also provide a practical guide to avoid and address STS.

2. Material and methods

2.1. Patients

Approval from the institutional review board was obtained to perform a retrospective case series analysis on RNS patients with STS treated at the University of Colorado Epilepsy Clinic. Data were extracted from charts, including age, age at epilepsy onset, results of ICM and cortical mapping, location of RNS leads, number and types of leads placed, STS clinical

manifestations, changes made to RNS stimulation settings, and any effect on seizure frequency. Descriptive statistics were employed.

2.2. Definition and adjustment of RNS stimulus parameters

Stimulation-triggered signs or symptoms were defined as recurrent sensory or motor phenomena experienced by patients directly and reliably associated with each RNS stimulation pulse at specific electrode leads or contacts, not explained by epileptiform activity seen on the corresponding electrocorticogram. Stimulation-triggered signs or symptoms were elicited either under anesthesia during RNS placement in the operating room (OR) or during postimplantation clinic appointments. We developed a detailed protocol to eliminate STS, as described below.

2.2.1. Set-up for characterization of STS—In the OR, RNS electrodes are tested under anesthesia, and the neurologist observes for motor signs related to electrode activation. During STS testing, the patient should not be on paralytics or inhalational anesthetics since both suppress motor responses, but rather total intravenous anesthesia. In clinic, the patient can assist in identification of motor or sensory STS. The patient should be blinded to current delivery when testing new settings by either closing their eyes or turning the monitor away from patient view. The electrocorticogram is monitored during this process to rule out that interictal discharges or seizures are causing STS.

In the following paragraphs, RNS settings during the testing for STS will be described by using the usual shorthand for RNS montages in which “+”, “−”, or “0” are used for the polarity of a contact. Two leads are represented by two sets of brackets containing four symbols. Brackets containing a single symbol represent the generator, which can also become part of a montage. Examples (from 1 to 3, charge density gets successively lower):

1. (+--+)(+--+)(0) — bipolar montage between lead contacts,
2. (----)(++++)(0) — lead-to-lead stimulation, and
3. (----)(0000)(+) — cathodal stimulation between a lead and generator.

2.2.2. Identification of the electrode leads and contacts causing STS—In the OR, when several RNS leads are placed close to motor cortex:

1. Deliver current to *one lead at a time* by turning all contacts in the other lead to “0” and observe for stimulation-induced movement. Apply current with a high local charge density, such as provided by a bipolar montage (+--+), with values of at least 6 $\mu\text{C}/\text{cm}^2$.
2. If lead stimulation is associated with movement, consider excluding this lead from RNS treatment, if adjacent leads are available and thought to be effective at seizure control.

In the outpatient clinic, where leads cannot be switched or removed because this requires surgery, identify the lead and then contacts responsible for STS noted during test stimulation for new current settings.

1. Identify the STS-associated lead by delivering current to *one lead at a time*, turning all contacts in the other lead “0”.
2. Apply current with a high local charge density by using a bipolar montage (+++--)(0000)(0), at the charge density that caused STS.
3. To identify contacts responsible for STS, send current to just one set of adjacent contacts (bipolar connection), with the other two contacts in a lead turned to “0”, (++--00)(0000)(0).
4. Deliver current to just one contact within the lead that produced the symptoms, by connecting the contact to another lead that is 3 cm away or to the generator (--000)(0000)(+).

2.2.3. Modification of electrode lead or single contact parameters—Once the lead and contacts causing STS have been identified, there are several possible modifications available to reduce or eliminate STS:

1. Reduce the stimulation frequency (SF) from a default setting of 200 Hz to a lower frequency, e.g., 100 Hz.
2. If the STS is still present, decrease the pulse width (PW) from the default of 160 μ s to 120 μ s, or lower.
3. If STS still occurs, consider changing the montage. A bipolar montage can be changed to lead-to-lead stimulation or to cathodal stimulation, thereby reducing charge density.
4. If STS persists, consider removing the contact from the montage by setting the contact to “0”, e.g., (--0--)(++++)(0).

3. Results

3.1. Patients

Patient data are detailed in Table 1. Of 58 patients with RNS treated at our institution between August 2015 and May 2019, six had STS (10.3%). Patient ages ranged from 20 to 57 years, three were female. Age at seizure onset was between 4 months and 25 years, with a period of 4–47 years from diagnosis to RNS implantation. Patients 2, 4, and 5 had nonlesional magnetic resonance imaging (MRI), the others had cortical dysplasias.

3.2. Intracranial monitoring and RNS electrode placement

Five patients underwent ICM with stereo-electroencephalography (SEEG) depth electrodes. One patient had independent bilateral temporal seizures on scalp EEG and was implanted without invasive EEG. Stereo-electroencephalography showed a unilateral focus in Patients 1, 2, and 3, and bilateral foci in the others. Cortical mapping during SEEG revealed motor responses for two patients with frontal foci (Patients 1 and 3), no other areas of eloquent cortex were identified in the remaining patients. Patients 2 and 5 each had two implanted RNS leads. Patients 1, 3, 4, and 6 each received three to six leads, though only two “active” leads were connected to the generator. Active leads were cortical strip electrodes in Patients

4, 5, and 6, depth electrodes in Patients 1 and 3, and a combination of strip and depth electrodes in Patient 2. Electrode locations for all patients can be seen in Fig. 1A and B.

3.3. Stimulation-triggered signs or symptoms

Three patients experienced cortical STS with *contralateral* or nonlateralizing distribution (Fig. 1A). Patient 1 had right-hand and Patient 3 right-thigh twitching, triggered by stimulation of contralateral frontal depth electrodes within the primary motor cortex. Patient 2 had sensory symptoms consisting of nausea and a “warm feeling” over both eyebrows with stimulation of a temporoparietal strip electrode. Three patients had *ipsilateral* peripheral STS related to subtemporal strip electrodes within the middle cranial fossa close to cranial nerve branches (Fig. 1B). Patient 4 had tingling along the lower jaw consistent with stimulation of the mandibular branch of the trigeminal nerve. Patient 5 had stimulation-induced painful tingling in the area of the maxillary branch of the trigeminal nerve. Patient 6 had twitching of the ipsilateral eyebrow related to stimulation of facial nerve fibers.

3.4. Adjustment of RNS stimulation parameters

Using the process outlined in Sections 2.2.1–2.2.3, attempts were made to control STS in each of the six patients. For Patient 1, intraoperative testing of electrodes allowed removal of the lead associated with right-hand twitching. For Patients 2–6, modification of SF, PW, or montage eliminated or reduced the STS (details in Table 1).

3.5. Effect on seizure control

Modifying RNS parameters to eliminate STS allowed Patients 1, 4, 5, and 6 to have further seizure improvement with each increase in RNS stimulation current. In Patient 2, modifications made to reduce STS improved seizure frequency, but further increases in current resulted in seizures worsening. Seizure burden remained unchanged in Patient 3 who did not tolerate increased stimulation currents due to return of the STS, despite removal of contacts.

4. Discussion

In this report, we describe six patients who experienced RNS stimulation-induced sensory or motor effects, which we termed STS. Previous descriptions of STS-like phenomena have included rare visual and motor symptoms, which resolved with modification of the RNS output [2,4].

As RNS electrodes are increasingly placed across more of the cortical landscape, there will likely be further reports of varying manifestations of STS. Stimulation-triggered signs or symptoms can be distressing to patients and can limit RNS current increase to improve seizure control. The clinical impact of STS is illustrated by one patient who had significant motor STS, making additional adjustments impossible. Fortunately, five others were able to undergo changes to RNS stimulation parameters that either directly resulted in or allowed for further RNS optimization improving seizure outcomes. Though it remains unclear what seizure outcomes would have been, had there been no need for RNS parameter changes.

We find that STS are not uncommon, and for best RNS effectiveness, STS should be prevented. Placement of RNS electrodes should take into account that STS can occur when lead placement is close to eloquent cortex or near the path of cranial nerves. In this paper, we introduced a systematic protocol that can be used to identify and mitigate STS if it is found after lead placement. At electrode placement, stimulation under anesthesia can identify motor signs, and electrodes in other positions can be substituted, when more than one lead is placed. Stimulation-triggered signs or symptoms encountered when increasing current in clinic can be eliminated by identifying involved leads and contacts, reducing SF and PW, changing montages, and removing contacts, if necessary.

Acknowledgments

A.M.H would like to acknowledge fellowship support from the NIH - F30 AI136403-01A1.

C.D. would like to acknowledge the tireless effort and support from all Neuropace© field engineers.

Abbreviations:

RNS	responsive neurostimulation
STS	stimulation-triggered signs or symptoms
ICM	intracranial monitoring
OR	operating room
SF	stimulation frequency
PW	pulse width
Hz	Hertz
MRI	magnetic resonance imaging
SEEG	stereo-electroencephalography

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A Lead Positions Causing Cortical STS **B Lead Positions Causing Peripheral STS** **Fig. 1.**

Responsive neurostimulation (RNS) can cause stimulation-triggered sensory or motor signs or symptoms (STS) in patients with epilepsy. (A) and (B) show coregistrations of brain and RNS leads causing STS for all patients in this case series. The lead causing STS is colored red and indicated with a white arrow, while the leads not associated with STS are colored turquoise. The anterior direction is indicated by yellow arrows. (A) shows RNS leads causing STS due to cortical stimulation for Patients 1, 2, and 3. Patient 1 experienced a right-hand twitch associated with stimulation of a lead near the hand motor area (green) identified by fMRI. Patient 2 experienced “nausea” and a “warm sensation over both eyebrows” associated with a temporoparietal electrode. Patient 3 experienced a right thigh twitch due to an electrode in the primary motor cortex, leg area. (B) shows RNS leads causing STS due to peripheral/cranial nerve stimulation, lead position in relation to the cortex (top) and skull base (bottom). The incomplete appearance of the skull base is an artifact related computed tomography (CT) image quality. Patient 4 experienced a tingling sensation in the right lower jaw associated with strip contacts close to foramen ovale (blue arrowhead) stimulating the mandibular nerve. Patient 5 experienced a painful sensation in the left mid-face due to strip contacts close to foramen rotundum (blue arrowhead in general vicinity) stimulating the maxillary nerve. Patient 6 experienced a twitch and electrical

sensation in the right eyebrow due to stimulation contacts close to facial nerve fibers at the level of the petrous bone.

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Table 1

Summary of information on RNS patients experiencing STS.

Pt	Age, hand, sex	Age at Sz onset	MRI lesion	SEEG performed/Sz onset zone	RNS leads Types and locations	Stimulation-triggered symptoms or signs (STS)	RNS adjustments	Stim settings last visit: current, PW, CD, Dur, Freq [mA], [μs], [μC/cm ²], [ms], [Hz]	Sz frequency pre-/post-RNS (at last visit)
1	50 yo, RH, F	5 mos	Cortical dysplasia in the left frontal lobe	Yes/onset in left frontal lobe focus in close proximity to hand motor area	3 depths, superior left frontoparietal region. 2 depths active.	In OR, right hand twitching at 6 mA (charge density of 3 μC/cm ²), associated with single depth lead	STS eliminated by removing that depth electrode from montage, and connecting the other two leads to generator	#1: (0000)(---)(+) 5.0, 160, 2.5, 100, 200 #2: (---)(0000)(+) 5.0, 160, 2.5, 100, 200	Pre: 3/week Post: 3/week (reduced severity)
2	35 yo, LH, F	19 yrs	Nonlesional	Yes/onset in right posterior temporal lobe	1 strip in right temporoparietal region and 1 depth in right posterior temporal region. Both strip and depth active.	In clinic, nausea and warm sensation over both eyebrows at > 2.0 mA, associated with temporoparietal strip lead	STS reduced by changing stimulation montage from lead-to-lead to lead-to-generator (cathodal), decreasing SF to 100 Hz and PW to 120 μs	#1: (---)(0000)(+) 3.0, 120.1.3.100.100 #2: (0000)(---)(+) 3.0, 160.1.5.100.200	Pre: 1/week Post: 1-2/month
3	20 yo, RH, M	4 mos	Cortical dysplasia in the left frontal lobe	Yes/left frontal lobe focus in close proximity to leg motor function	6 depths, left frontoparietal region. 2 depths active.	In clinic, right thigh twitching at >4.5 mA (3.4 μC/cm ²), associated with frontal depth lead	STS eliminated by identifying and removing two contacts from montage, and decreasing SF to 100 Hz and PW to 100 μs	#1: (0000)(00---)(+) 4.5, 120, 4.6, 100, 100 #2: (---)(0000)(+) 7.0, 160, 4.1, 100, 100 Patient could not tolerate higher currents.	Pre: 1/week Post: 1/week (no change)
4	30 yo, RH, M	23 yrs	Nonlesional	Yes/onset in bilateral temporal lobes	2 strips, bilateral subtemporal regions and 1 depth, left hippocampus. 2 strips active.	In clinic, electrical sensation from right lower jaw, into right lower incisor at >3.5 mA (1.8 μC/cm ²), associated with subtemporal strip lead	STS reduced with decreasing SF to 168 Hz in right subtemporal contacts	#1: (---)(0000)(+) 4.5, 160, 2.3, 100, 200 #2: (0000)(---)(+) 3.5, 160, 1.8, 100, 168	Pre: 2/day Post: 1/month
5	57 yo, LH, F	25 yrs	Nonlesional	No/scalp EEG showed onset bilateral temporal lobes	2 strips, bilateral subtemporal regions. Both strips active.	In clinic, painful sensation left mid-face at >3.0 mA, associated with single subtemporal strip contact	STS eliminated by turning off contact, lowered PW to 120 μs	#1: (0000)(---)(+) 5.5, 120, 2.1, 100, 200 #2: (0---)(0000)(+) 4.5, 120, 2.3, 100, 200	Pre: 2/week Post: 2/month
6	38 yo, RH, M	13 yrs	Multiple bilateral nodular heterotopias along lateral ventricles and in subcortical white matter	Yes/onset at L hippocampus, L lateral temporal cortex, R subtemporo-occipital foci	4 strips, 2 in left lateral temporal region, 1 right subtemporal and 1 lateral inferior frontal. 2 strips active (left lateral temporal and right subtemporal).	In clinic, twitch and electrical feeling in right eyebrow at 4.5 mA (2.3 μC/cm ²), associated single subtemporal strip contact	STS reduced when decreasing SF to 168 Hz and when lowering PW to 120. Patient decided to keep original settings, so SF and PW were ultimately not changed.	#1: (---)(0000)(+) 4.5, 160, 2.3, 100, 200 #2: (0000)(---)(+) 4.5, 160, 2.3, 100, 200	Pre: 1/week Post: none for 4 months

Standard default RNS settings for stimulation parameters other than current and charge density (which are usually being adjusted): PW 160 μs, burst duration 100 ms, SF 200 Hz.

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Abbreviations: #1 and #2: First and second burst of stimulation, active: electrodes connected to the generator, CD: charge density, F: female, Hand: handedness, LH: left-handed, M: male, RH: right-handed, RNS: responsive neurostimulation, MRI: magnetic resonance imaging, PW: pulse width, SEEG: stereo-encephalography, SF: stimulation frequency, stim: stimulation, STS: stimulation-triggered sign or symptom, Sz: seizure.