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Chronic subthreshold cortical stimulation: A promising therapy for motor cortex seizures

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ABSTRACT

Chronic subthreshold cortical stimulation (CSCS) is a form of neurostimulation consisting of continuous or cyclic, open-loop, subthreshold electrical stimulation of a well-defined epileptogenic zone (EZ). CSCS has seen limited clinical use but could be a safe and effective long-term treatment of focal drug resistant epilepsy, in particular when the EZ is located in the motor cortex. We present a case of a 49-year-old woman suffering from debilitating focal motor seizures. Treatment with CSCS resulted in significant clinical improvement, enabling her to walk unaided for the first time in years.

1. Introduction

Approximately 30 % of epilepsy patients suffer from drug resistant epilepsy (DRE), defined as a failure to achieve seizure freedom after having taken 2 or more anti-seizure medications (ASMs) [1]. The gold standard treatment for focal DRE is resective surgery, provided that the epileptogenic zone (EZ) is located in non-eloquent cortex. In patients who are ineligible for resective surgery, neurostimulation treatments such as vagus nerve stimulation (VNS), deep brain stimulation of the anterior thalamic nucleus (ANT-DBS) and responsive neurostimulation (RNS) are widely used, with high-quality evidence supporting their efficacy [2].

VNS and ANT-DBS are thought to decrease general brain excitability and inhibit the propagation of seizures by modulating neuronal activity in brain regions at a distance from the EZ, the so-called "network approach" in epilepsy treatment [3]. In RNS, on the other hand, epileptic activity originating from one or two mesial temporal or neocortical seizure foci is detected and used to trigger local electrical stimulation of the EZ in a closed-loop manner [4] A 2016 review reported long-term seizure reduction and ≥6 month seizure freedom rates of respectively 55 % and 5,5–8,25 % for VNS, 69 % and 16 % for ANT-DBS and 56 % and 23 % for RNS [5]. These results represent clinically significant improvements, but also show that a significant proportion of patients do not achieve seizure freedom, highlighting the need for new treatment options.

Chronic subthreshold cortical stimulation (CSCS) is an alternative neurostimulation approach consisting of continuous or cyclic, open-loop, subthreshold electrical stimulation of a well-defined EZ. Case series support its usefulness in neocortical epilepsy, particularly when the EZ is located in motor cortex [6]. Eligibility for CSCS depends on the results of a trial stimulation, which can be conducted during invasive video-electroencephalography (EEG). Using the temporary electrodes already implanted for the invasive recording, the effect of different stimulation parameters on seizure frequency, intensity, and duration can be evaluated over multiple days. If trial stimulation results in significant clinical improvement, permanent electrodes for CSCS can subsequently be implanted. We present a case of DRE with focal, motor-onset seizures in which trial stimulation and subsequent treatment with CSCS led to significant clinical improvement, allowing the patient to walk unaided for the first time in years.

2. Case report

A 49-year-old woman with focal DRE since childhood was referred to us in 2016. She experienced nocturnal seizures with brief tonic contraction of the right leg/foot and daily reflex seizures with negative

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or positive myoclonus of the right leg/foot, sometimes involving the right hemicorpus, and triggered by activity (walking, cycling) or stimulus (placing right foot on uneven ground). She had also experienced focal-to-bilateral tonic-clonic seizures. Daily reflex seizures caused repeated falls, making it impossible for her to walk unaided from the age of 35.

Presurgical evaluation had previously been performed in another center. Magnetic resonance imaging (MRI) had shown no abnormality. Video-EEG and ictal single-photon emission computed tomography suggested an EZ in the left motor cortex. Resective surgery was cautioned against due to concerns about post-operative motor deficits. ANT-DBS was proposed but she refused.

Upon presentation in our hospital, 10 ASMs had been tried. She was enrolled in a clinical trial in which high-frequency repetitive transcranial magnetic stimulation (rTMS) was used to modulate the left motor cortex [7]. Each rTMS session consisted of 5 continuous theta burst trains, each comprising 600 pulses presented in 50 Hz triplet bursts every 200 ms during 40 s, delivered at 10-min intertrain-intervals. Per session, 3000 stimuli were delivered, with a total of 12.000 stimuli over the entire 4-day treatment. This did not result in a reduction in seizure frequency or severity. A new video-EEG recording confirmed left frontal seizure onset. 7T-MRI and fluoro-deoxy-glucose positron emission tomography were normal. No abnormalities were observed during magneto-encephalography.

Invasive video-EEG recording was performed with a 4x5-contact subdural grid over the left dorsofrontal convexity and two 4-contact subdural strips placed interhemispherically facing the medial aspect of the left frontal lobe (Fig. 1). Seizure onset was consistently observed on 2 contacts (A4 and G4). Cortical mapping showed these to be located over primary motor cortex of the right leg. Given the overlap between EZ and motor cortex, resective surgery was not proposed. A treatment with multiple subpial transections (MST) was considered. Given the risk of postoperative deficit after MST, we decided to perform a trial with cortical stimulation using the temporary subdural electrodes implanted for invasive recording. Hospital ethics committee approval and patient consent were obtained. Based on previous reports [8–10], biphasic, high-frequency stimulation (100 Hz, pulse width (PW) 120 μs) between electrodes A4(+)-G4(-) was first tried. Stimulation intensity was gradually increased in 0.1 V increments. Intensities higher than 5.8 V caused clonic movements and/or paresthesia in the right foot/toes. Subthreshold high-frequency stimulation at 5.8 V during 24 h resulted in abolishment of reflex seizures and decreased nocturnal motor seizures. Both subthreshold biphasic low-frequency stimulation (5 Hz, PW 450μsec, 5.0 V) between A4(+)-G4(-) and 2-channel high-frequency stimulation (100 Hz, PW 120μsec) between G4(+)-G2(-) (5.5 V) (channel 1) and A4(+)-P1(-) (4.5 V) (channel 2) during 24 h resulted in absence of reflex seizures but a marked increase in nocturnal seizures. Finally, rechallenge with high-frequency stimulation (100 Hz, PW 120 μs) between A4(+)-G4(-) resulted in freedom from reflex seizures and a marked reduction in nocturnal seizures. She was allowed to walk around the ward with a physiotherapist and was able to walk unaided for the first time in years (Fig. 2).

After obtaining ethics committee approval and patient consent, permanent subdural electrodes (Medtronic model 977C265, medical need program) were implanted in the region covered by A4/G4. After implantation, she had mild paresis of the right leg/foot, which recovered completely. Reimbursement of the pulse generator could not be obtained at short notice, and she was discharged without active stimulation and unaltered ASMs. She remained seizure-free for 2 weeks. Seizures subsequently recurred, but seizure frequency remained low (weekly instead of many per day) for several months. Thereafter, seizure frequency gradually returned to baseline (frequent daily seizures). This led to implantation of a pulse generator (Medtronic, Intellis Adaptive Stim, rechargeable, ref. 97715, serial number NME797950H) and initiation of continuous, high-frequency CSCS (100 Hz, PW 120 μs, 4.0 mA) on March 22nd 2022, 15 months after trial stimulation. She quickly

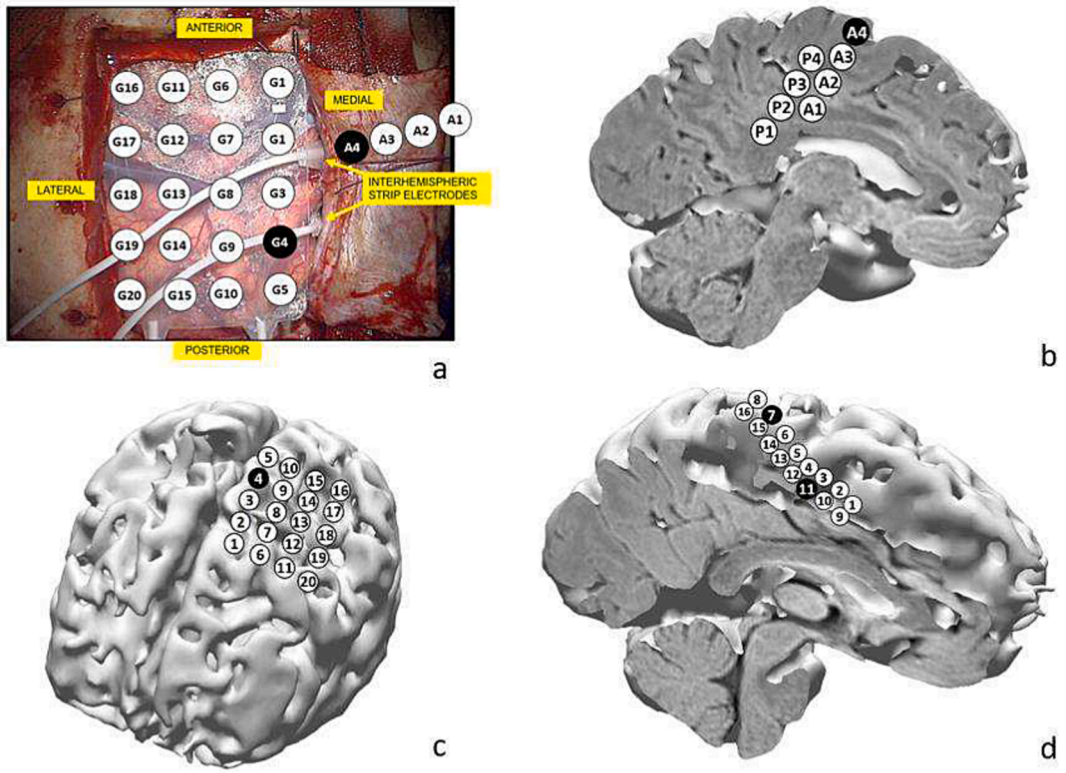

Fig. 1. Schematic representation of electrode positions. a) intraoperative view b) 3d reconstruction-sagittal view showing the interhemispheric strips. c) top down view of the subdural grid over the left paramedian convexity (*electrodes G1-G16 are labelled 1–16).* d) sagittal view showing position of permanent electrodes (CSCS applied between electrodes 7 and 11).

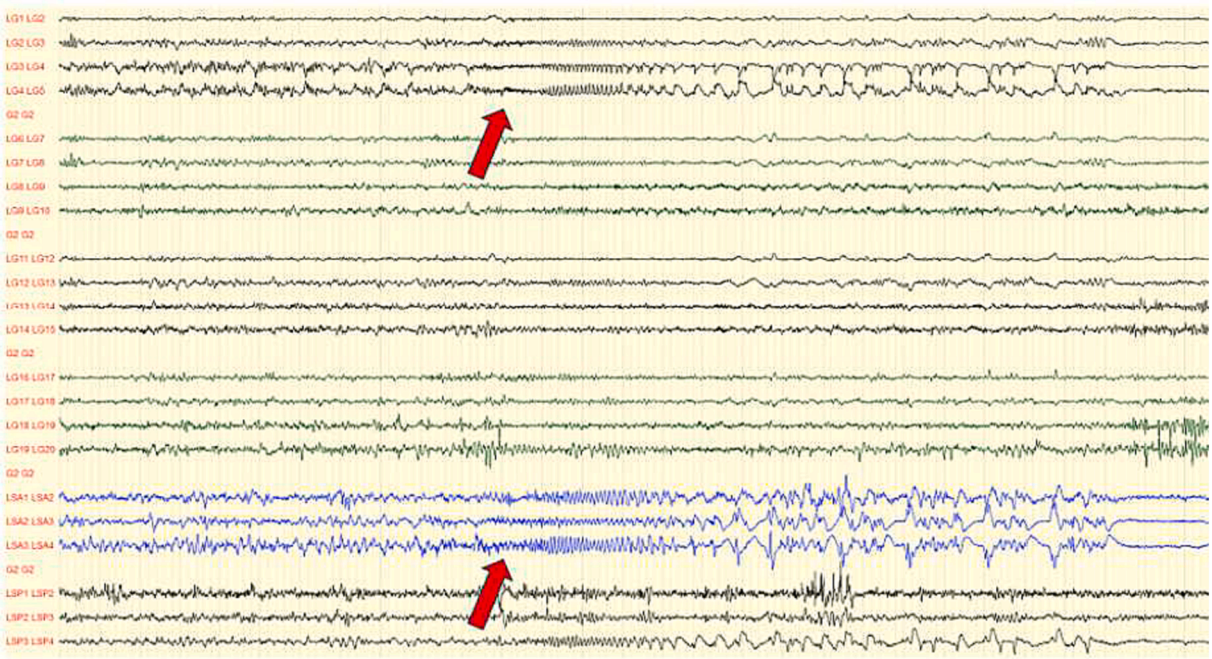

Fig. 2. Ictal activity recorded by invasive eeg(1.6 Hz, 120 Hz, 30 sec, 800 μv/cm). Low voltage fast activity Is seen at A4 and G4 (arrows) which evolves into rhytmic activity.

became seizure-free. 15 weeks later, she had a brief relapse with daily seizures during an episode of bronchitis, with spontaneous improvement. Subsequently, she experienced only sporadic (once every few months) myoclonus of the right leg, with no falls and no impact on her ability to walk unaided. Stimulation was gradually changed from continuous to cyclic mode (15 min ON – 15 min OFF) to prevent battery depletion. She experienced one mild nocturnal seizure over a period of 8 months. Duty cycle was changed to 15 min ON – 30 min OFF. Three months later, she reported recurrence of gait problems due to a feeling of instability in the right leg. Stimulation was switched back to 15 min ON – 15 min OFF and these symptoms disappeared (Fig. 3).

3. Discussion

In our patient, CSCS led to a reduction of more than 90 % in seizure frequency and extended periods of seizure freedom, demonstrating efficacy comparable to earlier reports [6,8–13]. While there are no randomized trials that directly compare CSCS to RNS, VNS or ANT-DBS, it has been suggested that CSCS may have a higher efficacy than other neurostimulation treatments for epilepsy [6]. For RNS, mean seizure reduction (MSR) was reported to be 53 % at 2 years follow-up [14]. The SANTE-trial (ANT-DBS) [15] and the Vagus Nerve Stimulation Study Group [16] respectively reported 56 % and 44 % MSR at the 2-year mark. A review which compared the initial pivotal trials of all 3 neurostimulation modalities found DBS and RNS to have comparable efficacy while VNS performance trailed [2]. At later points in time, the

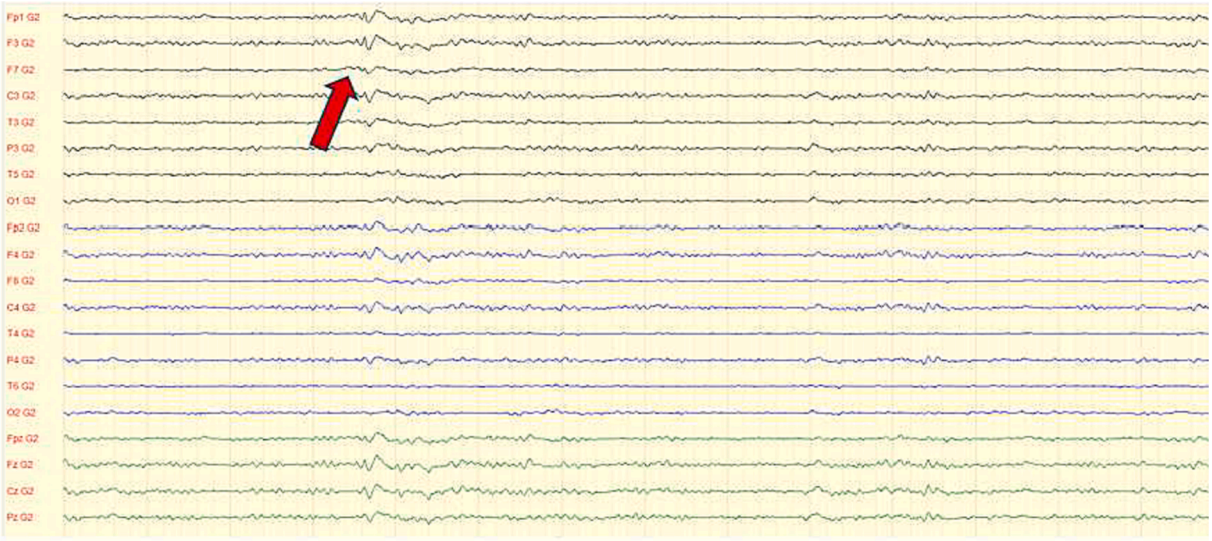

Fig. 3. Interical activity recorded by scalp eeg (0,530 Hz, 120 Hz, 15 sec, 400μv/cm). A sharp wave-slow wave complex (arrow) over the left frontal to frontocentral region.

difference in degree of improvement in seizure frequencies of the three modalities may not be statistically significant and long term (7-15y) MSR varies around 75 % for RNS and ANT-DBS and 52–76 % for VNS [17]. Seizure freedom intervals (≥6 months) at long-term follow-up were studied prospectively for ANT-DBS (18 %) [15] and RNS (28 %) [18] but only retrospective data is available for VNS, with one large registry study and systematic review reportering a terminal rate of seizure freedom of 8 % [19]. A 2022 retrospective, single center study which includes the largest cohort of CSCS patients to date and compared the effect of CSCS to other neurostimulation treatments in focal DRE reported that CSCS had the highest MSR and the most patients reporting ≥ 3 months of seizure freedom. MSR was 61 % for the entire cohort (n = 159), 85 % for CSCS (n = 32), 63 % for centromedian thalamic nuclei DBS (n = 19), 52 % for ANT-DBS (n = 38), 50 % for RNS (n = 30) and 50 % for VNS (n = 40) [6]. A 2018 review which included 21 CSCS and 230 RNS patients concluded that CSCS seemed to provide a larger reduction in seizure frequency but mentioned strong publication bias, since RNS studies reported on well-controlled large-sample clinical trials while CSCS articles were case reports [20].

Several factors may account for any difference in efficacy of CSCS compared to other neurostimulation treatments. Local stimulation of the EZ, as is done in CSCS and RNS, may be more effective for preventing seizures than the network approach used in VNS and ANT-DBS. However, this has not been convincingly shown since RNS currently does not appear to have a higher efficacy than ANT-DBS. Conversely, the open-loop approach of CSCS may be more effective than the closed-loop approach of RNS because seizure activity may have substantially recruited at submillimeter scale before it is detected by the RNS system, potentially reducing the efficacy of latter [11]. The high efficacy of CSCS in our patient could also be related to its use in motor cortex or paracentral epilepsy, which may respond particularly well to focal stimulation [6]. Subgroup analysis of the RNS pivotal trial showed an 81 % MSR in patients with an EZ in primary motor cortex, compared to 70 % in patients with frontal and parietal seizure onset, 58 % in temporal neocortical onset and 51 % in multilobar onset [21]. We identified 17 cases where CSCS was used in epilepsy originating in motor cortex or the paracentral region [8,10–12,22]. Follow-up ranged between 4 and 101 months. Nine patients achieved seizure freedom at last follow-up and 4 experienced a > 90 % seizure reduction. Three of these patients also presented with epilepsia partialis continua (EPC) which was promptly halted with stimulation [8,11,12]. In one other patient, seizure severity reportedly decreased from 8/10 to 0/10 [12]. Seizure reducution rates in the remaining patients were 82 %, 51 % and 0 %. The preponderance of reported CSCS cases involving the paracentral/motor region may be due to selection bias, given that patient selection for trial stimulation depends on high seizure frequency, which may be more common in frontal lobe epilepsy [23]. Finally, the higher efficacy of CSCS may result from the process of trial stimulation, which allows for better selection of responders compared to other neurostimulation approaches. However, trial stimulation also complicates patient selection, since a high seizure frequency is required to discern the effects of stimulation in the limited time available during invasive video-EEG recording. Patient selection by trail stimulation could be facilitated by establishing electrophysiological biomarkers for long-term outcome of CSCS. However, there currently appears to be no clear correlation between decreased interictal epileptiform activity on EEG during trial stimulation and outcome at the individual level [12].

While trial stimulation is an important step in selecting suitable candidates for treatment CSCS, most previously published cases and case series provide little or no information about the approach and parameters used during trail stimulation [6,8–11,13]. A highly individualized response to different stimulation parameters has been reported, with both high- and low-frequency CSCS improving seizure control in some but exacerbating seizure frequency in other patients [8]. Individual differences in response might be related to multiple factors including location, size and connectivity patterns of the seizure focus. We performed trial stimulation of different combinations of electrodes chosen to affect a smaller or larger brain region in and around the EZ, using both high- (100 Hz) and low-frequency (5 Hz) stimulation, in 24 h periods. In our patient, only high-frequency stimulation of a smaller area corresponding to the EZ reduced all seizure types, whereas low-frequency stimulation of the EZ and high-frequency stimulation of a larger area surrounding the EZ abolished reflex seizures but worsened nocturnal seizures.

In our patient, the effect of CSCS was initially sustained when stimulation was switched from continuous to cyclic mode. Cyclic stimulation has previously been reported to be effective [10], disputing the assumption that it leaves time for epileptic activity to evolve and spread. However, seizures eventually recurred when the duty cycle was lowered to 15 min ON – 30 min OFF, suggesting that there may be a threshold which could be highly individual.

Interestingly, our patient had previously been treated with rTMS of the left leg motor cortex [7] which did not result in significant improvement. This could be because the EZ was located interhemispherically, which may have been out of reach of the magnetic field induced by rTMS.

Our patient experienced a temporary reduction in seizure frequency for several months after trial stimulation and implantation of the permanent electrodes but before initiation of CSCS. This may have been an implantation effect [12] or a carry-over effect of the trial stimulation [10]. A seven-year-old child was previously reported to be seizure-free at 20-month follow-up after trial stimulation, without implantation of permanent electrodes [24].

We observed no major side-effects or complications from electrode implantation and stimulation in our patient. CSCS seems to be safe, since no major side effects were reported in a study which included 32 patients with follow-up during several years [6]. Apart from reducing seizures, CSCS may also improve neurologic functioning by modifying dysfunctional cortex, as has been reported in 2 patients who experienced improvements in motivation and dexterity [25].

To conclude, CSCS led to sustained, highly significant improvement in seizure control in our patient, further supporting the notion that it could be a safe and effective long-term treatment for focal DRE. Seizures originating in the motor cortex or paracentral region could respond particularly well to CSCS. More studies are needed to define patient selection criteria, optimize stimulation parameters, and establish electrophysiological biomarkers relating to long-term outcomes.

Declaration of competing interest

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

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