THE EFFECTS OF VAGUS NERVE STIMULATION UPON EEG AS RECORDED FROM OCCIPITAL SUBDURAL ELECTRODES IN A HUMAN CASE

Piotr W. Olejniczak, John D. England, and Michael E. Carey

Departments of Neurology and Neurosurgery at the Louisiana State University Medical Center in New Orleans

Abstract. Although vagus nerve stimulation (VNS) can reduce clinical seizure frequency, human EEG studies using scalp recordings have failed to demonstrate an effect of VNS on either interictal epileptiform or background activity. The purpose of the study was to examine the effects of VNS on intracranially recorded EEG activity in humans. We report a patient with a vagus nerve stimulator who was subsequently admitted for implantation of subdural electrodes for video/EEG analysis in preparation for epilepsy surgery. The EEG background power spectra recorded from a left intracranial occipital contact were smaller with the VNS device "on" compared to when the device was "off". Despite these changes in EEG background, VNS did not prevent or alter the course of electrographic seizures. **Key words.** Vagus nerve stimulation (VNS) – intracranial electrodes – seizures - EEG background activity – power spectra.

INTRODUCTION

Vagus nerve stimulation (VNS) using the Neuro-Cybernetic Prosthesis (NCP) system by Cyberonics™ was approved by the Federal Drug Administration (FDA) in July 1997 for use as an adjunctive therapy in reducing the frequency of seizures in adults or adolescents over 12 years of age who have medically refractory partial onset seizures. Although its efficacy in the treatment of partial-onset seizures has been established (Salinsky et al. 1995; Handforth et al. 1998), the exact mechanism of action of VNS remains unknown. Recent studies suggest that metabolic activation of certain thalamic, brainstem, and limbic structures may be important in mediating the effect of VNS (Fisher and Handforth 1999). Animal studies have shown that stimulation of the cervical portion of the vagus nerve can terminate electrographic seizure discharges in epileptogenic foci caused by topical or systemic administration of strychnine or pentylenetetrazol (PTZ) (Zabara 1992)) and can block the development of kindled seizures (Fernandez-Guardiola et al. 1999). Human EEG studies using scalp recordings have failed to show any effect of VNS upon interictal epileptiform activity or background activity. Hammond et al. (1992) studied 9 patients with medically intractable seizures who were participating in an epilepsy clinical trial of chronic vagus nerve stimulation. Stimulation at various stimulus frequencies and amplitudes had no noticeable effect on EEG background activity whether the patient was under general anesthesia, awake, or asleep; however vagus nerve stimulation interrupted ongoing ictal EEG activity in one patient. Similarly, Salinsky and Burchiel (1993) found no VNS effect on background activity. In our

initial description of the VNS effects on intracranial EEG activity (Olejniczak et al., American Clinical Neurophysiology Society Meeting Abstracts, Nov. 99') we demonstrated that VNS at 30 Hz (but not 5 Hz) and 1.0 mA decreased the frequency of interictal rhythmic sharp waves recorded from a hippocampal depth electrode in a patient with medically intractable complex partial seizures of temporal onset. VNS did not, however, influence the frequency of hippocampal interictal spikes. Thompson et al. (American Epilepsy Society Meeting Abstracts, Dec. 99') found that VNS at 30 Hz and 1.5 mA induced significant changes (mostly increases) in gamma power (i.e. EEG beta rhythm above 40 Hz) in direct cortical and thalamic recordings. A significant power increase was noted in the delta power at 1.0 mA.

CASE REPORT

A 13-year old girl with tuberous sclerosis had medically intractable daily multifocal partial seizures with secondary generalization. Approximately 60% of the seizures consisted of an aura with a vague gastric discomfort followed by staring, lip smacking and turning of the eyes and head to the right. The typical episode lasted 2-3 minutes, followed by postictal confusion of 20-30 minutes. Less common seizures had more abrupt onset and a strong motor component, mostly focal clonic movements of the right extremities and frequent secondary generalization. The motor seizures would last 30-60 seconds on the average but those with secondary generalization would extend to 3 minutes and be followed by postictal confusion. A Neuro-Cybernetic Prosthesis (NCP) by Cyberonics^{TM} was implanted one year before the current study with approximately a 15-20%

decrease of seizure frequency. Despite this modest seizure reduction the patient continued having frequent seizures, and, so, was evaluated further for epilepsy surgery. Previous video/EEG monitoring with scalp electrodes had demonstrated that approximately 60% of the seizures originated focally from the left parietal/occipital head region. The remaining seizures had a diffuse bihemispheric electroencephalographic onset with a strong motor component localizing behaviorally to the left cerebral hemisphere. She was admitted on 6/7/99 **(**day 1**)** for surgical implantation of left hemispheric subdural electrodes: a 28-contact parietal grid, a 6-contact superior medial strip (SM - motor area), a 6-contact anterior temporal strip and two occipital strips a (4- and 6-contact)(FIGURE 1). The VNS was put in the "off" mode immediately before the implantation surgery and the patient's phenytoin was discontinued immediately after it. On day 4 the patient developed frequent partial seizures **(**designated for this report as type 1**)** which often began with a cry, followed by staring, obtundation and finally rhythmic clonic movements of the right arm. Electrographically, these type 1 seizures were characterized either by diffuse onset or an onset within the superior medial strip (SM – motor area, contacts 3, 4, and 5). Since the seizures became extremely frequent with prominent interictal activity mostly in the superior medial contacts, the patient was given two 500 mg PE (phenytoin equivalents) boluses of fosphenytoin on day 4. The seizures continued almost unabated through day 5 requiring treatment with an additional fosphenytoin dose of 1250 mg PE. On day 5 the patient was also started on felbamate at a dose of 600 mg po bid. After this therapeutic adjustment the behavioral manifestations of the seizures changed with

less pronounced motor components but with more periods of unresponsiveness associated with lip smacking (designated type 2**)**. Electrographically, these type 2 seizures had their onset from 9 contiguous parietal grid electrode contacts (15, 16, 22, 23, 24, 29, 30, 31, 32) with spread to adjoining SM contacts (1-6). Seizure frequency decreased significantly on day 7 allowing for vagus nerve stimulator testing from 4 till 5 pm. On this day the patient had 5 seizures type 2 before vagus nerve stimulation, 4 during vagus nerve stimulation, and one after. The trough blood phenytoin level was 15.2 ug/ml on day **7** and day 8**,** while the trough blood felbamate level was 14 ug/ml on day 8. Functional cortical stimulation was performed on day 8 and revealed the presence of eloquent cortex under several grid and strip electrode contacts. The motor functions were localized to the 6-contact SM strip. Tactile sensory functions were detected by stimulation of contacts 5-6 on SM strip and contact pair 15-16 on the grid. Speech arrest was noted with stimulation between grid contact 8 and contact 4 on the anterior temporal strip. Visual phenomena were elicited by stimulation of contacts 3 and 4 on the superior and inferior occipital strips. Lowest afterdischarge thresholds were found with stimulation of grid electrode contacts 12, 20, 21, 22, 23, 24, 28, 29, 30. Seizures type 2 were induced after stimulation of electrode pairs 21-22 and 23-24. Resective brain surgery (left posterior parietal “topectomy”) was performed on day 9. Nine contact points (12, 20, 21, 22, 23, 24, 28, 29, 30) of the grid associated with seizure type 2 onsets and not linked to identifiable sensory and/or motor functions were identified. A trapezoidal piece of cerebral cortex under these electrodes was electrocoagulated and removed to the underlying white

matter. This partial cortical parietal resection (a “topectomy”) resulted in a 75% seizure reduction judged in a year-long follow-up.

METHODS

VNS was temporarily restarted on postoperative day 7 after obtaining appropriate consent from the patient and her guardian. The following stimulus parameters were used: square wave, 30 seconds “on” (real time 34 s) alternating with 30 seconds “off” (real time 34 s), output current 1.0 mA, pulse width 500 us, pulse frequency 30 Hz. Power spectra analysis included 30 periods “on” alternating with contiguous 30 periods “off “ with the patient awake and watching TV. 4-second long artifact-free epochs at the end of each period (preferably 29^{th} - 32^{nd} second) were selected for spectral analysis. The VNS – induced artifact was monitored in two EKG channels (FIGUREs 3 and 4).

For background evaluation needle scalp electrodes Fz and Cz (10-20 system) were referred to the left occipital scalp electrode O_1 (FIGURE 2) and the underlying contact SO_1 (FIGURE 3) on a subdural 4-contact strip electrode overlying the visual cortex. The power spectra were calculated using Telefactor^{TM} Twin 1.50 system separately for the delta (0.0 to 4.0 Hz), theta (4.0 to 8.0 Hz), alpha (8.0 to 13.0 Hz), beta (13.0 to 40.0 Hz), and total band (0.0 to 100.0 Hz) ranges.

RESULTS

EEG power spectra recorded from the left intracranial occipital contact (SO1) were smaller with the VNS device “on” compared to the device “off” (Tables 1a and 1b). In this case the difference was greatest for the theta ($p=0.007$ for Fz reference and $p=0.004$ for Cz) and total frequency bands ($p=0.008$ and 0.007). The difference in delta and beta bands were not statistically significant. The smallest difference was noted for the alpha frequency band.

The EEG power spectra recorded from the needle scalp electrode at the O_1 site (10-20 system) showed decreased power only for the delta and total bands (Tables 2a and 2b), however, these differences did not reach statistical significance. Of note is the fact that the scalp power spectra were significantly greater in the beta band with the device “on” compared to the device “off”. This is likely explained by the fact that the device generates signals at 30 Hz, a frequency in the beta range.

The electrographic seizures occurred with VNS in both “off” (FIGURE 4) and “on” (FIGURE 5) modes. The site of onset and dynamics of evolution between the “off” and “on” seizures did not differ significantly.

Table 1a. Average power spectra for Fz- SO1 reference (uV^2)

Band range	power spectra with VNS		comparison of on/off difference by t-test (p-value)
	On	Off	
Delta	422.3369	512.8254	0.077
Theta	253.9224	359.3966	0.007
Alpha	142.3164	169.733	0.124
Beta	206.0248	241.3979	0.044
Total	1077.091	1325.247	0.008

Table 1b. Average power spectra for Cz- SO1 reference (uV^2)

Band range	power spectra with VNS		comparison of on/off difference by t-test (p-value)
	On	Off	
Delta	411.7746	502.349	0.074
Theta	245.6192	351.3749	0.004
Alpha	139.9269	164.5737	0.175
Beta	201.54	238.9052	0.036
Total	1049.409	1300.633	0.007

Table 2a. Average power spectra for Fz- O_1 reference (uV^2)

Band range	power spectra with VNS		comparison of on/off difference by t-test (p-value)
	On	Off	
Delta	11.3551	15.3815	0.218
Theta	5.8228	5.2823	0.667
Alpha	3.3335	3.2812	0.95
Beta	6.6311	2.4075	6.027E-11
Total	30.5097	26.3553	0.316

Table 2b. Average power spectra for Cz- O_1 reference (uV^2)

Band range	power spectra with VNS		comparison of on/off difference by t-test (p-value)
	On	Off	
Delta	7.1414	9.3755	0.269
Theta	3.7583	3.2311	0.475
Alpha	2.4908	2.4123	0.897
Beta	5.042	2.008	8.913E-11
Total	21.282	17.4123	0.118

DISCUSSION

Using intracranial subdural recording we have shown that VNS at 1.0 mA and 30 Hz can significantly affect power spectra of occipital waking EEG by desynchronizing the background activity (i.e. decreasing the power spectra) in the delta, theta (most robust effect), and alpha bands. We agree with Thompson et al. that in the beta band (at 30 Hz) there is a significant driving effect increasing the beta power. Despite these effects upon occipital EEG activity, we were unable to demonstrate an effect of VNS upon the frequency or dynamics of electrographic seizures.

Stimulation of the vagus nerve in experimental animals can cause profound changes in the EEG (Zanchetti et al. 1952; Chase et al. 1967 and 1968; Chase and Nakamura 1968; Hammond et al. 1992; Salinsky and Burchiel 1993). Acute effects of VNS on EEG were found in cats by Rutecki (1990). Zanchetti et al. (1952) discovered that VNS blocked spindle-like activity and reduced the amplitude of the EEG background. Chase et al. (1967 and 1968) found a complex relation between VNS and EEG with either synchronization or desynchronization of the rhythms depending upon the population of stimulated nerve fibers. Magnes et al. (1961) by directly stimulating one of the afferent terminations of the vagus nerve, the nucleus tractus solitarius, induced synchronization or desynchronization of the EEG depending on the exact location of the stimulation electrode, frequency of stimulation, and the animal's state of arousal. Although high frequency stimulation (>30 Hz) resulted in EEG desynchronization, slower stimulation (1-17 Hz) caused synchronization.

Studies in humans using scalp electrode monitoring have not shown demonstrable effects of VNS on background EEG activity (Hammond et al. 1992; Salinsky and Burchiel 1993). Thompson et al. (1999) in their case report claim that VNS synchronized the EEG background activity recorded from subdural strip electrodes in a patient evaluated for resective epilepsy surgery. Our experience was different: the EEG displayed reduced power spectra with VNS "on" compared to VNS "off". Unfortunately, we were unable to compare the stimulation periods to a baseline with longer periods "off". However, VNS did not appear to affect the development of electrographic seizures. Attempts to compute the power spectra for individual seizures produced inconsistent results and will be the subject of a separate study. Prior to initiating the stimulation, the observed background activity was very unstable and contaminated by movement artifacts and prominent carry-over effects from seizure activity. Significant VNS carry-over effects from periods "on" are also expected to extend into periods "off".

VNS achieved a modest degree of seizure reduction (15-20%) in the year prior to cortical resection. The cortical resection, however, gave a more significant 75% reduction in seizure frequency and improvement of quality of life. The major unanswered question that arises from this case is why VNS appeared to decrease the frequency of clinical seizures, yet paradoxically, had no clear effect upon electrographic seizures. The answer is likely complicated (Schachter and Saper 1998) and may be influenced by the limitations of this study. A few possible explanations include the following: (1) Trauma associated with surgical implantation of intracranial electrodes and occurrence of electrographic and

clinical seizures preceding the VNS analysis may have influenced background or epileptiform activity during baseline and stimulation periods (Gotman 1991). (2) The duration of restarted VNS (30s “on”/30s “off”) could have been too short to develop any therapeutic activity. Perhaps with further monitoring one might have shown decreased frequency of electrographic seizures with VNS “on”. (3) VNS may not have been effective in controlling seizures originating in areas not covered by intracranial electrodes. After all, many clinical studies have shown only a modest decrease in frequency of seizures with VNS (Fisher and Handforth 1999; Shachter and Saper 1998). (4) Finally, VNS may be more effective in suppressing epileptiform activity in some individuals compared to others. Comparisons with the only other center (Thompson et al. 1999) investigating VNS effects on intracranial EEG recordings are difficult because of different study paradigms (essentially designed “ad hoc” in both groups).

REFERENCES

Chase MH, Nakamura Y, Clements CD: Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. Brain Res 5:236-249, 1967.

Chase MH, Nakamura Y: Cortical and subcortical EEG patterns of response to afferent abdominal vagal stimulation: Neurographic correlates. Physiol Behav 3:605-610, 1968.

Fernandez-Guardiola A, Martinez A, Valdes-Cruz A, Magdaleno-Madrigal VM, Martinez D, Fernandez-Mas R: Vagus nerve prolonged stimulation in cats: effects on epileptogenesis (amygdala electrical kindling): behavioral and electrographic changes. Epilepsia 40(7):822-829, 1999.

Fisher RS and Handforth A: Reassessment: Vagus nerve stimulation for epilepsy. A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 53:666-669, 1999.

Gotman J: Relationship between interictal spiking and seizures: human and experimental evidence. Can J Neurol Sci 18(4):S573-S576, 1991.

Hammond EJ, Uthman BM, Reid SA, and Wilder BJ: Vagus nerve stimulation in humans: I. EEG effects. Epilepsia 33(6):1013-1020, 1992.

Handforth A, DeGiorgio, CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW: Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51(1):48-55, 1998.

Magnes J, Moruzzi G, Pompeiano O: Synchronization of the EEG produced by low frequency electrical stimulation of the region of the solitary tract. Arch Ital Biol 99:33-67, 1961.

Olejniczak PW, Butterbaugh G, Fisch B, and Carey M: Effects of vagus nerve stimulation on EEG using hippocampal depth electrodes: a case report and

review. American Clinical Neurophysiology Meeting, St. Louis, MO 1999. Abstracts, C103, p.29.

Rutecki P: Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 1990;31(suppl 2):S1-6.

Salinsky MC and Burchiel KJ: Vagus nerve stimulation has no effect on awake EEG rhythms in humans. Epilepsia 34(2):299-304, 1993.

Salinsky M, George R, Sonnen A, and Vagus Nerve Stimulation Group: A randomized controlled trial of chronic VNS for treatment of medically intractable seizures. Neurology 45(2):224-230, 1995.

Schachter SC and Saper CB: Progress in epilepsy research. Vagus nerve stimulation. Epilepsia 39(7):677-686, 1998.

Thompson JL, Jr, Zaveri HP, McCarthy K, Carpentier A, Spencer SS, Spencer D: Vagus nerve stimulation effects on intracranial EEG spectra recorded from cortex and thalamus. Epilepsia 40(7):S138, 1999.

Zabara J: Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 33(6):1005-1012, 1992.

Zanchetti A, Wang SC, Moruzzi G: The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol 4:357, 1952.

FIGURES

FIGURE 1. Lateral skull X-Ray obtained after implantation of subdural strip and grid electrodes. 6 electrode contacts in the upper row belong to the SM strip (motor area) . The extreme right contact is number 1, extreme left – number 6. Right below the SM strip is a 28-contact parietal grid. Grid contact 32 lies under SM contact 4. Grid contact 30 lies under SM contact 6. The anterior temporal (AT) strip is identifiable anterior and inferior to the grid. The superior (SO) and inferior (IO) strips can be identified behind the low posterior corner of the grid.

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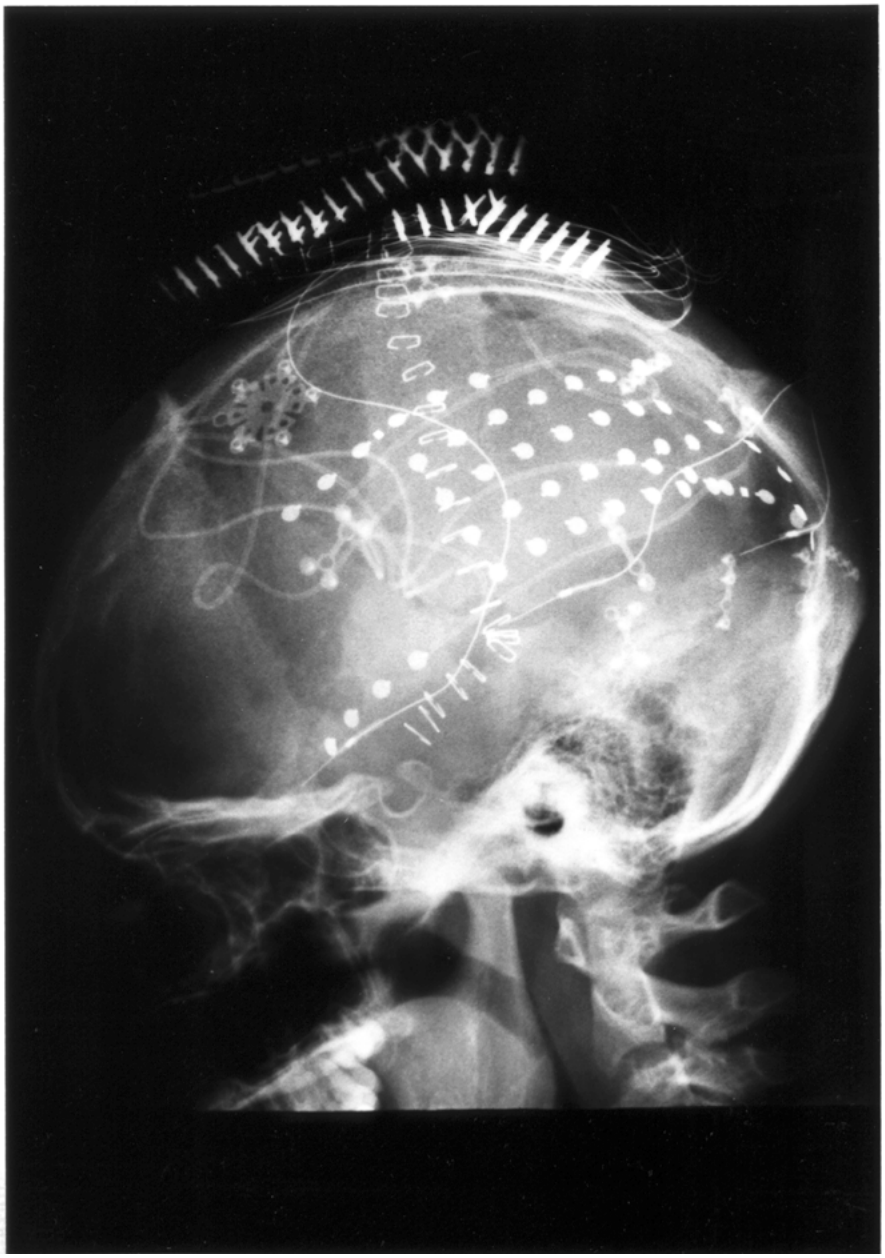

FIGURE 2. Interictal background activity recorded using $\mathbf{O_1}$ (10-20 system) reference. The dashed arrow indicates VNS artifact in 2 EKG channels. **X** marks the beginning of electrical stimulation. No significant background change can be appreciated with VNS.

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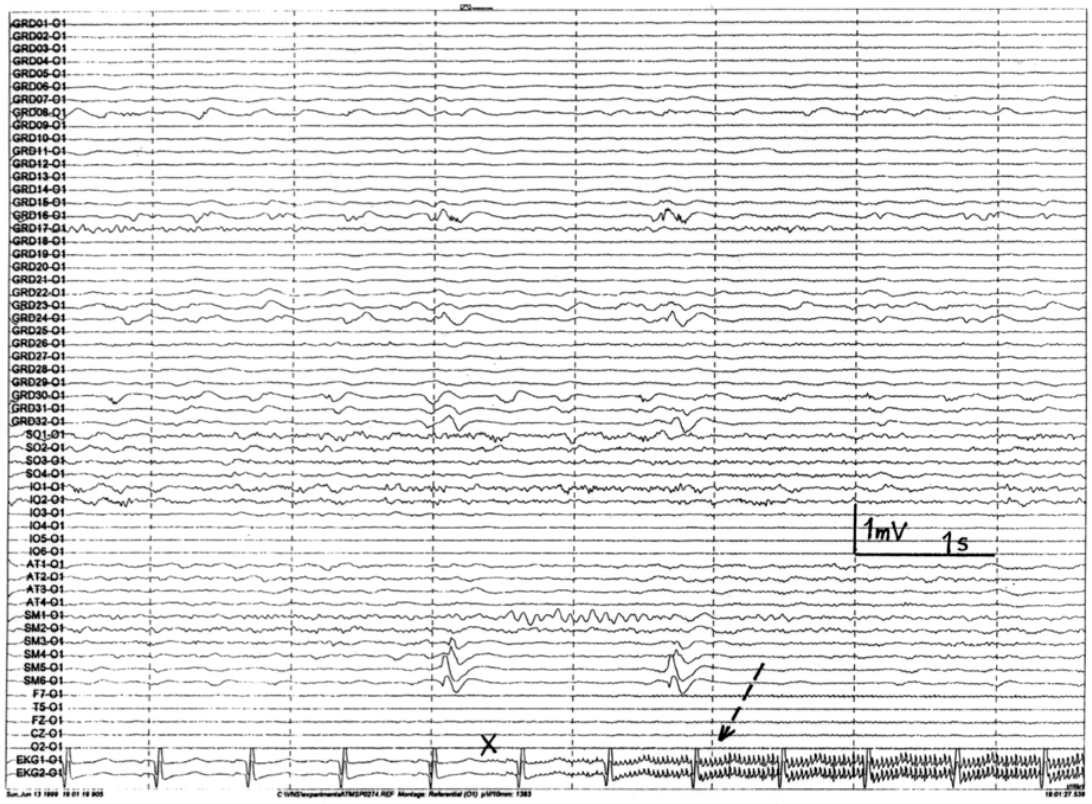

FIGURE 3. Interictal background activity (same epoch as in Figure 2) recorded using **SO1 (**contact 1 in the subdural superior occipital strip) reference. The dashed arrow indicates VNS artifact in 2 EKG channels. **X** marks the beginning of electrical stimulation. Onset of significant background change is marked by solid arrow.

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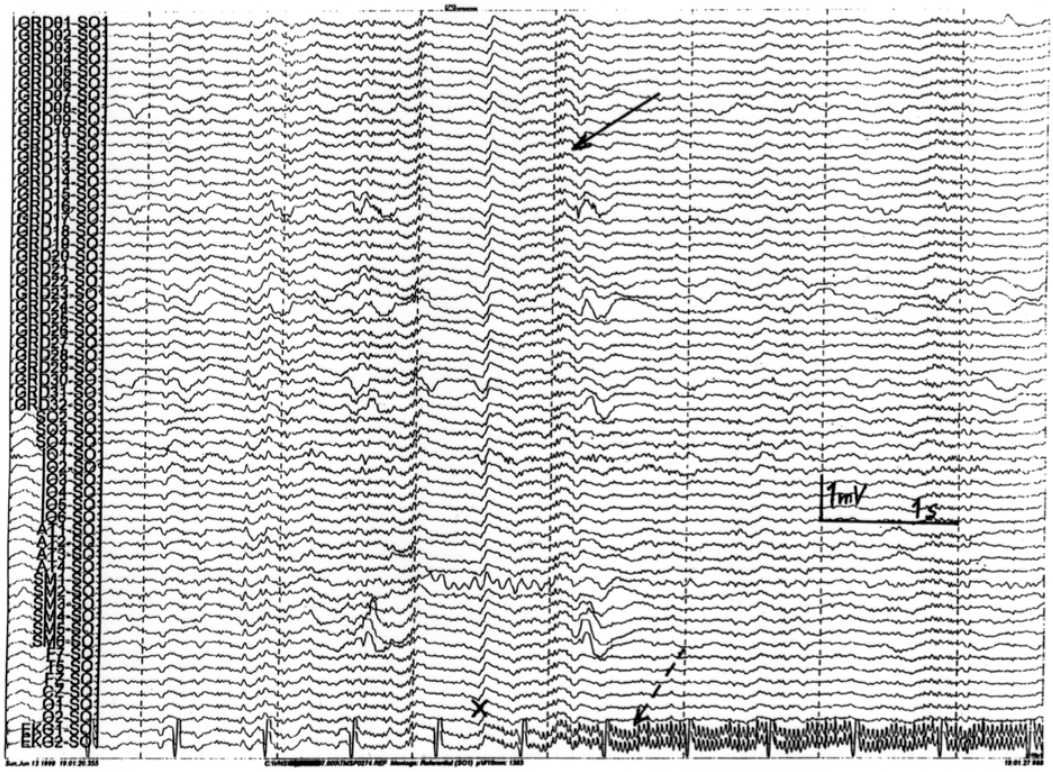

FIGURE 4. A seizure recorded with VNS in the “off “ mode.

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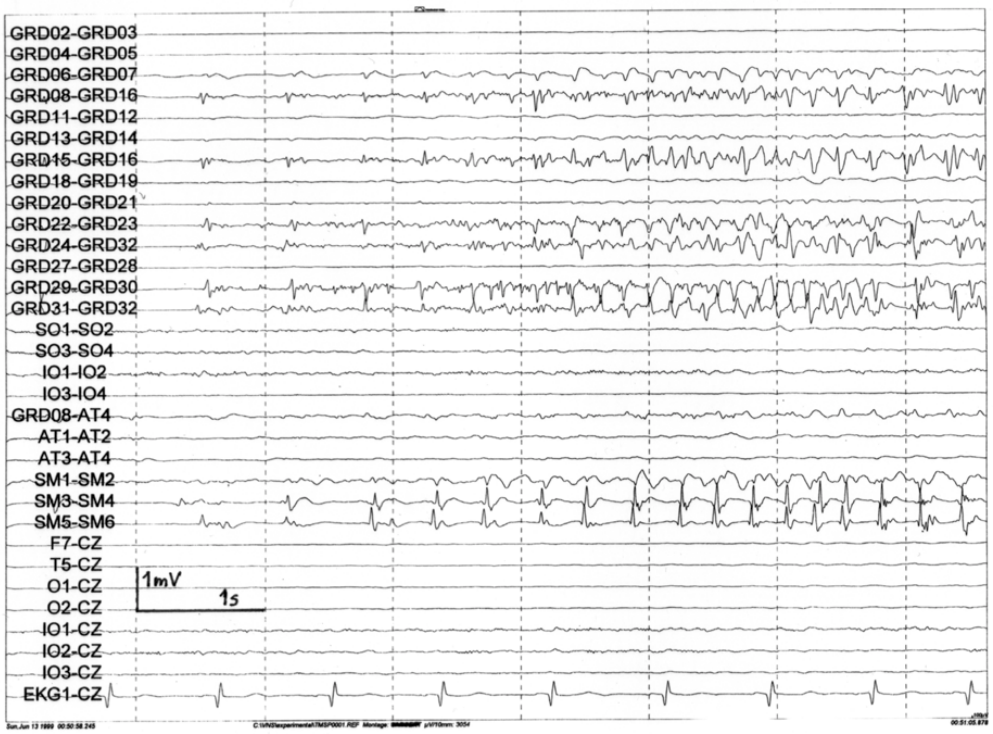

FIGURE 5. A seizure recorded with VNS in the “on” mode. The arrow indicates VNS artifact in EKG channel.

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