Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review

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Object. The wide application of deep brain stimulation in the management of movement as well as other degenerative neurological and psychiatric disorders has renewed the interest in using deep brain stimulation in the management of medically intractable epilepsy. Various stimulation targets have been used with significantly varying results in aborting seizure activity. Electrical cerebellar stimulation (CS) has been used for more than 50 years in the management of epilepsy, with conflicting results. In the current study, the authors review the pertinent literature to outline the role of CS in the management of medically refractory epilepsy.

Methods. The PubMed medical database was systematically searched for the following terms: "cerebellar," "epilepsy," "stimulation," and "treatment," and all their combinations. Case reports were excluded from this study.

Results. The pertinent articles were categorized into 2 large groups: animal experimental and human clinical studies. Particular emphasis on the following aspects was given when reviewing the human clinical studies: their methodological characteristics, the number of participants, their seizure types, the implantation technique and its associated complications, the exact stimulation target, the stimulation technique, the seizure outcome, and the patients' psychological and social poststimulation status. Three clinical double-blind studies were found, with similar implantation surgical technique, stimulation target, and stimulation parameters, but quite contradictory results. Two of these studies failed to demonstrate any significant seizure reduction, whereas the third one showed a significant poststimulation decrease in seizure frequency. All possible factors responsible for these differences in the findings are analyzed in the present study.

Conclusions. Cerebellar stimulation seems to remain a stimulation target worth exploring for defining its potential in the treatment of medically intractable epilepsy, although the data from the double-blind clinical studies that were performed failed to establish a clear benefit in regard to seizure frequency. A large-scale, double-blind clinical study is required for accurately defining the efficacy of CS in epilepsy treatment.
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Key Words • cerebellum • complication • epilepsy • outcome • medically refractory seizure • cerebellar stimulation

It is well known that epilepsy represents the most prevalent serious neurological disorder across all age groups.[45] It has been reported that approximately 1% of the US population suffer from epilepsy, and this percentage increases to 5% among children and adolescents in the US or Western Europe.[24] Approximately one-third of these patients will eventually develop epilepsy that is refractory to any kind of pharmacological treatment.[25] The actual incidence of medically intractable epilepsy has been reported to be approximately 6 of 100,000 people per year, which translates to 17,000 new cases annually in the US alone.[26] Even though surgical treatment is a valuable alternative to medical treatment in very carefully selected cases, unfortunately a large percentage of these patients are not good surgical candidates.[45] It is apparent that the development of a novel treatment modality is of paramount importance for these patients.

The recently exponentially increasing clinical applications of deep brain stimulation—mainly in movement disorders, but also in a large spectrum of degenerative neurological disorders—have reignited the interest in using electrical stimulation to abort or prevent seizure activity.

The concept of brain stimulation in the management of seizure activity is not new. Pelops from Alexandria, approximately 20 centuries ago, was able to abort something that could represent a simple partial seizure, by tying

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a ligature around the affected limb.[17,46] Later on, Brown-Séquard, Jackson, and Gowers independently suggested that counterirritation could be a potential mechanism for abating seizure activity.[6,20,31,46] Use of deep brain stimulation has been performed in several animal experimental studies and human trials for managing epilepsy. Various stimulation targets, such as the cerebral cortex,[33,36] the anterior thalamic nucleus,[12,27,32] the centromedian thalamic nucleus,[7,51,56,57,59] the head of the caudate nucleus,[7,50,51] the hippocampus,[50,51,58] and the subthalamic nucleus[3,44] have been used, with significantly varying clinical results.

In this study we performed a systematic review of the existing animal and human studies in which CS was used in the treatment of medically refractory epilepsy. Meticulous review of the pertinent literature was done to summate the existing experience with CS, identify any controversies, and outline the potential role of this treatment modality in the management of medically refractory epilepsy.

Methods

An extensive literature search through the PubMed medical database was performed using the terms "cerebellar," "stimulation," "epilepsy," "treatment," and all possible combinations. The retrieved articles were meticulously reviewed and were categorized into 2 large groups: animal experimental studies and human clinical studies.

Articles referring to case reports were excluded from our study. Every effort was made to identify any repetition of cases among the published clinical series and/or repetition of reports in different journals. In these cases, only the original clinical series were included in our study. It has to be mentioned, however, that this task was not easy, and the reader must be aware of potential redundancies in the reported data.

In reviewing the human studies, particular attention was paid to the design of the study, its methodological characteristics, the number of participants, the type of seizures, the duration of epilepsy, the surgical technique and its associated complications, as well as the type of electrodes implanted, the stimulation parameters, and the outcome regarding seizure frequency. Data regarding psychological or social performance were also reviewed, whenever available.

Results

Animal Experimental Studies

Numerous studies exploring the role of CS in aborting seizures have been published in the literature. All of these studies were based on the widely accepted functional anatomical and electrophysiological concepts that the cerebellum exerts an inhibitory effect on the thalamus and the cerebral cortex through the synaptic action of Purkinje cells and its efferent fibers traveling via the superior cerebellar peduncle.[9,29,40,61] The output of the cerebellum to the ascending reticular formation may be implicated in the inhibitory effect of the cerebellum to the basal ganglia neuronal network, which results in decreased activity of the excitatory thalamocortical projections.[9,16] This process ultimately results in inhibition of cortical excitability. There is a wide variation in the animal models used, the seizure induction methodology, the exact stimulation target, the stimulation methodology, and the stimulation parameters. Therefore, the observed results demonstrated a significant variation and contradictory conclusions were occasionally extracted.

Cooke and Snider[8] reported on the results from their cat model, in which cerebellar surface electrical stimulation could arrest seizures induced by direct electrical stimulation of the cerebral cortex. Similarly, Hutton et al.,[28] working with cats in a penicillin-induced seizure model, found that stimulation of the cerebellar vermis, the paramedian lobulus, and the dentate nucleus resulted in seizure inhibition. Dow et al.[14] published similar findings after working with rats in a cobalt powder–induced seizure model. They stimulated the anterior cerebellar lobe and observed inhibition of the induced epileptiform activity. Mutani and Fariello[42] found that stimulation of the anterior surface of the cerebellar cortex resulted in inhibition of cobalt-induced seizures. Bantli et al.[2] also observed significant seizure reduction after applying cortical CS in their penicillin-induced seizure model.

However, a series of later animal studies in cats and monkeys could not reproduce similar results; neither lateral nor midline cortical CS had an effect on seizure activity or even provoked electrographically confirmed seizures.[15,22,38,48,52,53] Reimer et al.[48] found that stimulation of the vermis produced prolongation of the seizures induced by cortical application of cobalt powder in their cats. Likewise, Hablitz[21] and Myers et al.[43] found that CS had no effect on seizure activity in their penicillin-induced seizure models. Godlevskii et al.,[19] using a penicillin-induced seizure model, found that cortical stimulation of the paleocerebellum resulted in a decreased amount of interictal spikes, but had no effect on actual seizure activity. In addition, Brown et al.,[5,13] working on a monkey seizure model in which electrical cortical stimulation was used to abort seizures, performed light and electron microscopic examinations of cerebellum specimens obtained in the experimental animals. Specimen examination revealed attenuation of the molecular layer of the cerebellum cortex and loss of Purkinje cells in the surface areas of electrode contact. The authors found that electrical charge densities of up to 5 times the necessary threshold for cerebellar efferent activation resulted in no additional cortical damage beyond that produced by the presence of the implanted electrode. They postulated that charge densities ≤ 7.4 μC/cm^2/phase should be considered safe for stimulation of the human cerebellum, whereas a further electrical current increase may lead to cortical tissue damage, and thus, it may make the stimulation ineffective.

Electrical stimulation of the vermis appeared to arrest seizure activity caused by hippocampal stimulation in animal studies.[30,39] Similarly, stimulation of the nucleus fastigius of the cerebellum stopped seizures induced by the application of cobalt powder to the hippocampus in the animal study performed by Babb et al.[1] Interestingly, they observed that stimulation of the dentate nucleus in their study resulted in prolongation of the induced seizures. In

contrast, Hemmy et al.,[26] working with an animal model of direct stimulation-induced seizure, found that either cortical or deep nuclei CS had no effect on seizure activity. Rubio et al.[49] recently reported on their experience working with an amygdala-kindling animal model, and found that CS resulted in an initial facilitation of the induced limbic seizures. However, CS resulted in slower propagation and arrest of the secondary generalized seizures.

A review of the cerebellar animal studies shows that surface stimulation has been used significantly more frequently than deep nuclei stimulation. Laxer et al.[35] reviewed the results of 22 previously published animal experimental studies in which CS was used. They drew the conclusions that vermian and superomedial cortical stimulation appeared to be more efficient than lateral cortical stimulation, and that CS seemed more effective in models of generalized or focal epilepsy of the limbic system than those of focal epilepsy of the sensorimotor cerebral cortex. In our current review, it appears that CS of deep structures has been used in only 3 animal experimental studies, and in 2 of these there was inhibition of seizure activity,[1,28] whereas in the other study there was no effect.[26] Interestingly, stimulation of the dentate nucleus showed seizure inhibition in one study,[28] no effect on seizure activity in another,[26] and prolongation of seizure duration in the third.[1] It has to be mentioned, however, that the stimulation parameters showed a significant variation in these 3 studies, as in the majority of animal studies of CS.

Human Clinical Studies

The promising results of the early animal experimental studies and the lack of adverse events led to the design and execution of the first clinical study. Cooper and his coworkers[9–12] reported on their findings from applying cortical CS to parts of both paleo- and neocerebellum for treatment of patients with medically refractory epilepsy. Their surgical technique consisted of the implantation of 4 or 8 pairs of bipolar platinum electrodes embedded in a silicon mesh, via an occipital approach.[10] The electrodes were stimulated through an antenna fixed subcutaneously on the chest by transepidermal inductive coupling. The authors reported on 32 patients suffering medically intractable epilepsy with a mean duration of 17.6 years.[9] The included patients suffered from partial or focal seizures, generalized seizures, or partial and generalized seizures. A 4-tier outcome scale was used in their study, with 1 indicating mild improvement and 4 representing great improvement. The psychological status of their patients was evaluated pre- and poststimulation by using the Wechsler Memory Scale, the Wechsler Adult Intelligence Scale, and the Bender-Gestalt test. The stimulation parameters they used were empirically developed and were ultimately set at a rectangular pulse of 1-msec duration.[10] In the initial phase of their study there was patient-controlled periodic stimulation, whereas during the last phase of their study automatic stimulation was delivered. In the aforementioned study[9] they found that 18 (56.2%) of 32 of their patients demonstrated a 50% or more reduction in seizures, whereas 9 (28.1%) of 32 showed no response at all. The beneficial effect of CS was maintained for at least 3–42 months postoperatively (mean follow-up time 18 months), showing no

seizure rebound effect. Furthermore, they documented that all their responders showed some psychological improvement, with increased alertness and improved postoperative concentration and ability to perform routine daily activities. The authors also reported that there was significant postoperative improvement of the verbal, performance, and memory IQ in their patients poststimulation, although without providing any statistical data in their study. In regard to the safety of their procedure, they reported a 1% mortality rate due to postoperative hemorrhage, and a 9% cumulative procedure-related morbidity rate (Table 1). Among the 200 patients included in a subsequent study, Cooper et al.[10] observed postoperative CSF leakage in 7 (3.5%), development of transient cerebellar edema in 3 (1.5%), infection in 4 (2%), and hydrocephalus in 1 (0.5%). The authors reported no adverse neurological or psychological events in their series. In a subgroup of 5 of their patients, cerebellar biopsy samples were obtained from the site of the electrode implantation.[11] Histological analysis of the specimens demonstrated reduction in the thickness of the molecular layer, significant decrease or depletion of the Purkinje cells, and decreased populations of stellate cells.

Sramka et al.[51] published their results from a series of 10 patients suffering various forms of medically intractable epilepsy. However, CS was used in only 3 patients, whereas in the remaining 7 patients stimulation of either the caudate nucleus or caudate and dentate nuclei was applied. The anatomical target was the dentate cerebellar nucleus, and bilateral stimulation was delivered through occipital stereotactically implanted electrodes. The stimulation parameters consisted of 10- and 100-Hz frequency, 1-msec duration, and voltage of 10 V. Stimulation was delivered once a day for a total of 3 minutes, during a 1–8-day period. They observed improvement in all their cases; however, that improvement was temporary. The authors raised concerns in their study regarding the development of a kindling phenomenon secondary to the stimulation being used.

At approximately the same time, Gilman et al.[18] reported their results from applying cortical CS in 6 patients suffering medically refractory epilepsy of various origins and with different types of seizures. In 4 of their patients, an 8-contact electrode was placed over the surface of the anterior cerebellar lobe, and a second 16-contact electrode (both from Avery Labs, Inc.) was placed over the cerebellar hemisphere, through a small suboccipital craniectomy. In the other 2 patients, an 8-contact electrode was bilaterally placed over the cerebellar hemispheres. The implanted electrodes were connected to 2 receivers (Avery Labs, Inc.) subcutaneously implanted in the anterior chest wall. The stimulation parameters used were as follows: square waves, 1-msec duration, and 10-Hz frequency. A single-blind trial was performed. The authors found that 5 (83.3%) of their 6 patients demonstrated reduced seizure frequency in the poststimulation period compared with the preimplantation baseline. They also noted that grand mal and psychomotor seizures seemed to respond better than focal motor seizures. Cerebellar tissue biopsy was possible in 4 of their 6 cases during the electrode implantation procedure. Histopathological examination of their specimens revealed severe loss of the Purkinje cells, degenerative changes

TABLE 1: Literature review of the most important clinical series in which CS was used in the treatment of medically refractory epilepsy

Authors & Year	No. of Patients	Stimulation Target	Stimulation Parameters	Sz Outcome	Poststimulation Psychological Outcome	Complications
Cooper et al., 1973	32	cerebellar cortex (paleo- & neocerebellum)	1-msec rectangular pulses	56.2% w/ >50% decrease in sz frequency	improved; increased alertness, increased verbal & memory IQ	1% mortality, 9% morbidity
Sramka et al., 1976	3	bilat dentate nucleus	10–100 Hz, 1 msec, 10 V	100% w/ temporary improvement	NA	development of kindling phenomenon
Gilman et al., 1977	6	anterior lobe & cerebellar hemispheres	square waves, 1 msec, 10 Hz	83.3% had decreased sz frequency	NA	NA
Levy & Auchterlonie, 1979	6	cerebellar cortex	3 V, 10 pps	33.3% w/ significant improvement & 33.3% w/ minor improvement	33.3% developed depression	all patients had poststimulation headache, & 16.6% developed wound infection
Davis & Emmonds, 1992	30 w/ spasticity & epilepsy; 6 w/ epilepsy only	superomedial surface of cerebellar cortex	1–1.4 mA, 0.5 msec, 150 pps, 4-min ON/ OFF sequencing	71% sz free; 42% sz free	mild improvement	2 cases of wound infection
various clinical series accumulated by Krauss & Koubeissi	36	cerebellar cortex	various	33.3% sz free; 91.6% w/ significantly decreased sz frequency	NA	NA
Van Buren et al., 1978	5	superior cerebellar cortical surface	10–14 V, 10 & 200 Hz	no decrease in sz frequency	no change in IQ & memory quotient	60% w/ CSF leakage
Wright et al., 1984	12	superior cerebellar cortical surface	7 mA, 10 pps	no decrease in sz frequency	no change in psychometric test results	25% w/ electrode migration, 16.6% w/ wound infection, & 8.3% w/ mechanical failure
Velasco et al., 2005	5	superomedial surface of cerebellar cortex	2 μC/cm²/phase, 0.45 msec, 3.8 mA, 10 pps	41% w/ decreased sz frequency	NA	60% w/ electrode migration, 20% w/ wound infection

* NA = not applicable; sz = seizure.

of the remaining Purkinje cells, and concomitant proliferation of Bergmann astrocytes. These authors postulated that patients with marked loss of Purkinje cells responded poorly to CS in their study, whereas those with less marked changes had a better response.

Likewise, Levy and Auchterlonie[37] reported their results from a series of 6 patients suffering from medically intractable epilepsy (generalized motor seizure pattern). All their participants underwent electrode implantation for cortical CS. The stimulation parameters used were 3 V and 10 pps in the vast majority of their patients. Their pre- and poststimulation evaluation included a detailed neuroradiological, electroencephalographic, and psychological examination. The authors reported that 2 (33.3%) of their 6 patients demonstrated significant seizure frequency improvement poststimulation, another 33.3% showed some minor improvement, whereas 1 (16.6%) of 6 showed some increased seizure frequency poststimulation. They reported that all of their patients complained of headache postoperatively, which could not be proven to be associated with the stimulation process, and that there was a postoperative wound infection in 1 (16.6%) of 6 patients. Two of their participants developed depression postoperatively, but no other neurological or psychological side effects occurred in their study.

Davis and Emmonds[13] published their results from a series of 30 patients with spasticity and epilepsy and 6 patients suffering medically refractory epilepsy only. Their anatomical target was the superomedial surface of the cerebellum, and twin pad electrodes were bilaterally implanted. The Avery radiofrequency system was used, and during the last phase of their study a totally implantable pulse generator was coupled to the radiofrequency system (Neurolith 601, Pacesetter Systems). The applied stimulation parameters were as follows: current intensity 1–1.4 mA, duration 0.5 msec, 150 pps, monodirectional pulses, and 4-minute ON/OFF sequencing. In one group of 7 of their patients with an average stimulation duration of 13.6 years (range 10–15 years) they found that 71% were seizure free, whereas the remaining 29% had reduction of their seizures. In another group of 12 patients with an average stimulation duration of 8 years (range 2–13 years), 42% were seizure free, 33% had reduced seizures, and 25% had no improvement. In addition, they found that the necessary amount of anticonvulsant medications was decreased in 65% of their patients. The authors reported no complications except for 2 cases of postoperative infection, for which the implanted systems had to be removed.

A number of small clinical series in which cortical CS was used in patients suffering from various forms of medically intractable epilepsy of various origins, with insufficient or no data regarding the exact stimulation target, the stimulation parameters used, and the type of the implanted electrodes, has been reported in the literature. In an attempt to summarize the results of these series, Krauss and Koubeissi[34] found that a total of 36 patients had been reported to have undergone cortical CS for their epilepsy.[4,14] The seizure frequency was found to be reduced in 33 (91.6%) of the 36 patients, whereas 12 (33.3%) had become seizure free.

Van Buren et al.[54] published their results from a series of 5 patients undergoing cortical CS for medically intractable epilepsy. Their cohort included patients with generalized, myoclonic, and/or partial seizures of various origins. Two 4-contact electrodes (Avery Labs, Inc.) were bilaterally implanted on the superior cerebellar cortex, 1 cm lateral to the midline, and were connected to 2 receivers (Avery Labs, Inc.) that were subcutaneously implanted in the anterior chest wall. All patients had pre- and poststimulation evaluation of their seizure frequency, intelligence and memory quotients, surface electroencephalograms, CSF neurotransmitters (norepinephrine, γ-aminobutyric acid, cyclic adenosine monophosphate, and cyclic guanosine monophosphate), measurements, and their family's subjective evaluations (including seizure frequency, duration and type of seizures, administered therapy, and psychological and social performance). The stimulation parameters used were as follows: 10–14 V, and 10-Hz frequency for all types of seizures but myoclonic ones, in which they applied 200 Hz. Their stimulation trial consisted of 4 phases, each of which lasted 4–6 weeks. The first evaluated early responses of patients in whom stimulation was turned ON and OFF in a nonblinded fashion, the second evaluated their responses in a double-blind fashion, and the other 2 phases evaluated the respective responses after a 10-month period of stimulation. Their statistical analysis showed no significant differences between observed seizure frequency pre- and poststimulation. The only statistically significant difference was between the observed seizure frequency in the early and late ON stage phases. In addition, no meaningful differences were noted on the electroencephalograms obtained pre- and poststimulation in their study. Similarly, the full-scale intelligence and memory quotients demonstrated no essential changes between the pre- and poststimulation evaluations. The CSF levels of norepinephrine showed some increase after stimulation, whereas the CSF levels of γ-aminobutyric acid were decreased and the cyclic adenosine monophosphate and cyclic guanosine monophosphate levels had remained essentially unchanged. Interestingly, the patients' families thought that the stimulation made the patients more alert, more sociable, less depressed, and more independent. The authors reported no major neurological or psychiatric complications in their series. Leakage of CSF occurred in 3 (60%) of 5 patients, despite the meticulous efforts to achieve watertight dural closure. They also had the opportunity to obtain cerebellar tissue biopsy samples in 3 of their patients, which showed a significant decrease of the Purkinje cell populations (in 2 cases there was a > 75% decrease compared with normal controls).[47]

Similarly, Wright et al.[60] presented their results from a double-blind prospective clinical trial, in which they used cortical CS to treat 12 patients with medically refractory epilepsy of various origins. The participants suffered epilepsy of various clinical patterns (grand mal, petit mal, atonic, absence, and myoclonic seizures) and of long duration (average 20.6 years). Their surgical technique included the implantation of bilateral 8-contact electrodes (Avery Labs, Inc.) on the superior cerebellar cortical surface, through occipital bur holes. The electrode arrays were positioned parasagittally, approximately 2 cm from the midline. The electrode leads were tunneled

subcutaneously to 2 receivers, which were implanted into subcutaneous pockets in the anterior chest wall or the axilla. The implanted receivers were activated by specially modified external transmitters (Avery Labs, Inc.). The applied stimulation parameters were as follows: intensity of 7 mA and frequency of 10 pps. The stimulation trial was divided into 3 phases, each lasting 2 consecutive months for all participants. Patients received 2 months of continuous stimulation, 2 months of contingent stimulation, and 2 months of no stimulation. The sequence of the phases was randomly selected for each participant. All patients were evaluated pre- and poststimulation by a psychiatrist, and they were clinically assessed pre- and poststimulation by 2 independent neurologists. There were data for 11 of 12 patients. The investigators found no decrease in the frequency or the severity of the patients' seizures during the stimulation periods. However, the vast majority of patients reported that the implanted stimulators helped them significantly. There were no adverse psychiatric events during the stimulation period, and the psychometric tests revealed no difference pre- and poststimulation. The authors reported no procedure-related death, but they observed electrode migration in 25% of cases, wound infections in 16.6%, and mechanical failure in 8.3%. They concluded that CS may not be a suitable treatment for patients with medically intractable epilepsy.

Recently, Velasco et al.[55] reported on their experience applying cortical CS in patients suffering medically intractable motor seizure epilepsy. In their double-blind, prospective clinical study, they included 5 patients with generalized tonic-clonic seizures (all 5 patients), tonic seizures (4 of 5 patients), drop attacks (2 of 5 patients), and myoclonic and atypical absence seizures (1 of 5 patients). All of their patients had between 8 and 22 seizures per month. Their implantation technique consisted of 4-contact electrodes (Medtronic, Inc.), which were inserted through bilateral suboccipital bur holes. The electrodes were placed 1.5 cm from the midline, on the superomedial cerebellar cortex, and their final position was verified by intraoperative fluoroscopic imaging. The electrode leads were connected through a Y-shaped connector cable to the implanted battery-operated pulse generator, which was positioned in a subcutaneous pocket in the anterior abdominal wall. The stimulation parameters were as follows: charge density 2 μC/cm^2/phase, pulse width 0.45 msec, current intensity 3.8 mA, and frequency 10 pps. The implanted pulse generator was the cathode and the case was the anode. The stimulation was turned ON for 4 minutes and then OFF for another 4 minutes throughout the day. No stimulation was delivered for 1 month after the implantation (sham period), whereas for the next 3 months a double-blind trial was done, in which 3 patients received stimulation and 2 did not. During this period, both the patients and the evaluators were blinded in regard to whether the stimulator was ON or OFF. After this double-blind stimulation period, all the implanted stimulators remained ON until the end of the study. The authors found that there was no significant seizure frequency difference in the sham period. However, during the 3-month double-blind period, there was no decrease in seizure frequency among the patients who had their stimulator OFF, whereas in the 3 patients with their stimulators ON, there was a 33% decrease in seizure frequency. This difference was found to be statistically significant. Similarly, during the 6-month period when all patients had their stimulators ON, there was a mean 41% decrease in the seizure rate. The authors reported electrode migration in 3 (60%) and wound infection in 1 (20%) of the 5 patients.

Discussion

Although it has been more than 3 decades since the publication of the first clinical series of patients undergoing CS for the treatment of medically intractable epilepsy,[8–10] this treatment methodology remains experimental. Numerous animal studies have demonstrated that electrical stimulation of the cerebellum may abort electrically or chemically induced seizures and drastically alter the electrophysiological profile of the neuronal tissue in vitro and in vivo.[1,2,5,8,13–15,19,21,22,26,28,30,35,38,39,41,42,48,49,52,53] However, there are several issues that remain to be resolved and important questions that need to be answered.

The mechanism of action of CS in aborting seizures is still unclear.[34] The previously proposed theory that stimulation of the Purkinje cells may intensify the inhibitory cerebellar output to the thalamic neuronal network, and subsequently weaken its excitatory output to the cerebral cortex, cannot be supported by the histopathological findings of several animal and human reports. These reports described significantly decreased populations of Purkinje cells in epileptic patients.[9,18,54] It has been proven that stimulation of the cerebellar cortex resulted in further degeneration and population decrease of Purkinje cells.[34] In addition, Dow et al.[14] had demonstrated in their animal experimental study that electrode stimulation resulted in a decrease in the firing rate of the Purkinje cells located adjacent to the implanted electrode. Moreover, Mutani et al.[41] have demonstrated that repetitive electrical CS completely suppressed spontaneous Purkinje cell activity.

The exact stimulation target in the cerebellum remains to be defined. The vast majority of the animal experimental studies but also the clinical trials have used the cerebellum cortical surface as stimulation target, with frequently contradictory results.[8,5,14–16,22,23,38,48,52,53] However, the stimulation of the deep cerebellar nuclei appears to provide more solid data and better seizure control.[1,35] There are several mechanisms that may explain this discrepancy in the results of the cortical CS in animal and human studies. Different areas of the cerebellum's cortical surface have been used in the published studies. Stimulation of the superior and medial surface of the cerebellum appears to provide more consistent results than stimulation of the posterior lobe. It has to be emphasized at this point that the implantation of an electrode in a certain cortical area in an animal experimental study or even in a human study does not necessarily mean that the stimulation site remains the same during the trial and is the one that was selected preoperatively, because in a large number of studies there no reports regarding verification of the final position of the implanted electrodes. Moreover, electrode migration was a commonly occurring complication, even in recent human studies.[55,60]

The interface between the implanted electrode and

the cerebellar surface has remained another puzzling issue, which may interfere in the propagation of the delivered electrical stimulus. Previous studies have demonstrated that dense arachnoidal reactive tissue usually develops at the implantation site.[18] The formation of this reactive tissue may well alter the impedance of the implanted electrode, and it may modify in an unpredictable way the characteristics of the ultimately delivered electrical stimulus.

The stimulation parameters per se represent another variable that may well be responsible for the significant variation observed in the published animal and human CS studies. There is a significant variation in the charge densities used in the previously published animal experimental studies, depending on the animal species and the seizure models. In contrast, the charge density of 2 $\mu C/cm^2/phase$ was used in the vast majority of the human studies. However, the stimulation frequency varied significantly from low (10 Hz) to high (200 Hz) frequencies.[18,54,55,60] It seems that there is a consensus regarding the charge density and the low-frequency stimulation used in human studies.[19,55,56,61]

A significant confounding factor in the evaluation of the CS studies in humans is the inclusion of patients with epilepsy of various origins and different seizure patterns.[8–11,18,34,54,55,60] It is very unlikely that medically intractable epilepsy secondary to dysplastic changes and epilepsy due to the presence of vascular pathological features would respond to CS of standard parameters. Similarly, it is very unlikely that generalized motor seizures would respond to the same stimulation patterns that atonic or absence seizures would. It seems reasonable that certain seizure patterns may require specific stimulation characteristics or even different stimulation targets.[55] Because in the vast majority of epilepsy cases there are periods of bursts of pathological electrical cortical activity, the development of systems that would detect abnormal electrographic patterns and that would automatically activate the delivery of an electrical stimulus through an implanted stimulator could be more efficient in aborting or preventing seizures.

The placebo effect of the stimulation constitutes another confounding factor in the accurate evaluation of CS in the treatment of medically intractable epilepsy. In several human studies the investigators found that although the actual number of poststimulation seizures remained essentially unchanged compared with the preimplantation baseline, the patients and their relatives reported decreased seizure frequency and improved psychological and social functioning.[54,60] The execution of double-blind clinical trials significantly contributed in minimizing the placebo effect and any potential investigators' or participants' biases.[54,55,60] Interestingly, 2 of the 3 double-blind studies failed to prove any statistically significant differences in seizure frequency before and after stimulation.[54,60] There was a lot of criticism, however, by other clinical investigators[55] regarding the seizure outcome interpretation performed and the statistical analysis of the results. For example, in a study published in 2005, Velasco et al.[55] commented on the analysis of the results of the other 2 double-blind studies, and postulated that there are reports in the literature that support the idea that analysis outcome was inconsistent in Van Buren and co-workers' study. After making the appropriate corrections, it can be shown that the vast majority of their patients had decreased seizure frequency in the ON phase when compared with the OFF phase.[55] Likewise, the majority of the patients included in Wright and associates' study actually demonstrated decreased seizure frequency after the application of CS.[55] In their recent study, Velasco et al. attempted to explain the differences between their results and those of Van Buren et al.[54] and Wright et al.[60] They postulated that the criteria for patient selection, the variance in seizure types, the stimulation parameters used, the implantation technique and any procedure-related pitfalls, the design and the applied methodology of the double-blind trial, and the length of the follow-up period may be responsible for the observed differences.[55]

A critical review of the existing animal and human studies shows that stimulation of the cerebellum may be a treatment option worth exploring for carefully selected patients suffering certain types of medically intractable epilepsy who are not suitable candidates for other types of resective epilepsy surgery. The recent experience from double-blind studies indicated that generalized tonic-clonic seizures or other seizure types that are associated with supradiencephalic structures may respond better to CS than tonic seizures.[55] It seems that the most commonly used charge density of 2 $\mu C/cm^2/phase$, the frequency of 10 pps, and a pulse width of 0.45 msec may be a good set of initial stimulation parameters for superomedial cortical CS.[55] Designing a double-blind study with long-term follow-up, examining not only the seizure frequency but also other characteristics such as seizure type, seizure severity, presence of auras, duration of postictal confusion, and cognitive and psychosocial functioning, is necessary for the accurate evaluation of this emerging neuromodulative treatment option. The development of high-accuracy imaging techniques, the availability of small implantable electrodes, and the continuously improving software technology that can detect and analyze epileptiform activity, may lead in the near future to the development of a novel responsive stimulation system for cerebellar cortex. Furthermore, the continuous development and improvement of high-accuracy frameless stereotactic systems may resurrect interest in evaluating the role that stimulation of deep cerebellar nuclei plays in aborting seizures.

Conclusions

The superomedial surface of the cerebellar cortex remains a target of interest for stimulation in the management of disease in patients with certain types of medically refractory epilepsy who are not candidates for resective surgery. The existing clinical data suggest that CS may be of potential benefit. Further double-blind, large-scale clinical studies and long follow-up periods are necessary for better definition of the stimulation parameters and more accurate evaluation of the efficacy of CS in seizure management. Evaluation of seizure outcome along with detailed cognitive, psychological, and social examinations pre- and poststimulation are of paramount importance for outlining the role of CS in the management of medically intractable epilepsy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fountas. Analysis and interpretation of data: all authors. Drafting the article: Fountas, Kapsalaki. Critically revising the article: Fountas. Reviewed final version of the manuscript and approved it for submission: Fountas.

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