Electricity in the treatment of nervous system disease

H. Fodstad¹ and M. Hariz²

¹ Veterans Affairs Medical Center, New York, USA
² Institute of Neurology, London, UK

Summary

Electricity has been used in medicine for almost two millennia, beginning with electrical shocks from the torpedo fish and ending with the implementation of neuromodulators and neuromodulators. These implantable stimulators aim to improve functional independence and quality of life in various groups of disabled people. New indications for neuromodulation are still evolving and the field is rapidly advancing. Thanks to modern science and computer technology, electrotherapy has reached a degree of sophistication where it can be applied relatively safely and effectively in a variety of nervous system diseases, including pain, movement disorders, epilepsy, Tourette syndrome, psychiatric disease, addiction, coma, urinary incontinence, impotence, infertility, respiratory paralysis, strokes and blindness.

Keywords: Deep brain stimulation; electricity, electrotherapy; nervous system; neuromodulation; neuromodulator; neuroprosthesis; neurostimulation; insanity.

"Is it a fact – or have I dreamt it – that by means of electricity, the world of matter has become a great nerve, vibrating thousands of miles in a breathless point of time? Rather, the round globe is a vast head, a brain, instinct with intelligence; or shall we say it is itself a thought, nothing but thought, and no longer the substance which we dreamt it.

Nathaniel Hawthorne (1804–1864)

Historical background

By definition, electricity is a fundamental entity of nature consisting of negative and positive charges, observable in the attractions and repulsions of bodies electrified by friction and natural phenomena, and usually utilized in the form of electric currents.

The first known use of electricity in medicine was in AD 46 when Scribonius Largus, a pharmacist from Nero and physician to the Roman Emperor Claudius, applied electrical currents from a torpedo fish to treat headaches and painful gout [61, 94]:

"A chronic and intolerable headache which insidiously manifests itself can be eliminated once if treated by applying a live torpedo fish, black in color, to the site of the pain and leaving it there until the pain stops and the part is swollen."

The real breakthrough for electrotherapy came with the scientific progress of the 18th century, especially after the discovery of the Leyden jar in 1746 [11]. In 1777, Cavallo published "A complete treatise on electricity, in theory and practice, with original experiments." He reported cures of epilepsy, paralysis, chorea, deafness, blindness, rheumatism and glandular enlargement. He was also the first to recommend electricity as means of artificial respiration [11]. As early as 1774, Benjamin Franklin noted muscle contractions on exposure to static electricity [43]. After Franklin's invention of lightning rods in 1775, there were three important milestones in the history of electrotherapy: The discovery of animal electricity by Luigi Galvani in 1787, the discovery of bimetallic electricity by Alessandro Volta in 1794 and the discovery of inductive electricity by Michael Faraday in 1831 [34, 81] (Table 1). Volta also invented the first electric battery in 1800. In 1804 Aldini, a nephew of Galvani, recommended galvanism for deafness, insanity, atheroma, and to produce artificial respiration [11].

Andrew Ure in 1818 used the body of a hanged criminal immediately after execution to stimulate the phrenic nerves in the chest with galvanic electricity, thereby producing contractions of the diaphragm [106]. He thought
the method might be used to resuscitate humans with intact vital organs. Ure vividly described the events to the Glasgow Literary Society:

"The left phrenic nerve was now laid bare at the outer edge of the sterno-thyroidus muscle, from three to four inches above the clavicle; the cutaneous incision having been made by the side of the sterno-clido-mastoideus. Since this nerve is distributed to the diaphragm, and since it communicates with the heart through the eighth pair, it was expected, by transmitting the galvanic power along it, that the respiratory process would be renewed.

The success was truly wonderful. Full, now, laborious breathing instantly commenced. The chest heaved and fell; the belly was protruded, and again collapsed, with the relaxing and retiring diaphragm. This process was continued, without interruption, as long as I continued the electric discharges. Extraordinary grimaces were exhibited every time electric discharges were made on the

Fig. 1. (a) Title page of Duchenne de Boulogne's monograph 3rd edn 1872. (b) Duchenne stimulating the facial muscles in a patient
supraorbital nerve. His countenance was simultaneously thrown into fearful action: rage, horror, despair, anguish, and ghastly smiles, united their hideous expression in the murderer's face, surpassing for the wildest representations of a Fuselli or a Keen. At this period several of the spectators were forced to leave the apartment from terror or sickness, and one gentleman fainted."

In 1824, Florence in Paris reported on faradic stimulation and ablation of the cortex in experimental animals [72]. The following year Salandier proposed the use of acupuncture needles in galvanization, so that the current could be applied directly on the desired nerve or organ. The method was called electropuncture and was used for resuscitation by Leroy-D'Étioles in 1840 [64].

In 1855, the French physician Guillaume Duchenne de Boulogne published his pioneering monograph: "De l'électricisation localisée et de son application à la physiologie, à la pathologie et à la thérapeutique" [31] (Fig. 1a and b). Duchenne was the first to successfully use transcutaneous faradic stimulation of the phrenic nerves for artificial respiration. He was followed by Hugo von Ziemssen, who applied a DuBois-Reymond faradic stimulator (shocking coil) to the phrenic nerve to resuscitate a gas-poisoned patient [34]. At the same time Remak founded a German school of electrotherapy using galvanic current [111]. Interestingly, Duchenne was unwilling to admit the reality of the discoveries of Remak, and Remak rejected the conclusions of Duchenne. A comprehensive overview of contemporary electrotherapy was published by Erdmann in 1858 [32].

Evolution of neurostimulation and lesioning

In 1870, Frisch and Hitzig [41] observed limb movement when stimulating the motor cortex of the dog, and in 1873 Ditmar used guided electrodes experimentally for the study of the vasomotor center in the medulla oblongata [29]. The first documented account of applying electrical stimulation to the living human brain was in 1874 by Roberts Bartholow in Cincinnati [10]. The patient was a 30 year old woman with an "epilepsia" (meningioma) and an open ulcer in the posterior portion of the skull. Bartholow was able to stimulate the parietal cortex with a "Galvano-Faradic Company double cell battery" and insulated needles. He noted muscle contractions on electrical stimulation which also triggered a grand mal seizure. In 1884, Victor Horsley applied electrical stimulation of occipital tissue in a patient with an encephalocele [109]. The conjugate eye movements he observed led him to identify the stimulated tissue as lamina quadrigemina. Ewald's investigations in Germany in 1896 may have been the first where the brains of fully awake, unrestrained animals were stimulated over a long period of time [107]. Tallberg described the technique and his own extension of Ewald's work in 1900 [100].

In 1908, Victor Horsley and Robert Henry Clarke applied their stereotactic instrument and electricity to study cerebellar structures and functions in monkeys [57]. They described in detail the use of direct current (versus radiofrequency) to make lesions, a technique later adopted in animal experiments worldwide [38, 78, 84]. In 1912, Clarke wrote about his instrument [38]:

"This invention relates to what may be termed stereotaxic surgical apparatus for use in performing operations within the cranium of living human beings."

Clarke's prophecy became reality 35 years later when Spiegel and Wycis performed the first stereotactic operation in man [96, 97]. In subsequent years, electrical stimulation and recordings from selected subcortical regions through stereotactically implanted probes were performed in patients with parkinsonism, epilepsy and psychiatric disease by Magnus Petersen [107], Robert Heath [53-55], Carl Wilhem Sem-Jacobsen [88, 91], Orlando Andy [5], N P Rechtewere [112] and José Delgado [27]. Alberts and coworkers documented the improvement of dystonia with intracerebral stimulation in awake patients [2, 3].

Sem-Jacobsen was a controversial Norwegian psychiatrist and neurophysiologist. In 1963, he published an article about depth-electrographic observations in psychotic patients [88]. He stated that "electrical stimulation in some regions in the ventro-medial part of the frontal lobe resulted in a temporary improvement to complete freedom from symptoms."

Sem-Jacobsen was accused by Norwegian colleagues of receiving grants from the CIA to perform experiments on mentally ill patients. His name was cleared by a government appointed review commission in December 2003, twelve years after his death.

Jose Delgado used remote radio stimulation of bull's brains to abruptly stop their aggressive behavior in the arena [107]. In 1965 he summarized [26]:

"Autonomic and somatic functions, individual and social behavior, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and men, by electrical stimulation of specific
cerebral structures. Physical control of many brain functions is a demonstrated fact, but the possibilities and limits of this control are still little known.

In the nineteen twenties, Walter Rudolph Hess in Switzerland and Stephen Ramson in USA used electrostimulation to explore the different regions of the hypothalamus and related neural structures in animals [56, 83]. Their experiments provided support for the speculative theory proposed in 1937 by James Papez that the

limbic system (cingulate-hippocampus-fornix mamillary bodies-anterior thalamus) in conjunction with the hypothalamus may constitute the anatomical circuit which regulates emotions [79] (Fig. 2a and b). In 1948, Hess postulated that the hypothalamus consists of an anterior trophatropic zone, which dominates during resting and restorative activities, and a middle-posterior ergotropic zone, which regulates physiological reactions accompanying high arousal levels [56]. Hess received the Nobel
Prize in Physiology and Medicine 1949 for discovering the role played by certain parts of the brain in determining and coordinating the function of internal organs. He shared the prize with the Portuguese neurologist and politician, António Egas Moniz, who introduced prefrontal lobotomy for psychiatric diseases [33]. This highly controversial procedure was soon to be replaced by less destructive psychosurgeries using the stereotactic technique [33, 36, 63, 75]. Concurrently, electroshock therapy for psychiatric disease and depression was introduced by Ugo Cerletti [20]. Based upon Hess’ studies of the posterior hypothalamus in man [87], stereotactic thermoablation in the “strogesmic triangle” in 21 patients with pathologically aggressive behavior produced marked calming effect in 95% of the cases. The procedure, which was called “sedative therapy” encouraged a German group to perform stereotactic hypothalamotomies in 20 cases of pedophilia, hypersexuality and exhibitionism “with complete harmonization of sexual and social behaviour” [73]. A few years later, Nadvorňák and his group in Bratislava published a paper on thermoablation in the anterior hypothalamus for “hedonism,” which they defined as “not only excessive smoking, tobaccoism, but also excessive inclinations to good eating and drinking, lechery and bacchism” [74]

In 1974 Quada, Vernaert and Larsson performed stereotactic stimulation and electrocoagulation of the lateral hypothalamus in obese humans [82]. Three patients with gross obesity subjected to lesions in the lateral hypothalamus showed “a statistically significant, but transient decrease from preoperative to postoperative spontaneous calorie intake.”

Despite the reported effectiveness of hypothalamotomy as a method to control behavioral disturbances, serious moral, ethical and legal objections to these procedures have been raised [33, 65, 107].

As stereotactic neurosurgery progressed, stimulation became routine for localization of targets in the brain. Hassler, a former graduate researcher with Rudolph Hess, recognized that thalamic stimulation caused cessation of tremor and might mimic the same effect as a lesion [51, 52]. Similar observations of the stimulation of various subcortical targets were made by Spiegel and colleagues [43, 98] and Ronald Tasker and his group [101].

Melzack and Wall’s “gate control theory of pain” published in 1965 [69] laid the foundation for the start of pain management by neuromodulation, including transcutaneous electrical stimulation (TENS) [62], peripheral nerve stimulation [99, 111], spinal cord stimulation [76, 92], cortical stimulation [60, 105], and deep brain stimulation (DBS) [58, 70, 85]. DBS and spinal cord stimulation were also used for treatment of spasticity and dyskinesia [93, 95]. Early neurostimulators consisted of extracerebral parts (radiofrequency and antenna) and implanted components (receiver and electrode) [42].

Electrophonic stimulation (diaphragm pacing) for chronic ventilatory insufficiency was developed by William Glenn in the 1960’s [45, 46]. The initially enthusiastic reports on spinal cord stimulation in multiple sclerosis could not be substantiated in later trials [21, 43]. Visual cortex stimulation for blindness was first described by Brindley in 1968 [18], and the first clinical study on the use of vagal nerve stimulation for intractable epilepsy appeared in 1990 [47].

Current use of neuromodulation

Neuromodulation is defined as the use of electrical stimulation by implanted stimulators to treat various neurological conditions [1, 43]. Neurostimulation has experienced a renaissance in the past two decades with the introduction of totally implantable neuromodulators and image-guided surgical systems, and the field is rapidly advancing [66]. Neuroaugmentation to subcortical structures via implanted electrodes has largely replaced lesioning all over the world. DBS is a nonablative and reversible procedure with a low incidence of permanent complications, and it is considered safer than ablative lesions. The anatomical targets in the brain for DBS remain more or less the same as for stereotactic radiofrequency lesioning.

The current FDA (Food and Drug Administration) approved indications for DBS in the United States are unilateral or bilateral stimulation of the ventralis intermedius (Vim) nucleus of the thalamus for essential tremor and parkinsonian tremor, and unilateral or bilateral stimulation of the internal globus pallidus (GPi) and subthalamic nucleus (STN) in Parkinson’s disease [13, 14, 71]. FDA approval was based on the report of ‘The Deep-Brain Stimulation for Parkinson’s Disease Study Group’ published in 2001 [103]. However, the report has been subjected to criticism for inaccurate documentation of side effects [49]. Benabid introduced STN as the main target in Parkinson’s disease, but STN stimulation is hampered by psychiatric side effects due to the nucleus’ proximity to hypothalamus and the limbic circuitry [14, 80].
Some DBS surgery complications may be closely related to the experience and techniques of the neurosurgical team. Hardware complications (electrode migration, lead breakage, stimulator malfunction) and other side effects occur in a significant number of patients [16, 42, 50, 77]. The use of single-cell microelectrode recordings for alleged accurate target placement of the electrode, which has become routine in many centers, may increase the surgical complications, including hemorrhage [48]. The modern neuropsychomakers require repeat programming of the electrical paradigms by a specially trained health employee to meet the changing needs of each individual patient. The implanted non-rechargeable batteries need to be changed every three to five years.

The exact mechanism of action of DBS is not yet known. Possible mechanisms include depolarization blockade, channel blocking, synaptic failure, anterograde and retrograde effects, effects on non-neuronal cells, effects on the local concentrations of ions or neuroactive molecules, and neuronal energy depletion [68]. The long-term effect of chronic electrical stimulation on brain tissue and function is not well understood.

The indications for DBS in movement disorders include (but are not limited to) tremor, bradykinesia, dyskinesias, rigidity, dystonia and gait disturbance [7, 17, 24]. In addition, DBS has been reported to be successful in treating chronic deafferentation pain [58], cluster headaches [9, 39], epilepsy [15, 22, 108], obsessive-compulsive disorder [4, 6], Tourette syndrome [110], depression [59, 67], violent behavior [40] and other neuropsychiatric disorders [86]. Motor cortex stimulation has been applied for chronic pain [60, 105] and the auditory cortex has been stimulated magnetically and electrically for intractable tinnitus [25]. Transcranial non-invasive magnetic stimulation has been reported by several authors to be effective in controlling intractable epilepsy [28, 102]. Neurostimulation and neuromodulation is also used for restoration of hand function and gait [1], improvement of peripheral circulation [8, 30], bladder control [76], fertility management [1], respiratory paralysis [37, 46], chronic hiccup [35], blindness [44], cerebral palsy [23] and coma [104].

DBS is now an established method in treating movement disorders and pain. Thanks to functional imaging, new areas in the brain are shown to be involved in some pathological processes. These areas are now being subject to DBS to see if they can be electrically inhibited [9, 66]. DBS should still be regarded as experimental in psychiatric disease and embryonic in many other mentioned disorders until the reported results have been verified in controlled studies in a larger number of patients. DBS should be considered only for patients in whom other established therapeutic modalities have been carried out. Current practice and ongoing trials of DBS including brain targets are shown in Table 2a and b.

History seems to repeat itself, as electricity is currently being tried for almost any kind of nervous system disease with physicians looking for specific stimulation targets in the brain for certain symptoms and diseases. Neuronal circuits rather than specific nuclei are frequently targeted, and different targets often respond equally to electrostimulation for the same disorder. The voluminous recent literature on DBS indicates that it is in danger of becoming a new method in search for more diseases.

Table 2. (a) Routine use of DBS

<table>
<thead>
<tr>
<th>Parkinson's disease</th>
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<tbody>
<tr>
<td>- nucleus ventralis internus (Vim), nucleus pallidus internus (GPI), substantia nigra (STN), zona incerta</td>
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<tr>
<th>Dyskinesia</th>
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<tr>
<td>- globus pallidus internus (GPI)</td>
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<tr>
<th>Tremor (essential, cerebellar and MS)</th>
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<tr>
<td>- nucleus ventralis internus (Vim), zona incerta</td>
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<tr>
<th>Chorea</th>
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<tr>
<td>- nucleus ventralis internus (Vim), nucleus ventro-oralis posterior (Vop), globus pallidus internus (GPI), zona incerta</td>
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<th>Deafferentation pain</th>
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<tr>
<td>- nucleus ventro-postero-mediales (VPM), nucleus ventro-postero-laterales (VPL), centromedian nucleus (CM), periaqueductal gray (PAG), periventricular gray (PVG)</td>
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Table 2. (b) Current trials of DBS

<table>
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<tr>
<th>Epilepsy</th>
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<tr>
<td>anterior thalamus, centromedian nucleus (CM), substantia nigra (STN), hippocampus</td>
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<th>Cluster headache</th>
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<tr>
<td>- posteromedial hypothalamic</td>
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<tr>
<th>Obsessive-compulsive disorder</th>
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<tbody>
<tr>
<td>anterior limb of the internal capsule, nucleus accumbens</td>
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<tr>
<th>Tourette syndrome</th>
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<tbody>
<tr>
<td>- centromedian nucleus (CM), nucleus ventro-oralis internus (Vim), globus pallidus internus (GPI), periventricular gray (PVG)</td>
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<table>
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<tr>
<th>Depression</th>
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<tr>
<td>anterior limb of the internal capsule, nucleus accumbens, anterior cingulum</td>
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<th>Drug addiction</th>
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<tr>
<td>- nucleus accumbens</td>
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<tr>
<th>Violent behavior</th>
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<tr>
<td>- posteromedial hypothalamic</td>
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<tr>
<th>Obesity</th>
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<tr>
<td>- anterior hypothalamic</td>
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The only commercially available deep brain stimulator (Medtronic Inc) is unreasonably expensive, and aggressive marketing and sponsoring by the sole supplier raises concerns about conflicts of interest.

Thanks to past trials and errors together with scientific progress and technological advancements, we have reached a point where electricity can be applied safely and effectively in the management of a great variety of nervous system disorders. However, improvements in screening and standardization of techniques will be needed in the future. There remains no consensus on best DBS practices, and the refinement of transplantation procedures and controllable genetically engineered stem cells may render these systems irrelevant and obsolete in the future. In the world of contemporary neuroaugmentative procedures, one must always keep in mind the cautionary words of Malcolm Carpenter, renowned neuroanatomist (19):

"Personally, I feel that stereotactic surgery has much to offer, if properly controlled and used judiciously. Some of the wild things that are done without a scientific rationale jeopardize the entire effort."

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Correspondence: H. Fiedler, 130 East 18 St. Apt. 17H, New York, NY 10003, USA. e-mail: Mail@Viking@Gmail.com