

Pathways of Translation: Deep Brain Stimulation

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Abstract

Electrical stimulation of the brain has a 2000 year history. Deep brain stimulation (DBS), one form of neurostimulation, is a functional neurosurgical approach in which a high-frequency electrical current stimulates targeted brain structures for therapeutic benefit. It is an effective treatment for certain neuropathologic movement disorders and an emerging therapy for psychiatric conditions and epilepsy. Its translational journey did not follow the typical bench-to-bedside path, but rather reversed the process. The shift from ancient and medieval folkloric remedy to accepted medical practice began with independent discoveries about electricity during the 19th century and was fostered by technological advances of the 20th. In this paper, we review that journey and discuss how the quest to expand its applications and improve outcomes is taking DBS from the bedside back to the bench. *Clin Trans Sci* 2013; Volume 6: 497–501

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What is Deep Brain Stimulation?

Deep brain stimulation (DBS), a type of neuromodulation, is a restorative functional neurosurgical approach that has been established as an effective therapy for essential tremor,¹ dystonia,² and the movement disorders associated with Parkinson's disease (PD).³ DBS is also an emerging therapy for depression,⁴⁻⁶ obsessive-compulsive disorder (OCD),^{7,8} and epilepsy.⁹⁻¹¹ More than 80,000¹² people have been successfully implanted with DBS devices worldwide; this number is expected to grow dramatically.

Current DBS systems use a continuous, high frequency (100–250 Hz) pulse train applied to a surgically implanted stimulating electrode.¹³ The procedure involves obtaining stereotactic coordinates for the target structure from software that merges magnetic resonance imaging (MRI) of the patient's brain with a brain atlas. During surgery, microelectrode recording verifies a trajectory to the target using region-specific neural activity as functional landmarks.¹⁴ Once verified, the microelectrode is withdrawn, a stimulating electrode implanted, secured to the skull, and connected subcutaneously to a pulse generator implanted in the chest area (*Figure 1*). After recovery, stimulation is initiated, and optimal stimulation parameters (amplitude, frequency, pulse width, and active contact) are empirically determined.

DBS is only one form of neuromodulation. Others include transcranial magnetic stimulation, electroconvulsive therapy, and motor cortex stimulation. Electrical stimulation was also used in early experiments aimed at localizing brain function and continues to be used in neurosurgical procedures requiring brain mapping. DBS differs from these in that the target structures are deep within the brain, such as the thalamus and globus pallidus. DBS, as we know it today, grew out of stereotactic functional neurosurgery aimed at the ablation of targeted areas thought to contribute to the pathology of dyskinesia and tremor in PD. Here we review the translational journey of DBS from anecdotal remedy to accepted therapeutic tool and discuss some remaining obstacles to its application.

Translating Scientific Discoveries and Technological Innovations into Treatment

Electrical stimulation of the nervous system for therapeutic benefit has a long history. In 46 A.D. Scribonius Largus, a Roman physician, recommended applying electric fish to patients' heads in order to relieve headaches.¹⁵⁻¹⁷ This practice for headaches

and other maladies, such as hemorrhoids, gout, and epilepsy, continued up to the 1700s. It was not until the late 1900s, however, that the pathway for translation of DBS from bench to bedside truly began. See *Figure 2* for a timeline highlighting major events in DBS' path of translation.

Early investigations into brain function

Early investigations into the localization of function in the brain employed either electrical stimulation or ablation. Pioneers in this work include Luigi Rolando,¹⁷ Marie Jean-Pierre Flourens,^{18,19} Giovanni Aldini,^{16,17,20} Gustav Fritsch and Eduard Hitzig,^{15-19,21} and David Ferrier.^{17-19,21} In 1809, Rolando utilized electrical current to stimulate the brains of animals, uncovering the functionality of certain parts of the brain.¹⁷ In contrast, Flourens developed ablation as a technique to define brain function.¹⁸ Flourens was opposed to theories of cerebral localization and believed that the cerebrum functioned as a whole. He published his landmark work in 1824, in which he concluded that the cerebral hemispheres were not excitable and that control of motor function lay with the brainstem.^{18,19} Aldini, after early experiments into the effects of electrical current on brain regions, theorized that electrical current may also have therapeutic potential.^{16,17} He began to validate his theory using cadavers and subsequently used electrical current to treat patients with various mental disorders. In 1802, Aldini publicly took the bodies of three recently deceased criminals and proceeded to stimulate both the body and brain of these criminals with electricity, producing muscular contractions.¹⁶ He observed that stimulating one side of the brain caused muscles to contract on the opposite side of the face. This discovery would go unheeded for nearly 70 years.^{16,20}

Mapping brain function and linking electrical activity in the brain to disease

Fritsch and Hitzig observed contractions similar to those observed by Aldini while treating soldiers during the Danish-Prussian war of 1863.^{15,21} They began to experiment on dogs to explore and expand on these observations using electrical current to stimulate their cortexes, triggering muscular contractions. In 1870, they published the results of these experiments, including the observation that increasing the intensity of the current could increase the intensity of the response. They were the first

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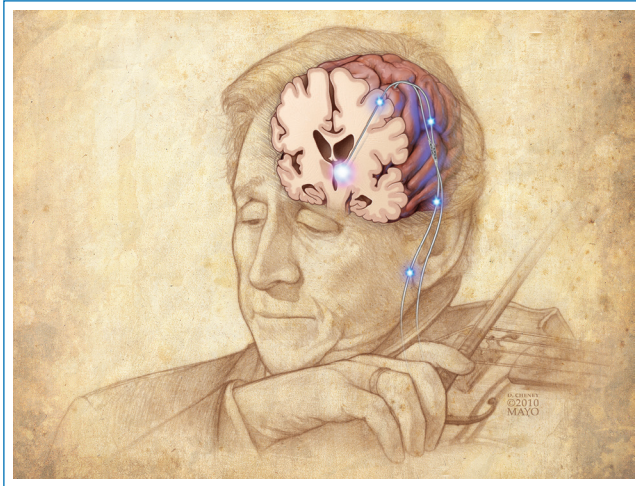


Figure 1. Illustration of deep brain stimulation electrodes. Illustration appears courtesy of David Cheney.

to provide evidence that the cerebral cortex was involved in motor function, that function was localized within the cerebral cortex, and that the cortex was electrically excitable. David Ferrier expanded on these findings through the use of both ablation and electrical stimulation.^{18,21} He published *The Functions of the Brain*

in 1876 in which he mapped the functions of sensory and motor areas across several species. Both Ferrier's and Fritsch/Hitzig's experiments were influenced by and helped to confirm the earlier clinical observations and hypotheses made previously by Robert Bentley Todd^{22,23} and later by John Hughlings Jackson.^{21,24-26} Todd hypothesized that epilepsy "...shows itself in the unnatural development of nervous force...which...may be compared to the electrical phenomenon described by Faraday..."²² Jackson, a student of Todd's, studied patients with epilepsy and proposed that the convulsions he saw in epileptic patients were the result of a "sudden disorderly expenditure of force."^{24,26} His idea was formalized in his 1873 definition of epilepsy as "the name for occasional, sudden, excessive, rapid, and local discharge of grey matter."²⁵ This was a milestone in that it linked electrical activity in the brain to disease.

From animal models to patients: a question of ethics

While the work of Fritsch, Hitzig, and Ferrier helped to confirm the suspicions of Todd and Jackson, none of their experiments were conducted in humans. This changed in 1874, when Roberts Bartholow began a series of experiments on Mary Rafferty, a 30-year-old cancer patient.¹⁹ The cancer and an associated infection caused a large area of her skull to erode, exposing the underlying brain tissue. Realizing that there was little that could be done to cure the patient, Bartholow sought Rafferty's permission to perform a series of experiments in which he electrically stimulated parts of

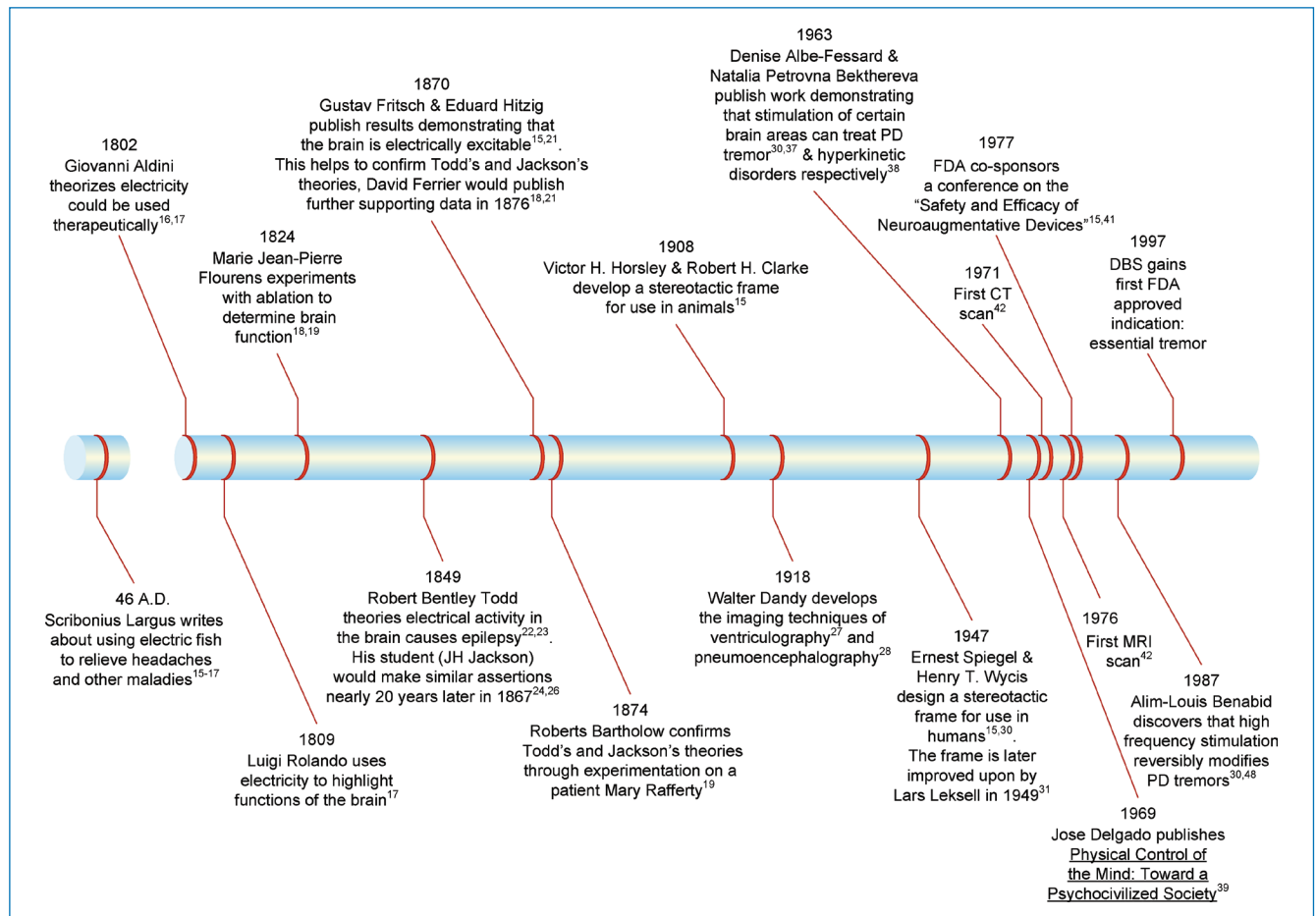


Figure 2. Timeline highlighting major events in the pathway of translation of deep brain stimulation (DBS). PD, Parkinson's disease; CT, computed tomography.

her exposed brain. He found that mechanical stimulation of the brain did not result in a reaction, whereas electrical stimulation caused a variety of muscular contractions and eventually seizures. In causing a seizure in Rafferty, he confirmed prior suspicions about the origin of seizures. However, Bartholow's experiments on Rafferty did not go unnoticed by the medical community.¹⁹ There was a great amount of opposition towards this experimentation, resulting in the American Medical Association's condemnation of his actions and proposition of a resolution stating that "no member of the medical profession is justified in experimenting upon his patient, except for the purpose... of saving said patient's life."¹⁹ In addition to the proposed resolution, the British Medical Journal published a blistering critique of Bartholow's experiment. Bartholow responded with an apology in which he stated that "I now know that I was mistaken" and "to repeat such experiment with the knowledge we have now... would be... criminal." Despite the objections of the medical community, it was recognized that his results did have scientific merit, and on this ground they were praised by Ferrier himself.¹⁹

Lost in translation

In 1882, Ezio Sciamanna experimented on Ferdinando Rinalducci, a patient with a traumatic brain injury.^{19,20} He electrically stimulated various parts of Rinalducci's exposed brain tissue and elicited various muscular contractions based on the site and intensity of stimulation. The patient died after four days of experimentation, however, unlike Bartholow's experiments, there was little international backlash, possibly because the report was published in Italian in a little known journal.¹⁹ The following year, Alberto Alberti began conducting his experiments on Severo Velo, an epileptic.²⁰ These experiments would continue for 8 months, during which time Alberti would, like those before him, stimulate the patient's brain with electric current and observe the resulting muscular contractions.

Ethical treatment revisited

Nearly 20 years after Bartholow's work was published, William Ransom used electrical stimulation on a patient whose cortex had been exposed due to trephination.¹⁹ He observed similar results as his predecessors. However, like Sciamanna and Alberti, Ransom did not face the same backlash as Bartholow. Ransom's patient presumably had normal intelligence, whereas Bartholow's patient was reported to have mental deficits; therefore, Ransom's patient was more capable of giving informed consent. Furthermore, Ransom's patient was studied for several months with no reported serious side effects, whereas Bartholow's died after a few days. Despite the lack of objection from Ransom's studies, further developments advancing DBS would not occur for another 16 years.

The dawn of stereotaxis and brain imaging

In 1908 Victor Horsley and Robert H. Clarke developed the first stereotactic frame for use in animals,¹⁵ which was crucial for the precise placement of electrodes. However, the original system was developed for small to medium sized animals and relied upon the use of coordinates and a brain atlas. Additionally, as a result of individual heterogeneity, it was not very accurate. This was partially mitigated in 1918 when Walter Dandy developed x-ray ventriculography²⁷ and pneumoencephalography.²⁸ With these techniques, neurosurgeons could visualize the brain for the first time. Despite the advantages these techniques had, they were still poorly tolerated by patients.

Pioneering the therapeutic use of electrical stimulation of the brain

With these visualization techniques, neurosurgeons were able to further explore the potential of electrical stimulation of the brain. In 1937, Wilder Penfield published the results of a series of 163 operations during which electrical stimulation was performed. Penfield was careful to state that "stimulation was only carried out when there was therapeutic justification for it."²⁹ Penfield used electrical stimulation to help him localize the origin of seizures in epileptic patients and to help him map out the sensory and motor functions of various areas within the cortex of the brain.

Despite advances in imaging technology and brain mapping, it was not until 1947 that Ernest Spiegel and Henry T. Wycis designed a stereotactic frame for use in humans,^{15,30} which was later improved upon by Lars Leksell in 1949.³¹ This ushered in a new era in neurosurgery; one that would eventually lead to the development of DBS.

In the following years, there were many advances in the field of electrical stimulation. Denise Albe-Fessard pioneered the use of microelectrodes to obtain intracellular recordings of mammalian brains.^{30,32,33} In 1955, she reported on intracellular recordings obtained from the cerebral cortex of a cat; later, she reported on microelectrode recording in the human brain as a means to localize surgery for conditions like Parkinson's and dyskinesias.³⁴⁻³⁶ Additionally, she observed that stimulation of the ventrointermediate nucleus of the thalamus at 100–200 Hz could inhibit tremor in patients with PD.^{30,37} That same year Natalia Petrovna Bekthereva published her groundbreaking work on chronic stimulation for the treatment of hyperkinetic disorders³⁸—the first report of DBS for movement disorders.¹⁷ Unfortunately, her work, published in Russian, was not well known at the time due to limited readership.

Early use of DBS in psychiatry

It was also in 1963 that Jose Delgado implanted an electrode in the brain of a bull, and in a famously theatrical display, used a radio signal to stop the bull from charging.¹⁷ Later, in 1969, he published *Physical Control of the Mind: Toward a Psychocivilized Society*,³⁹ in which he discussed techniques to implant intracranial electrodes in humans, their therapeutic and diagnostic use in psychological disorders, and the ethical implications of his work. Carl Wilhelm Sem-Jacobsen, another pioneer in the field of DBS, in 1963 published a paper describing the effect of electrical stimulation in psychiatric patients.³⁰ He found that electrical stimulation of areas of the frontal lobe resulted in a reduction in symptoms that were either temporary or resulted in a "complete freedom from symptoms." He would later report on the effects of electrical stimulation in patients with PD.³⁰ Of note, Sem-Jacobsen did not consider stimulation as a treatment but as a means to evaluate brain targets prior to lesioning.

DBS: an efficacious treatment versus placebo?

In contrast to Sem-Jacobsen's approach, Irving Cooper experimented with DBS as a treatment for a variety of conditions including cerebral palsy, epilepsy, and spasticity.^{15,40} In 1977, the FDA co-sponsored a conference on the "Safety and Efficacy of Neuroaugmentative Devices."^{15,41} It was concluded that, for most indications, the FDA felt there was not sufficient evidence of efficacy and safety.⁴¹ In response, Cooper performed a double blinded trial of cerebellar stimulation for cerebral palsy, only to

find that it was not as efficacious as originally believed and a large placebo effect was present.¹⁵

Advances in imaging: CT and MRI

Despite Cooper's setback, the 1970s were important decade for the development of DBS-related technologies. In 1971, the first computerized tomography (CT) scan was performed;⁴² its success led to its widespread use by 1980.⁴³ A few years later, MRI scans were first utilized and their efficacy tested.^{42,44,45} The chief advantages of CT scans and MRIs over previous technologies were that they were noninvasive and provided higher resolution.⁴⁶ Today, preplanning with MRI is common as it allows entry point and trajectory planning and intraoperative use.⁴⁷

Advent of modern DBS

In 1987, Alim-Louis Benabid and colleagues made a breakthrough discovery which helped to bring DBS to where it stands today. In patients with PD, they found that DBS at frequencies higher than 100 Hz reversibly modified patients' tremors, safely mimicking lesioning.^{30,48} This discovery reinvigorated research in the area of DBS, leading to the development and approval of the DBS systems available today.

Barriers to translation

DBS has proven to be a useful therapeutic option for many patients. However, several factors influenced, and continue to influence, the translational process. These factors include the need for technological and scientific discoveries/developments, economic and regulatory barriers, and ethical issues surrounding DBS. In order for DBS to progress, there needed to be several technological and scientific discoveries/developments. While significant progress has been made, a lack of a clear understanding of the mechanism of DBS, identification of the most appropriate targets and patients for treatment, and improving the devices and procedures in order to reduce complications all remain challenges to further development of this technology.^{49,50} The translation of DBS is further complicated by regulatory, social, and economic barriers. Investigators undertaking studies of DBS using existing devices require an Investigational Device Exemption from the FDA. This warrants data on the device, which is available only from the manufacturer, creating an additional barrier for investigators.⁵¹ Additionally, there is a potential for resource underuse due to restrictive intellectual property rights held by manufacturers.⁵²

Translating DBS to the clinic is difficult not only due to the high monetary cost, but also because of the emotional burden of the procedure and maintenance of the device. This barrier can be exacerbated due to a media bias which tends to overstate the benefits of the procedure and downplay the risks,⁵³ leading to false expectations for the public and scientific community. In order for DBS to progress there needs to be a concerted effort to accurately portray the risks, benefits, efficacy and cost-effectiveness^{54–56} of DBS; furthermore, additional efforts to make these procedures accessible to all eligible patients are needed.

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