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Noninvasive Human Brain Stimulation
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A Brief Summary of the History of Noninvasive Brain Stimulation

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In 43 AD, Scribonious Largus, a court physician to the Roman emperor Claudius, recorded in his book 'Compositiones Medicamentorum', a most detailed collection of drug compounds or recipes in use by physicians at that time. Among these he mentions the use of electrical currents to treat headaches and gout by applying electric torpedo fish to the affected regions or by placing painful extremities into a pool of water containing torpedo fish. The resulting electrical shocks presumably stunned the peripheral skin receptors, or affected spinal or brain structures inducing an immediate and residual numbness in the extremity and an associated transient period of pain relief. In this application electrical torpedo fish were a very early means of transcutaneous electrical nerve stimulation (TENS) for therapeutic purposes. This form of treatment reportedly became particularly popular for the treatment of gouty arthritis.

In the late 18th century, Luigi Galvani began laying the foundations for modern electrophysiology and bioelectric theory with his famous "animal electricity" experiments and the invention of the voltaic cell. While many people consider Galvani the father of modern electrophysiology, French physician Charles Le Roy actually began experimenting with the use of electricity to influence physiological function in 1755. In one application, Le Roy wound conducting wires around the head of a blind man and led one wire to his leg. The wires were connected to an array of Leyden jars and 12 shocks were administered in the hope that sight would be restored (Figure 1). Along with the pain of the stimulation the patient did perceive vivid flashes of light (phosphenes) and underwent the treatment several times in the following days. Nonetheless, he remained blind.

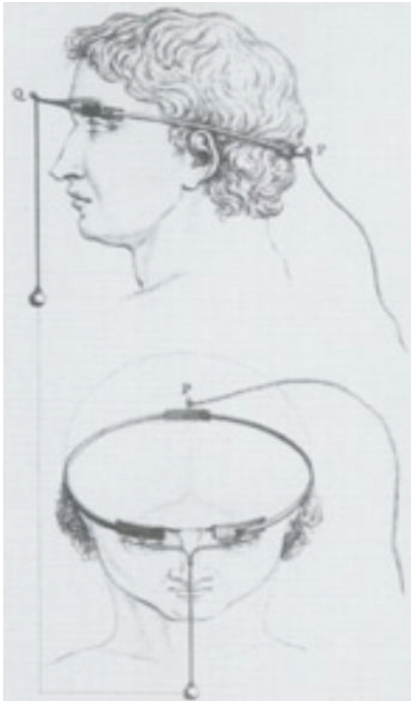

FIGURE 1: Charles Le Roy's stimulation of a blind person

Duchenne de Boulogne (1806-1875) became the first to systematically use electricity in the study of disease, both for diagnostic as well as therapeutic goals (faradization; Figure 2). In "L'Electrisation Localisee" (1855) Duchenne de Boulogne describes the method founded in the observation that a current from two electrodes applied to the wet skin can stimulate muscles without damaging the skin. Among other applications of faradization, he describes the case of a woman admitted to the Charité "whither she had been brought the night before stifled by carbonic oxide". Duchenne de Boulogne "very soon brought back the pulse and breathing, and caused the coma to disappear" by applying "faradization of the skin of the praecordia", an early form of cardioversion.

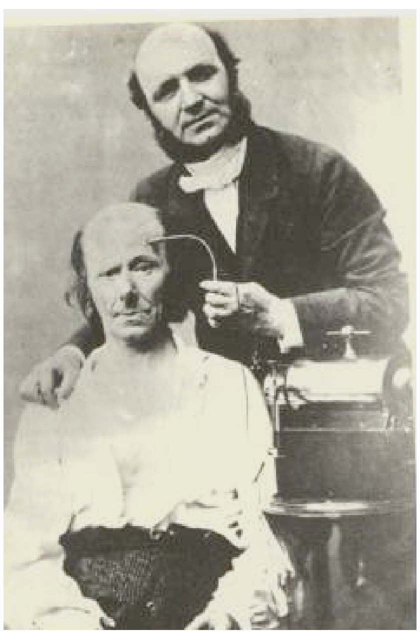

FIGURE 2: Duchenne de Boulogne applying faradization

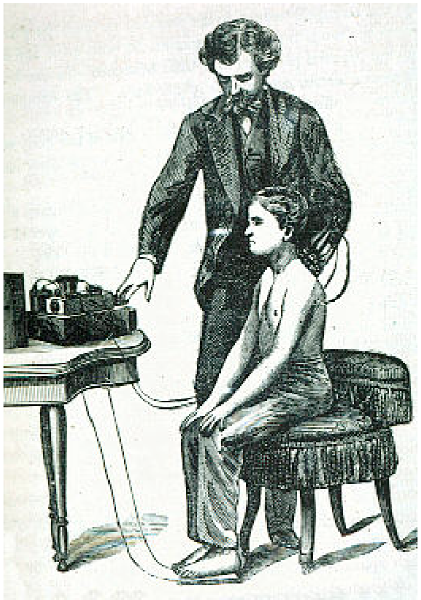

FIGURE 3: Bear and Rockwell's application of faradization

In 1871 in the US, Beard and Rockwell published their "Practical Treatise of the Medical and Surgical Uses of Electricity" arguing for the utility of faradizations for a wide range of indications (Figure 3). Even before, Giovanni Aldini (1762-1834), Galvani's nephew, published his "Essai Theorique et Experimental sur le Galvanisms" (1804) reporting experiments with electric 'therapy' to treat psychoses and melancholia and even to revive the dead. Here lie the origins of electroshock and cardioversion, but Aldini became a sort of traveling showman, demonstrating the effect of application of current to cadavers (Figure 4). Perhaps, the popularization of such 'circus acts' may have contributed to the fact that in scientific circles, noninvasive brain stimulation was mostly ignored for over 100 years.

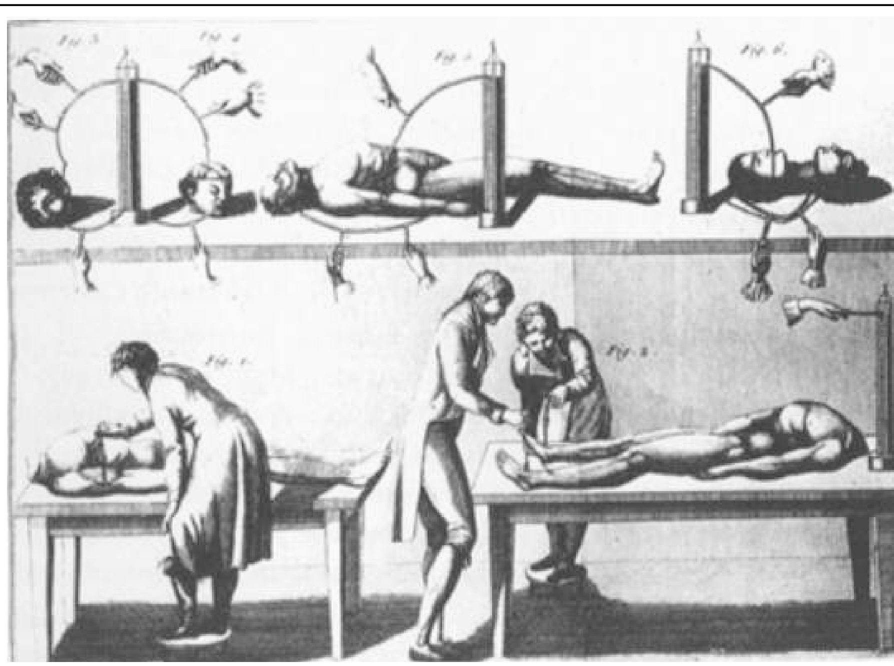

FIGURE 4: Aldini's experiments attempting to revive the dead

However, in the 1960's, researchers began experimenting with the use of weak DC currents applied directly to the exposed cortex of animals. For instance, Bindman showed that currents as low as 0.25 $\mu A/mm^2$ applied to the exposed pia via surface electrodes (3 μA from $12mm^2$ saline cup on exposed pia surface) could influence spontaneous activity and the evoked response of neurons for hours following just minutes of stimulation in rat preparations. Purpura and McMurtry (1964), showed similar effects in cat preparations for currents as low as 20 $\mu A/mm^2$ from cortical surface wick electrodes ranging in area from 10-20 mm^2. These scientists showed that currents, at magnitudes much lower than those necessary for the initiation of an action potential, could still lead to alterations in the level of neural excitability. These studies led researchers to start exploring the efficacy of weak DC currents to alter neural activity (108) and in recent years it has become apparent that transcranial DC currents can influence cortical activity in humans in a way similar to that seen in the experiments of Bindman and others.

Magnetic stimulation in its most primitive form was first investigated at the end of the nineteenth century by physicists studying fundamental aspects of electromagnetics and in particular the implications of Faraday's Law. In 1896, physicist and physician Jaques-Arsène d'Arsonval (Figure 5) reported in his paper entitled "Apparatus for Measuring Alternating Currents of All Frequencies," that "an intensity of 110 volts, 30 amperes with a frequency of 42 cycles per second, gives rise to, when one places the head into the coil, phosphenes and vertigo".

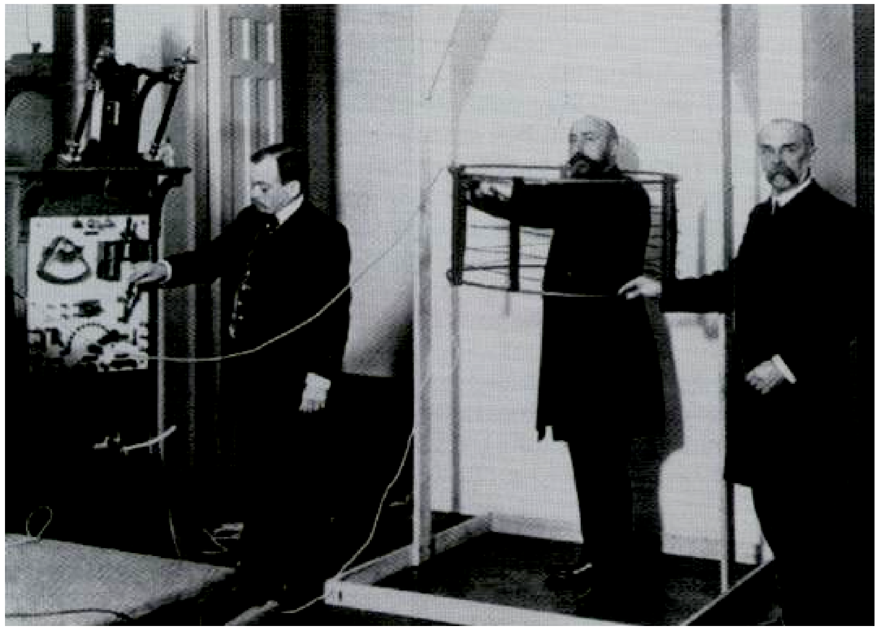

FIGURE 5: D'Arsonval (right) demonstrating the application of electromagnetic stimulation

Independently in 1910, Sylvanus P. Thompson (Figure 6) reported similar findings of perceived magnetophosphenes, the visual excitations of the retina induced by

FIGURE 6: S.P. Thompson demonstrating electromagnetic stimulation on himself.

the time varying magnetic fields (now it is understood that magneto-phosphenes can be initiated from the stimulation of the retina or occipital cortex). Magnetophosphene research continued sporadically throughout the first half of the twentieth century, but over half a century passed before time-varying magnetic fields were used to stimulate isolated nerves. In 1959, Kolin et al. clearly demonstrated that time varying magnetic fields could be used to initiate muscle contractions in frog sciatic nervegastrocnemius-muscle preparations. They applied both 60 and 1000 Hz fields of varying intensity to the sciatic nerve, wrapped around the insulated electromagnetic source, and induced an intense contraction in the muscle. They did not however directly record the neural or muscle action potentials, but rather recorded the muscle displacement via a force transduction mechanism. In 1965, Brickford and Femming non-invasively stimulated peripheral nerves within intact frogs, rabbits, and humans through a pulsed magnetic field (2-3 Tesla pulse over 300 μs). They concluded that "stimulation results from eddy currents induced in the vicinity of motor nerves," but were unable to record the nerve or muscle action potentials due to the limitations in their ability to remove the noise caused by the stimulating device. Irwin, Maass, Oberg, and others continued the work. But as with other early researchers, their magnetic stimulation devices were technically difficult to operate, prone to extreme overheating, and had no mechanisms to address the interference of the stimulating fields. In 1976, Anthony Barker and his group at the University of Sheffield overcame many of the earlier technical problems and developed a device capable of generating peak fields of 2 Tesla with an approximate rise time of 100 μs for the study of velocity selective stimulation of peripheral nerves. This work served as a precursor to developing a stable and reliable magnetic stimulator. In 1982 Polson, Barker, and Freeston described the design of a

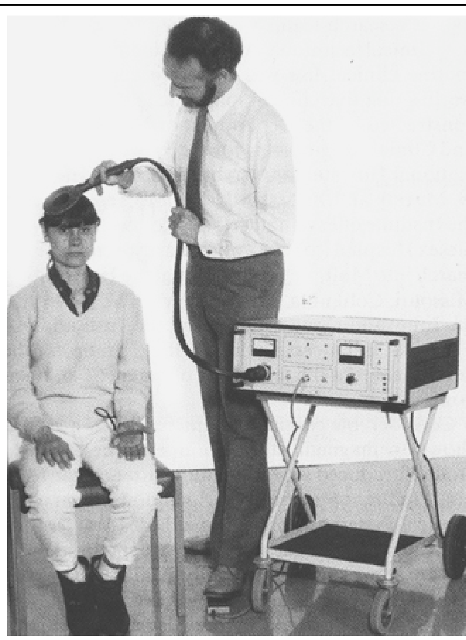

FIGURE 7: Anthony Barker demonstrating the application of TMS

stimulator proven effective for peripheral nerve stimulation that did not suffer from the earlier technical difficulties associated with magnetic stimulation. Subsequently, in 1985 Barker and colleagues introduced Transcranial Magnetic Stimulation (TMS, Figure 7), a non-invasive technique that uses the principles of electromagnetic induction to focus currents in the brain and modulate the function of the cortex. Today numerous TMS devices are commercially available and techniques abound in the clinic and laboratory settings.