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Introduction

Nanos, gigantium humeris insidentes

Implantable cortical stimulation (ICS) was officially introduced to medical practice in a 1991 publication by Prof. Tsubokawa's group in Japan. Since then, hundreds of cases have been published (although the exact number cannot be extrapolated due to duplicate publications), spanning the whole field of functional neurosurgery: pain, movement disorders, psychiatry, epilepsy and neurorehabilitation, with an apparent acceleration over the past few years. The primary reason for investigating ICS, given the general success of deep brain stimulation (DBS), is three-fold: first, both patients and physicians are more comfortable considering surgery if the risk of a potentially lethal intracerebral hemorrhage and infection is eliminated: the bleeding risk for DBS is <2% (range: 0.2% - 9.5%) vs virtually 0% for extradural ICS. Second, the benefit in some conditions is significant and superior to DBS (e.g. central pain). Third, ICS appears to be more cost-effective than DBS surgery. Double blind evaluations of ICS effectiveness are possible because the stimulation is subthreshold for either sensory or motor discrimination: such studies consistently show efficacy only when the device is on. Yet, despite an extensive literature, ICS remains an unapproved modality worldwide. It is true that many questions regarding ICS remain unanswered, but the same conclusion applies to other forms of neurostimulation.

What has become clear in recent years, though, is that ICS is superior in clinical efficacy to non-implantable cortical stimulation, e.g. transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). And yet, it was non-invasive methods of cranial electrotherapy that opened the way to modern neurosurgical ICS (for a historical account, see Mottelay 1922, Finger 1994; see also Canavero 2009). Here, we summarize the key steps. One caveat is in order. Is the concept of “non-invasive” really a misnomer? Is not anything that involves modulation of brain function inherently invasive?

History

The word “electricity” was introduced by William Gilbert (1546-1603), President of the Royal College of Physicians, from the Greek word for amber, which he used to produce frictional electricity. In the middle of the XVII century, special machines for creating electricity appeared and paralysis was one of the first therapeutic applications, if not the first. As major advances were made in the development of machines that could produce electrical charges, scientists became increasingly willing to try out their new

devices in therapeutic settings. The invention and dissemination of the Leyden Jar in 1745 made these efforts easier. The inventor was Pieter van Musschenbroek (1692-1761) of the University of Leiden. This jar allowed electricity to be built up and conserved until released, a marked advance over machines that simply produced sparks by friction. Non-physician John Wesley (1703-1791), the founder of the Methodist Church, grew so enthusiastic over the new technology that he wrote *“there is no remedy in nature for nervous disorders of every kind, comparable to the proper and consistent use of the electrical machine”* and suggested that 50-100 shocks should be used for most conditions. For paralysis, he recommended that *“the palsey be electrified, daily, for three months, from the places wherein the nerves sprang”*. Other two non-physicians, colonial American scientist and founding father, Benjamin Franklin (1706-1790) and French revolutionary Jean-Paul Marat (1743-1793) were among the many who grew enamored with electrotherapy (although Franklin expressed later doubts about electricity as a treatment for paralysis, while suggesting applying shocks to the head for depression). A Dutch physician, Jan Ingen-Housz, discoverer of photosynthesis, corresponded with Franklin regarding his electrical mishap:

“The flash...entered my forehead...I was struck down, I lost all my senses, memory, understanding and even sound judgment....” but, later *“I felt the most lively joye in finding as I thought at the time my judgment infinitely more acute... a liveliness in my whole frame, which I never had observed before.”* Small wonder that static machines soon found their way into many major hospitals, e.g. in England (1767-1777). British physician John Birch, who founded a department of electricity at St. Thomas’s Hospital, treated a *“melancholic porter”* and a *“suicidal singer”* in 1787. He reported that the singer then returned to practice *“boldly, without any serious inconvenience to the brain.”*

These reasoned approaches towards the treatment of depression and motor deficits thus originated more than two and one-half centuries ago.

Modern electrophysiology was born on September 20 1786 when Luigi Galvani (1737-1798), a professor of anatomy at the University of Bologna, in Italy, hung some fresh frog legs on brass hooks from the iron railings of his garden, and unexpectedly discovered the powers of “bimetallic electricity”. He looked upon the nerve as a conductor of electricity, much like a wire from a generator and actually substituted electricity for so-called “animal spirits”. Intense scientific debate then ensued between Galvani and Alessandro Volta who argued that the electrical currents in tissue derived from external metals, until Alexander Von Humboldt (1769-1859) finally settled the matter in favor of Galvani. However, in 1800, Volta invented the wet cell battery (*“la pila”*), consisting of the dissimilar metals zinc and silver, which allowed whole streams of current to be produced – a marked improvement over previous electrotechnology.

Galvani’s nephew, Giovanni Aldini (1762-1834), who also lived in Bologna, showed that electrical stimulation of the exposed brain could produce movements in decapitated criminals and demonstrated these rather “theatrical” feats both in Paris

and London. Here, the media coverage of the time would be such as to later inspire –along with similar experiments by others- Mary Wollstonecraft Shelley (1792-1851)’s Frankstein novel. However, exploiting Volta’s battery, Aldini introduced what we would now designate as tDCS to the field of psychiatry by treating the first depressive (melancholic) subject with a modern stimulation set-up (Fig.1).

Fig. 1: Giovanni Aldini’s experiments with the forerunner of transcranial direct current stimulation for the treatment of “melancholia”.

The XIX century witnessed an explosion of applications of galvanism to nervous system conditions, including paralysis, aphasia, pain, epilepsy, visual and auditory loss and insanity. Critics emerged, though, including Sigmund Freud (1856-1939).

In 1938, Ugo Cerletti and Lucino Bini developed electroconvulsive therapy. The focus of electroconvulsive therapy, however, was not on delivery of an electric stimulus per se, but on the induction of a cerebral convulsion. Certainly Cerletti’s description of his first patient was sufficiently theatrical to command attention:

“All had their hearts in the mouths...during the tonic phase with apnea, ashy paleness, and cadaverous facial cyanosis...which...now seemed painfully never ending-until at the first deep, stertorous inhalation, and first chronic shutters, the blood ran more freely in the bystanders veins as well: and, lastly, to the immense relief of all concerned, was witnessed a characteristic, gradual awakening by step. The patient sat up of his own accord, looked about him calmly with a vague smile... I asked him “what has been happening to you?” He answered, with no more gibberish: “ I don’t know, perhaps I have been asleep.””

In the 1950’s, deep brain stimulation (DBS) started its initially slow, yet later “brushfire” ascent into the Olympus of clinical neurology and psychiatry: DBS gained Food and Drug Administration (FDA) approval as a treatment for essential tremor

in 1997, for Parkinson's disease in 2002 and dystonia in 2003, and chronic, severe obsessive-compulsive disorder (OCD) in 2009. The huge success of DBS has eclipsed the related field of cortical stimulation which (re)started its slow ascent in 1985 with the introduction by Anthony Barker of TMS. Used initially as a diagnostic tool to measure conduction time, in the 1990's its use extended to therapeutic trials for neuropathic pain, Parkinson's disease, depression and then nearly the whole field of clinical neurology and psychiatry: in 2008 it was FDA-approved for the treatment of depression. At the end of the 1990's, tDCS was reintroduced, after a short revival in the 1960-1970's, especially in the former Soviet Union (Kropotov 2009). Yet, benefits from non-invasive cortical stimulation are transitory and sometimes even questionable (see full discussion in Canavero 2009).

ICS too had an early start. Alberts had already quenched Parkinsonian tremor using Delgado cortical stimulation paddles in the early 1970's and, in 1979, Woolsey et al wrote: "*Subthreshold electrical stimulation through implanted electrodes might be used to control marked tremor and strong rigidity in Parkinsonian patients*". The first clinical application of ICS was to be central pain, though, 10 years later, at the hands of Tsubokawa's group, in Japan. They also noted improved movements in post-stroke patients. In 1998, Canavero implanted the first Parkinsonian according to Woolsey's suggestion and in 2002, both the authors introduced ICS for stroke rehabilitation. In 2004 De Ridder treated tinnitus and around 2010 Kopell and others relieved depression. In 2008 Canavero announced initial results for the vegetative state. Finally on November 14, 2013, the FDA approved the closed-loop NeuroPace RNS® System for the adjunctive treatment of adults with uncontrolled partial seizures.

Issues

If we look at the results of ICS for some applications, we are stricken by the apparent dichotomy between more or less positive studies (the majority) and a handful of completely negative ones (e.g. pain and Parkinson). The fact is that, unlike DBS, ICS directly targets the cortex, a vast expanse of organic matter with myriad cyto- and neuro-chemical differences between individuals. The simple perception of polarity-specific neuronal modulation so rife in the ICS field is an oversimplification of complex effects, which are currently far less predictable than currently assumed (Krause and Kadosh 2014). ICS –as well as TMS/tDCS– effects are moderated by the pre-existing baseline excitation/inhibition (glutamate/GABA) balance (EIB), so called *state-dependency*. This is affected by factors such as individual differences in cortical morphology (gyri and sulci), pre-existing different interhemispheric connectivity patterns, age-related changes in EIB across the lifespan (decline of GABA levels, but also NMDA receptors, in the aged), circadian influences that are as yet to be clarified (e.g. time of day: morning vs night stimulations, sleep deprivation), interactions with other neurotransmitters, medications, fatigue, attention, even smoking and hormonal

fluctuations (in women). The actual state of brain functioning at the subject level and previous experiences can influence –and even flip- polarity-dependent effects: “more stimulation” may not lead to “more benefit”, but rather the opposite. Networking in the brain is such that stimulating one area may negatively interfere with another; even worse, while artificially enhancing plasticity one may actually “overshoot” the threshold of homeostatic plasticity and damage the patient more or less irreversibly (e.g. Canavero et al 1999). Thus, if baseline excitation is already high, ICS may add little or even be detrimental. It is suggested that for each patient his or her GABA and glutamate levels be assessed with MR spectroscopy (MRS) (Krause and Kadosh 2014). This adds in terms of cost, but may better guide programming.

Future

Where lies the future of ICS? Suppose that non-implantable transcranial (TMS, tDCS, tACS...) therapy requires physician-supervised re-treatments once monthly for a chronic condition. How long before its cost effectiveness comes into question? Three months? One year? Ten years? What if a procedure with low morbidity that requires a few hospital days can provide years of benefit before any further procedures are needed, especially since the advent of rechargeable devices? Is the cost-benefit ratio within reason when compared to repeated “non-invasive” procedures over the same period? Or is it better to be “tied” to the chair for repeated transcranial treatment? Studies have shown ICS to be safe. Surgical implantation frees the patient from the physician and frequent office visits, once he or she has been adequately trained in use of the device. Arguably, freeing the patient from the physician and giving over control of their health is a reasonable goal of modern health care and a psychological goal for health recovery. Moreover, Zaghi et al (2009) showed that tDCS (followed by rTMS) is the most cost-effective approach for pain therapy at 1 year, but ICS leads at 5 years! In our view, ICS, without ongoing side effects, enjoys the upper hand. It relieves the patient of the burden imposed by the need to call oneself ill.

That said, we dare venture into uncharted territory. Given initial promising results from non-invasive CS (Oliveira et al 2013, Floel 2014), can we expect ICS, a technique already demonstrated to be safe, to be deployed for permanent cognitive and memory enhancement – in the young as well as in the elderly? Can ICS, again a safe technique, be brought to bear on controlling deviant minds, such as psychopaths – a sort of Delgadian mind control (Canavero 2014)? Can the accidental generation of additional subjective limbs (Canavero et al 1999) or out-of-the-body experiences (DeRidder et al 2007) in the course of ICS (or even vivid memories as found by Penfield) portend a time when ICS will be harnessed to create new synesthetic “virtual realities”?

We must wait for the next generation of scientist/physicians to answer these questions. The field remains nascent even after so long a birthing.

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