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PII: S0026-0495(17)30014-8
DOI: doi: 10.1016/j.metabol.2017.01.010
Reference: YMETA 53527

To appear in: *Metabolism*

Please cite this article as: Costa e Silva Jorge Alberto, Steffen Ricardo Ewbank, The Future of Psychiatry: Brain Devices, *Metabolism* (2017), doi: 10.1016/j.metabol.2017.01.010

The Future of Psychiatry: Brain Devices

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Abstract

Recent advances in deep brain stimulators and brain-machine interfaces have greatly expanded the possibilities of neuroprosthetics and neuromodulation. Together with advances in neuroengineering, nanotechnology, molecular biology and material sciences, it is now possible to address fundamental questions in neuroscience in new, more powerful ways. It is now possible to apply these new technologies in ways that range from augmenting and restoring function to neuromodulation modalities that treat neuropsychiatric disorders. Recent developments in neuromodulation methods offer significant advantages and potential clinical benefits for a variety of disorders. Here we describe the current state of the art in neuromodulation methods, and some advances in brain-machine interfaces, describing the advantages and limitations of the clinical applications of each method. The future applications of these new methods and how they will shape the future of psychiatry and medicine, along with safety and ethical implications, are also discussed.

Key Words: Brain-Machine interfaces, Electrical Stimulation of the Brain, Transcranial Magnetic Stimulation, trends, psychiatry,

Introduction

The use of neural engineering technologies, such as implanted deep brain stimulators (DBS) and brain-machine interfaces (BMIs) is a multi-billion dollar industry and is expected to increase in the following years [1]. This growing field of DBS and BMIs has not only expanded the possibilities of neuroprosthetic applications, but also been instrumental in helping us understand how the mind works [2] . Together with advances in neuroengineering, nanotechnology, molecular biology and material sciences, it is now possible to address fundamental questions in neuroscience in new, more powerful ways. Historically associated with applications aimed at the recovery of loss of motor function, BMIs have opened up new avenues for assisting, augmenting, or repairing sensorimotor or cognitive functions [2]. From the implant of retinal chips for the blind [3] to cochlear implants to the deaf [4], advances in nanotechnology and neuroengineering have the potential to greatly improve our ability to not only treat, but also to understand mental disorders and how our mind works.

With the advances in technology, which become increasingly cheaper and more ubiquitous at an exponential pace, most of these applications involve the development of neuroprosthetics or some kind of neuromodulation, sometimes a combination of both, as a means to stimulate or inhibit the flow of action potentials through the nervous system [1]. Recent developments in neuromodulation methods offer significant advantages and potential clinical benefits. Here we describe the current state of the art in neuromodulation, describing the advantages and limitations of the clinical applications of each method in psychiatry. The future applications of these new methods and how they will shape the future of psychiatry and medicine, along with safety and ethical implications, are also discussed.

1. Modalities of neuromodulation

1.1. Direct electrical stimulation

One of the most basic modality of neuromodulation, direct electrical stimulation has historically been the main method of neuromodulation ever since Galvani first demonstrated that neurons could be electrically stimulated [5]. Conceptually, it works through the application of a potential gradient across a neuron using electrodes. The required potential gradients for stimulation can be generated in three ways: a) using voltage; b) current or c) charge controlled stimulators.

Voltage controlled

Through the direct application of a voltage between two electrodes, this is a simple method of direct neural stimulation. One of the obstacles to the implementation of this method, however, is the lack of control of charge delivered to the electrodes, leading to electrode degradation and toxic redox products [6]. Clinically, these stimulators are used in DBS [7] or muscular stimulation, as seen in pacemakers [8]. Since it has a relatively low power consumption and has repeatedly demonstrated its efficacy, it is still a viable alternative to some clinical interventions. With recent advances in stereotaxic neurosurgical methods, the application of this method for alleviating symptoms in psychiatric patients with well characterized psychiatric disorders, such as obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) have greatly expanded, as well and neurological disorders, such as Parkinson´s disease. Initially developed to treat patients with Parkinson's disease, DBS works by surgically placing electrodes, which are permanently connected to a neurostimulator, deep in the brain under the dura in target regions [9-12].

Following the successful application of DBS to movement disorders in neurology, the neuropsychiatric use of DBS began with work for treatment-resistant OCD patients. Based on the hypothesis that neuromodulation mediated by high frequency DBS would mimic ablation of the same target, a rare but tested procedure for the treatment of refractory OCD, patients were tested with electrodes implanted bilaterally in the anterior limb of the internal capsule [13, 14]. In an open trial with a series of patients in the US and Europe, not only the safety of ventral anterior capsule DBS procedure was demonstrated, but also the improvement in OCD symptoms. The development of DBS for MDD, however, has taken a different path than that used for OCD. Based on observations that OCD patients undergoing DBS to the anterior limb of the interior capsule showed mood improvement, independent of OCD symptoms changes, and that ventral capsulotomy had also been previously used to treat intractable MDD, this brain target was tested. Malone et al. [15] tested 15 treatment-resistant patients in an open-label experiment with the DBS electrodes as an adjunctive treatment. A response rate of 40% was seen in at 6 months. Other experiments have targeted the subcallosal white matter tracts adjacent to the subcallosal cingulate gyrus and the nucleus accumbens, in patients with anhedonia. Schlaepfer et al. [11] investigated the effects of bilateral high frequency stimulation to the nucleus accumbens (NAcc) directly, showing acute anti-anhedonic and short-term antidepressant effects [11] with long follow-up showing response on half of the patients [9]. There is, however, very few randomized placebo-controlled studies to determine actual clinical efficacy. Future research studies might in fact be designed to determine if DBS target selection might be optimized for individual depressed patients. Ethical and safety issues are also an important aspect related to DBS and other brain devices, and are discussed later.

Current controlled

In the current controlled method, current flow between two electrodes is controlled by applying a time-varying potential difference across the electrodes [6]. The main obstacle of this method, however, is the significant power waste, with implications for tissue damage and battery lifetime. The clinical applications of this approach can be seen in cochlear implants [16], first approved in the United States in 1985. All cochlear implant systems restore auditory sensation through the electrical stimulation of the auditory nerve. Presently, there are several startup companies developing advanced and low-cost multi-electrode cochlear implants.

Another application of this method is the use of transcranial direct current stimulation (tDCS), which has recently been used to study the physiology of the central nervous system in humans [17]. It is considered to be a clinically safe, non-invasive method, but with has low spatial resolution, a common drawback in most transcranial, non-invasive methods. Yet, more research is needed before drawing a useful conclusion on the efficacy and reliability of tDCS [18].

Charge controlled

The charge controlled modality, which combines voltage stimulation with a capacitor to control the charge delivered to the electrodes is another modality [19]. Regarding power consumption, this approach offers a mid-ground between current and voltage controlled stimulation, however, it is not yet been reported to be in clinical use.

1.2. Magnetic stimulation

In magnetic stimulation, potential gradients are induced in the tissue by a rapidly changing strong magnetic field (greater than one Tesla), and are typically generated by discharging large capacitors through an electromagnet or via a kilowatt amplifier [20]. In

clinical applications, they are usually implemented transcutaneously. The main example of this method is the non-invasive repetitive transcranial magnetic stimulation (rTMS). The lack of electrochemical issues associated with the electrodes is a major advantage of this method over direct electrical stimulation. One of the limitations of the method, however, is its poor spatial resolution and high power consumption [6]. Improvement of resolutions relies mainly on the design of the stimulation coils. Recently, reports on the redesign the coil through a micro-TMS (μTMS) system, which reduces the spatial resolution by an order of magnitude, have been reported [21]. Although the large power consumption is still a major obstacle for building a miniature-size, fully implantable stimulator, clinical application of rTMS has been expanding rapidly in recent years. Available stimulators produce two pulse types: biphasic or monophasic. A biphasic pulse is sinusoidal and has a shorter duration than a monophasic pulse, which involves a rapid rise from zero, followed by a slow decay back to zero. In addition to different pulse types, different types of coils are typically used. These include circular and figure-of-eight-shaped coils. In general, figure-of-eight-shaped coils produce a stronger more focused magnetic field with better spatial resolution of activation, while circular coils [7] tend to produce larger and deeper fields. The ability to achieve high stimulation rates have made rTMS a viable tool to investigate and treat many neuropsychiatric disorders by activating or inhibiting cortical activity, depending on stimulation frequency [13]. In general, low-frequency (~1 Hz) stimulation for a period of approximately 15 minutes induces a transient inhibition of the cortex [14], while stimulation is achieved at frequencies above 1 Hz [15].

There has been an increasing number of TMS equipment manufacturers recently, with varying ranges of frequencies and intensities that they provide, especially at stimulation frequencies greater than 20 Hz. Since its introduction in 1985, TMS has been touted to be an effective treatment modality for major depression, Tourette syndrome, and in reducing

auditory hallucinations in patients with schizophrenia. High-frequency rTMS to the left dorsolateral prefrontal cortex was cleared by the US Food and Drug Administration in 2008 for the treatment of MDD, and a total of 4 different TMS systems have been cleared since [22].

Thermal stimulation

Another neuromodulation method explores the changes in neural activity induced by heat, and the changes in transmembrane capacitance induced by changes in temperature and on changes in conductance dynamics of several ionic channels [23]. With localized heating, the reduced transmembrane capacitance leads to ionic current flow, depolarization and action potential initiation [23, 24]. The result is the creation of a stimulus proportional to the speed of temperature change. During slow heating, the changes to ionic channels dominate and in particular changes to Na^+ and K^+ activation/deactivation dynamics prevent action potential initiation and propagation. Stimulation can be achieved through optical and nanoparticle stimulation. While bench-top equipment has previously been required, an emerging method using a CMOS lab-on-chip micro-heater array has recently emerged. With optically induced thermal modulation, fast heating is achieved through the targeting of near infra-red laser light on a neuron or nerve [23, 25]. This enables a very fast action potential latency (milliseconds) and incredibly high spatial resolution (10 μm).

In microwave/radiofrequency (RF) heating of nanoparticles, magnetic nanoparticles can absorb RF radiation and therefore heat surrounding tissue. Combining these particles with proteins known to bind to specific protein targets on neural cell membranes has been shown to enable focused heating of target cells. Although this approach could potentially give very

good spatial resolution, the temporal resolution and power consumption of this technique remain poor and the safety of the nanoparticles is unclear [26].

1.3. Acoustic/Mechanical stimulation

Acoustic modulation is an emerging method. Experiments have indicated that on-off modulated ultrasound waves can elicit action potentials from retinal and brain cells [27-29]. However, little is understood about how mechanical deformations affect ion channels, membrane capacitances and neurons. Although the knowledge of the actual mechanism is not well understood, potential applications for non-invasive DBS and retinal prostheses are being investigated. Being non-invasive and likely to offer better spatial resolution than other non-invasive techniques, are characteristics particularly useful for applications like retinal prostheses [27]. The main limitation of this method, however, is the unwarranted stimulation of nearby neural tissue.

Emerging trends and future applications

The repair of lost or damaged function has traditionally been the main goal of most research on BMIs. Cochlear implants, for example, have been commercially available for decades. In 2013, the Food and Drug Administration approved the first retinal implant. The principle behind both devices is similar and was already discussed in the previous section. A video camera, or microphone in the case of the cochlear implant, captures images and sounds, processes them and stimulates a set of electrodes in the optic and auditory nerve. Although not technically a brain-machine interface, since it does not involve a feedback mechanism, DBS, used to treat diseases like Parkinson´s, sends electrical impulses into specific areas of the brain, activating pathways involved in motor control.

Augmentation of normal function, however, has been an emerging trend in the field of BMIs. The use of electrical stimulation can be used not only to repair lost function, but also to enhance some types of cognitive function, like spatial memory. In 2012, neuroscientists at the University of California, used a technique similar to DBS to enhance spatial memory [30]. Based on the idea that the medial temporal structures, including the hippocampus and the entorhinal cortex, are critical to our ability to transform daily experience into lasting memories, they applied DBS at these specific sites while subjects were taught to navigate a virtual city environment with a joystick, picking up passengers and delivering them to specific stores. Appropriate electrical stimulation to the brain during the game task increased their speed and accuracy in accomplishing the task [31].

Because of the risks and expenses associated with implanted devices, which require a sterile environment and skilled surgeons, extensive research on external devices, like the electroencephalograms, have been under way. The main drawback, however, is that, since they are not in very close contact with the neurons, they are also far less effective. To be effective, BMIs have to be wired directly into the brain to pick up the signals from a group of neurons. One important obstacle is biological, since implants must be nontoxic and biocompatible, evading our own immune responses, in addition to being energy-efficient enough as to not require being recharged. Neuroengineering, however, have been trying to surmount these problems. In 2015, an injectable “neural lace” was successfully implanted into two brain regions of anaesthetized mice, where they were able to both monitor and stimulate individual neurons. The mesh, consisting of several electrical elements, integrated tightly with the neural cells, with no signs of an elevated immune response after five weeks [32].

Safety and ethical issues

Neural engineering technologies such as implanted DBS and BMIs are potentially transformative tools for improving human mental health. Their current use and future prospects, however, raise safety, ethical and philosophical concerns. As funding for these technological advances expands, ethical issues must be carefully explored and analyzed. According to public surveys, such the Pew Research Center report, most Americans are more worried than enthusiastic about using biomedical technological advances, such as gene editing, brain implants and synthetic blood, to enhance or change human capabilities. Steps taken to safeguard safety and ethical aspects, such as the Presidential Commission for the Study of Bioethical Issues [33], for example, have focused on how advances in neuroscience raise complex issues related to cognitive enhancement, consent capacity, legal responsibility and decision-making. Exploring areas of ethical, social, and legal concern are important steps in addressing such concerns. The Hastings Center for Bioethics, for example has identified six core areas of ethical concern in neural engineering: identity, normality, authority, responsibility, privacy, and justice [34].

Regarding identity concerns, for example, Schupbach et al. reported that nineteen of twenty-nine patients who received DBS for Parkinson's symptoms reported important identity issues. Most had trouble recognizing themselves after surgery, and six of the twenty-nine experienced these issues noting, for instance, "I feel like a robot," and, "I don't feel like myself anymore"[35]. Regarding normalcy, Synofzik and colleagues describe a patient with a DBS system for anxiety and OCD that, after calibration sessions, reported feeling "unrealistically good" and "overwhelmed" by sensations of happiness and ease, and asked to have the stimuli reduced [36]. Implanted brain devices, designed to interface with existing nervous tissue in closed-loop systems, add complexity to how we think about our identities, changing not only our body schema, but our social identities as well. While this can be a positive development, they may also undermine identity in certain unpredictable ways. Other

areas of ethical concern, such as stigma and autonomy, should also be carefully considered [34].

Conclusions

In understanding the neural code, there is a long way to go. That's why the massive collaborative project, the BRAIN Initiative, announced in 2013 by President Barack Obama is so important. We need not only better tools for detecting signals from brain, but also more precise tools for sending information back, in addition to a different understanding of how different kinds of neurons work and how complex circuits work together. The fMRI brain images that have become so popular, have poor resolution and have been under criticism for its high rate of false positive results [37]. Firstly, they measure changes not in electrical activity but in local blood flow, an imperfect surrogate of actual neural activity. Secondly, they have poor resolution. Each three-dimensional pixel (or "voxel") in a brain scan contains a half-million to one million neurons. We still do not know how individual neurons work together to form circuits that translate into perception, consciousness and memory.

Advances in molecular biology, neuroscience and material science are almost certainly going to lead, in time, to implants that are smaller, safer and more energy-efficient. Coupled with powerful computers, advances in artificial intelligence and tools to decode the massive information received, these devices will be able to interpret directly the electrical activity inside the brain. Soon, they will transition from being used exclusively for severe problems such as paralysis, amnesia and mental disorders and start being used by people with less traumatic disabilities, enhancing and augmenting human performance. They will be used to improve memory, concentration, sensory perception and mood. The ethical considerations of

these advances must be carefully considered, as these cutting-edge biomedical technologies become more available and its consequences less predictable.

Acknowledgements:

Publication of this article was supported by the Collège International de recherche Servier (CIRS). The first author is a member of CIRS's Scientific Committee.

Conflict of interests:

None

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