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Non-Pharmacological Tools for Neuroenhancement

Neuroethical Issues*

Abstract

Advances in neuroscience and technology brought us several methods that have potential to non-pharmacologically influence our brain. Most of these methods are developed with the purpose of treating disorders, but also have favourable results on cognition and mood in the healthy, and the potential to be used for enhancement purposes. Two categories of methods are used for treatments of the brain, methods that apply a magnetic field and those that apply an electrical current through the scalp. Several methods have been developed that use one of these principles for treatment, most important being transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The aim of this review is to give a short overview of different aspects of the most widely used non-pharmacological techniques that can be used for enhancement purposes and state the most relevant ethical issues related to the safety, influence on character, justice and autonomy of their us. Irrespective of the amount of information on the mechanisms and modes of action for specific methods, the possible range and scope of their side effects and the implications of their potential use for enhancement, have not been emphasized enough. Outside clinical settings, these devices are unregulated, with no system in place to ensure their safety. Moreover, the all-pervading technology that we live surrounded by and the lack of public discourse, all contribute against a reasonable and slow approach to their implementation and resulted in the spreading and increase in their commercial use.

Keywords

neuroethics, neuroenhancement, non-invasive brain stimulation, transcranial magnetic stimulation (TMS), Shakti-8, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS)

Introduction

Recent progress in neuroscience and neurotechnology has enabled us to not only better understand, but also influence our brain. Although neuroscience research has been mainly focused on the development of various pharmacological and non-pharmacological therapies for different brain disorders, most of these interventions have the potential to influence cognitive and affective

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functions in healthy individuals as well. These effects broadly come together under the term of "neuroenhancement", which refers to the improvement of cognitive, affective and moral domains, above the level necessary to restore and/or maintain health (Farah et al. 2004, Husain & Mehta 2011). Whereas achievements in this field have not been questioned when applied for treating the impaired, an increasing number of demands for reaching a "better than normal" state of mind, raises a plethora of ethical issues (Larriviere et al. 2009, Chatterje 2004).

The prerequisite for talking about neuroenhancement is a clear definition of what it means to be healthy, i.e. where mental disorder stops and health starts. Unfortunately, the line between disease and health is vague, and a clear line between them cannot be drawn. According to A. Štampar, a Croatian public health pioneer and a founder of WHO, health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (Zubrinić 2008). Today, our "mental and social well-being" is jeopardized by an ever-faster pace of life and increasing demands that we place on ourselves. To cope with the duties of everyday life, we are already using a range of substances (coffee, cigarettes, various nutraceuticals, etc.) that apparently can influence our mental functioning and which are a widely accepted form of enhancement. Therefore, in our ever-growing set of neuroenhancement tools, the application of non-pharmacological techniques would not be a big change, but just a continuation of common practices.

Non-pharmacological treatments with the highest potential for neuroenhancement in both medical and non-medical environments are transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES or tES, also called transcranial current stimulation, tCS). TMS involves stimulation by a magnetic field, with the ability to focus and selectively treat relatively narrow brain areas. The technique works by delivering very brief single pulses, or brief and rapid trains of pulses of a strong magnetic field to the brain, using a device mechanically fixed to the surface of the skull (Luber & Lisanby 2014). On the other hand, TES (tCS) is used for electric stimulation of the cortex with low currents. It is a low-cost, easy to use technique that can modify cerebral excitability. Different types of electric stimulation are used, but the oldest and the most widespread is transcranial direct current stimulation (tDCS) (Bennabi et al. 2014). Both TMS and tDCS have been reported to have favorable results on cognition and mood (Luber & Lisanby 2014, Bennabi et al. 2014). At the same time, these techniques are becoming more accessible to non-medical professionals and to the public in general, who are not sufficiently informed about the potential effects and consequences of these treatments. Today we still do not understand enough about the mechanisms of action of these technologies, which are continuously spreading and increasing their commercial use.

Attempts to use electrical activity in medical treatments are not new and date from the time of the Roman Empire, when the physician Scribonius Largus (mid-first century AD) used electrical torpedo fish and eels to treat pain in the extremities or the head (Grout 2015). At the end of the 18th century G. Aldini and A. Volta continued studies on the effects of direct current on humans and animals and reported positive outcomes of treatments on melancholic patients. At the beginning of the 20th century, treatments with low currents were replaced with those with much higher intensities causing electroconvulsive therapy to gain more interest (Le & Lilve 2009). Later, in second half of the 20th century, Limoge succeeded in using lower than usual amounts of narcotics in anesthesia during surgeries while applying weak electricity at the same time (Limoge et al. 1999).

Essentially, both types of non-pharmacological techniques, those that apply magnetic fields or those that apply electric stimulation, influence the brain by inducing current in the brains tissue. The techniques that apply magnetic fields are inducing an electric current in the brain tissue, according the principle discovered by Faraday. A changing magnetic field applied to the scalp causes an electromotive force in the brain, which induces a circular current to oppose the change in the magnetic field. The differences between techniques that apply current directly and those that induce current by a magnetic field are in the size of treated brain tissue, as well as in the type (direct, alternating), the strength, and the frequency of the induced current. Treatment of the brain with electric currents, either directly or by a magnetic field, affects the normal firing of neurons, by facilitating or inhibiting certain pathways. In addition to modulating neuron membrane potentials and altering cortical excitability and activity as a function of the current through the targeted area, these treatments might exert a range of other possible physiological effects on glial cells, blood vessels, etc. (Zaghi et al. 2010, Woods et al. 2015, Karabanov 2015).

It is important to emphasize that due to the electro-chemical nature of the brain, pharmacological treatments similarly influence the firing and transfer of electrical impulses between neurons. However, as drugs usually act via certain types of receptors, pharmacological treatments come with greater specificity than in the case of non-pharmacological treatments. Nevertheless, the basic nature of the produced stimulus in the neurons, affecting various neurophysiological functions, is the same in both pharmacological and non-pharmacological brain treatments.

Brain stimulation using an electric field

Transcranial direct current stimulation (tDCS)

Brain stimulation using weak currents gained much interest in the last decade, following the landmark article from Nitsche and Paulus (Nitsche & Paulus 2000). These authors observed significant changes (up to 40%) in the excitability of the human motor cortex after weak transcranial direct current stimulation (tDCS), presumably due to the modification in neuronal membrane polarization. Since then, tDCS has become the most extensively studied technique (Kessler et al. 2013, Saturnino et al. 2015, Wagner et al. 2007). Many studies demonstrated positive clinical results of tDCS as well as its favorable effects on cognition (Nitsche et al. 2009, Luedtke et al. 2012, Mondino et al., 2014, Reis et al. 2009, Feng et al. 2013). There are also more than forty ongoing clinical trials, mostly in US, regarding several possible applications of tDCS for the treatment of different conditions such as depression, Parkinson's disease, multiple sclerosis, pain, stroke, etc. (EU Clinical trials register: "Clinical trials for transcranial direct current stimulation"; ClinicalTrials.gov, a service of the U.S. National Institutes of Health: "Clinical trials for transcranial direct current stimulation"; World Health Organization, International Clinical Trials Registry Platform: "Clinical trials for transcranial direct current stimulation").

During tDCS treatments, a weak (several mA) direct current is delivered to the scalp via two or more electrodes (Figure 1). One of the still unresolved issues is to what extent the applied current dissipates on the skin and skull and penetrates the brain tissue (Woods et al. 2015). Namely, the size and shape of the electrodes, as well as their exact positioning on the head, significantly alter the distribution of the current delivered to the scalp, and consequently the intensity of the brain stimulation. The proper montage of the electrodes is challenging, especially for an untrained person, due to different sizes and shapes of heads (Woods et al. 2015). In addition, delivering direct current to the scalp causes tingling and itching sensations, which makes gaining a proper control very challenging. Despite all this, as tDCS represents the simplest electrical stimulation technique by design, various instructions on the internet explain how to make a device and use it on your own, mostly for the purpose of cognitive enhancement.[1] In addition to the growing community of "do it yourself " tDCS users and internet bloggers, several companies (Foc.us, Soterix Medical, Magstim, The Brain Stimulator, etc.) produce and sell the cheap and affordable devices all over the world.

It has been considered that tDCS does not induce activity in resting neurons, but only modulates existing neuronal activity (Saturnino et al. 2015). The current delivered to the scalp during tDCS changes the membrane potential and affects spontaneous firing of neurons depending on the current polarity. Anodal and cathodal stimulation, for example, increases and decreases the excitability in the treated motor area, respectively (Zaghi et al. 2010), whereas in the visual cortex the opposite effects of anodal and cathodal current have been found (Antal et al. 2003). Differences in the polarization produced by tDCS probably depend on the orientation of neurons in the electric field. Action of tDCS, although mostly local, can possibly affect distant neural networks via various interneural circuits (Zaghi et al. 2010).

Although putative mechanisms of action for tDCS have been proposed, there are still many unresolved questions. Future studies should address the neurophysiological basis of tDCS in order to reveal its underlying mechanisms. This will lead to a safer application of this and similar techniques and shed more light on possible side effects that can result from their use.

Transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS)

Much less research has been performed regarding the influence of alternating current (AC) on the brain, using technique called transcranial alternating current stimulation (tACS). Both tDCS and tACS have often been applied at the same time in the same study, which makes results about the effects of a single stimulation type inconclusive (Paulus 2011). Sinusoidal alteration induced by the application of alternating current to the brain tissue may interact with physiological brain rhythms, possibly causing neuroplastic effects (Witkowski et al. 2015). Changes in the release of neurotransmitters and endorphins have been found following AC stimulation in several studies. Moreover, it has been shown that cranial AC stimulation may alter EEG pattern towards a more relaxed state, however the effects are dependent on the parameters of the specific stimulation (Paulus 2011). Several studies investigated the effects of AC on perception, memory, motor and cognitive function, as well as on mechanisms for cognitive control (Van Driel et al. 2015, Hamid et al. 2015, Antal & Paulus 2013). The obtained findings were heterogeneous and dependent on the frequencies and other experimental parameters used. Therefore, more conclusive results on the effects of tACS will require further investigation.

Another slightly different technique, transcranial random noise simulation (tRNS) uses alternating current with a random noise pattern in the frequency range from 0.1 to 640 Hz. It has been suggested that a tRNS signal, although probably too weak to exceed a neuronal firing threshold, may sum up with the sub-threshold neural oscillation and cause an increase in brain activity (Paulus 2011). This might explain why excitability in the motor cortex was detected after treatments in higher frequencies spectra (100–640 Hz), and not in the EEG range of low frequencies (Paulus 2011). Snowball et al. (Snowball et al. 2013) demonstrated improved learning and subsequent better performance on complex arithmetic tasks, lasting up to 6 months following tRNS treatments. Although the authors suggested that tRNS represents a viable approach to enhance learning and a method for a long-term manipulation of neuroplasticity, research on tRNS has begun only several years ago and more in depth studies are needed for any serious conclusions about the range and applications of this method.

Brain stimulation using a magnetic field

Transcranial magnetic stimulation (TMS)

Due to a much higher strength of currents that can be induced in the brain tissue, TMS is not only a neuromodulatory, but also a neurostimulatory technique (Luber & Lisanby 2014). The generated magnetic fields are of sufficient density and magnitude to penetrate the scalp and induce a current in the brain tissue below the coil (Figure 1). TMS induces a current that flows parallel to the plane of the stimulation coil, and therefore mostly activates neurons oriented horizontally to the brain surface (Wagner et al. 2007). As induced currents can be focused up to 6 cm in the brain, it can stimulate not only the cortex, but also deeper brain structures. TMS is usually integrated with brain imaging in order to stereoscopically enable better tracking of treated area (Wagner et al. 2007).

The first reliable transcranial magnetic stimulators were developed in the mid-1980s and used single pulses of magnetic field. However, with the beginning of the 1990s, researchers have introduced the application of more powerful repetitive pulses (rTMS). It has been shown that lower frequencies of applied rTMS (0.5–2 Hz) decrease cortical excitability, while frequencies above 5 Hz increase the brain excitability. Although TMS is generally considered safe when used under controlled conditions, with only slight discomfort and pain reported, in certain cases it can induce epileptic seizures (Chervyakov et al. 2015).

A PubMed search with the term "transcranial magnetic stimulation" (on 22 December 2015) resulted in almost 12,000 hits, indicating significant interest in this field, exponentially increasing in the last decade. Moreover, the same search performed on the clinical trial sites resulted in 950 on-going clinical trials all over the world, with almost 800 in the USA (ClinicalTrials.gov, a service of the U.S. National Institutes of Health: "Clinical trials for transcranial magnetic stimulation"; EU Clinical trials register: "Clinical trials for transcranial magnetic stimulation"; World Health Organization, International Clinical Trials Registry Platform: "Clinical trials for transcranial magnetic stimulation"). In the year 2008, the US FDA approved the use of TMS for the treatment of drug-resistant major depressive disorder.

In addition to its application in the treatment of major depression and it's still investigated potential use in the therapy of different neurologic and psychiatric diseases (obsessive–compulsive disorder, schizophrenia, posttraumatic

1 See https://www.diytdcs.com and http://www.instructables.com/id/Build-a-Human-Enhancement-Device-Basic-tDCS-Suppl/(accessed on January 2, 2016).

stress disorder, addiction, Parkinson's disease, epilepsy, pain, stroke, migraine, etc.), TMS has been shown to improve memory, visuospatial processing and motor tasks performance in healthy subjects (Luber & Lisanby 2014, Chervyakov et al. 2015, Bersani et al. 2013, Sparing & Mottaghy 2008). Consequently, several companies manufacture TMS instruments (Neuronetics, Neostim, Brainsway, Neosync, etc.) and various clinics all over the world are now offering treatments for depression using TMS. Although there is limited access to TMS instruments due to their price, creative individuals are finding ways to treat the brain with magnetic field in a home setting (Reddit).

Shakti 8-coil

By delivering weak (0.1–1 microTesla) and complex magnetic fields in the area of the brain's temporal lobes, the Shakti technique induces sensory and neurophysiological alterations and abnormal perceptual phenomena (Tsang et al. 2004). Neurobiological changes as a consequence of Shakti treatments have been also observed in animals (Persinger et al. 2014). Most of the research in this field has been done by the group of M. Persinger, who have constructed a device consisting of eight solenoids attached to a helmet ("Koren" helmet). However, some of these studies do not seem to use a proper randomized, double-blind, placebo-controlled design. Hence, an insufficient amount of research, regarding the effects of this technology, has been performed in order to obtain conclusive results, with just a few methodologically rigorous and thorough studies. Nevertheless, a helmet used for Shakti treatments (also known as "Gods helmet") has been marketed and sold as a tool for meditation, mood enhancement and as a trigger for altered states of consciousness (Tsang et al. 2004, Gendle & McGrath 2012).

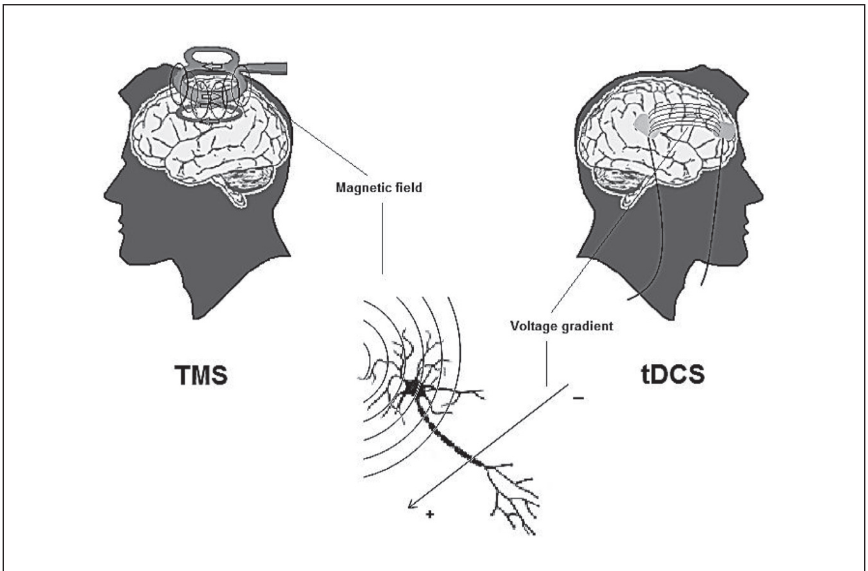

Figure 1. **Non-pharmacological treatments with the potential for neuroenhancement: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).** Treatment of the brain with electrical currents alters cortical excitability by modulating neuron membrane potentials and affecting the normal firing of neurons, either directly or by a magnetic field that induces an electrical current in the brain tissue. TMS works by delivering brief and rapid single pulses or trains of pulses of a strong magnetic field to the brain. tDCS treatments consist of a weak direct current delivered to the brain via two or more electrodes.

(Neuro)Ethical issues

Higher cognitive and affective abilities might help improve our lives by providing more effective and convenient ways of accomplishing a variety of tasks and are usually associated with a better life outcome. Namely, there is a strong correlation between higher IQ and more success at work, better health and less likelihood to suffer social and economic misfortunes (Bain 2003, Bostrom & Sandberg 2009). Therefore, cognitive enhancement is likely to have an impact on society in many ways, with applications that permeate all aspects of life, including education, research and business. According to Bostrom (Bostrom & Sandberg 2009), if the cognitive performance of a population would be increased by just a small percentage, it could have a huge impact on a global level. Such a small gain in cognitive abilities would hardly be noticeable in a single individual, but could have enormous benefits for society as a whole. This raises a dilemma of the morality of not using neuroenhancement that can possibly bring greater good to the entire society.

However, although the word "neuroenhancement" implies that our brain is somehow made better, the enhancement of our cognitive or affective functions does not have to be always better for our well-being. In the case of a perfect memory, when a person does not forget anything, huge amounts of information could impair the understanding and executive functions (creative and critical thinking) and might be a burden in everyday life. Similarly, enhanced sensitivity to vision and sound, which surpasses our physiological limits, could create problems in normal life and result in an overall loss. Therefore, even if we were to have the ability to influence any aspect of our mentation and mood at will, it would not at all be trivial to decide what should be enhanced to gain a perfect balance of our well-being and at the same time to contribute to society.

Our understanding and knowledge about the brain is still insufficient to oversee possible unintended consequences of treatments like TMS and tCS or their impact on various areas of life (Iuculano & Kadosh 2013). The complexity of neuronal networks, individual differences, as well as the insufficient precision of these techniques, all contribute to the uncertain outcome of the treatment (Karabanov et al. 2015). Ethical issues related to the application of TES and TMS techniques for the purpose of neuroenhancement, are mostly concerned with safety, justice, autonomy and character (Hamilton et al. 2011, Brukamp & Gross 2012). Some of these issues are more related to individuals, while others are more applicable to society as a whole, although it is hard to draw a clear line between them.

As safety is concerned, side effects and unintended consequences are the main problem of any medical treatment. However, they are particularly important and have a completely new dimension when the treated organ is the brain. In contrast to the physiological health that is at stake with other medical procedures, the treatment of the brain could result in various changes to our personality and/or psychological profile. Although, positive outcomes observed following short-term brain stimulation by either magnetic fields or electric currents might be undeniable (Nitsche et al. 2009, Luedtke et al. 2012, Sparing & Mottaghy 2008, Bersani et al. 2013), there is no evidence related to the regular long-term use of these techniques and the potential long-term consequences of altering cortical activity, especially in the case of treating children and their developing brain (Krishnan et al. 2015, Kadosh et al. 2012).

On the other hand, being external (extracranial), the effects of TMS and tCS treatments are intuitively perceived as more transient and mild than some other medical treatments, such as pharmacotherapy or surgery. Hence, these techniques are often referred to as non-invasive brain stimulation (NIBS), and as such they became more acceptable for a range of volunteers recruited for studies, but also for the "do it yourself" construction of devices. However, the attribute of "non-invasiveness" often creates an ungrounded illusion of comfort and security. Davies and Koningsbruggen (2013) suggested that

> "Any technique which directly affects brain tissue to generate such powerful, acute and long-lasting effects should be treated with the same respect as any surgical technique, and proper safety and ethical guidelines should apply in institutions where brain stimulation is in use." (Davis & Koningsbruggen 2013)

Although often discussed together, ethical issues for various brain stimulation techniques differ. TMS techniques that induce the highest current and supposedly have the worst health consequences are not accessible to the broad public. Therefore, the uncontrolled use is less of an issue for TMS compared to tDCS, which can be bought and used at home. However, the number of clinics and institutions where TMS has been applied is rapidly growing, causing safety issues related to the competence of the staff administering the treatment. For instance, the lack of proper training may lead to the misidentification of appropriate sites for brain stimulation (Woods et al. 2015, Kadosh et al. 2012).

On the other hand, tDCS is affordable and can be purchased and used by anyone irrespective of age, level of knowledge and experience with this technique, as well as without any guidance of appropriate montage and duration of applied treatment. It is particularly problematic that these devices are being marketed to help with learning and/or playing games and their advertising is targeting children and young people, irrespective of the unknown influence on developing brains (Krishnan et al. 2015, Kadosh et al. 2012). Hence, the establishment of safety guidelines for brain stimulation treatments as well as complying with them is crucial. Moreover, when brain stimulation is applied alongside learning and/or behavioral training, an appropriate combination of stimulation and behavioral training is essential.

Ethical questions with respect to justice are related to access and coercion. TMS treatments are presently very expensive and not affordable to most people. If TMS becomes a device of choice for the enhancement of our abilities, because of the price barrier it could become yet another resource that will with unfair and inequitable distribution mirror existing problems in society and widen the gap between the rich and the poor. The matter of price is not an issue for tDCS, which is in the "do it yourself" version more accessible and prone to all sorts of misuse with questionable outcomes and consequences (Farah et al. 2004, Hamilton et al. 2011, Brukamp & Gross 2012).

Another ethical issue that arises alongside the growing use of neuroenhancement practices is the explicit or implicit coercion to enhance, which is a question of justice but also a question of autonomy. In a situation of widespread neuroenhancement, implicit coercion implies pressure to enhance our brain to keep up with growing demands of competitive society. Explicit coercion is applicable to settings where a person is forced to enhance for the sake of some greater good against their will, for instance in a military environment or enhancement in children (Farah et al. 2004, Larriviere et al. 2009, Chatterje 2004, Hamilton et al. 2011).

Questions related to character include possible changes in our psychological profile due to unintended consequences of a brain treatment. Although most people find acceptable and even desirable an increase in memory and concentration, they find it inappropriate to manipulate our personality and identity

(Farah et al. 2004, Larriviere et al. 2009, Chatterje 2004). Further ethical issues are related to our values. Most of the societies and cultures value hard work and fairness. While doping in sport is unacceptable and punishable, it is not clear if cognitive enhancement in similar competitive situation, for instance in exams, will be treated in a similar way. There has not been sufficient public discourse about cognitive enhancement to allow the forming of positions of society about these issues.

Consequently, there are no regulatory policies related to the use of these techniques, even though such regulation is extremely important (Maslen et al. 2015). As Marta Farah emphasized in her article in Science (Farah 2015), the lack of epidemiological studies with enough statistical strength, lack of information about prevalence, risks and real benefits, all contribute to a situation where it is difficult to draw useful regulatory policy. Careful and well-designed research and clinical studies, which will include the ill and impaired but also healthy subjects, could bring more light onto these issues. However, the recruitment of both diseased and healthy volunteers for brain studies with unforeseen consequences is challenging and ethically problematic.

Conclusion

Many new achievements in human history have been looked at first with skepticism and fear, but have become completely accepted with time. On the other hand, today's omnipresent technology has blunted our critical thinking, causing us to unconditionally and without enough caution accept new techniques and instruments. A promise of a better life that neuroenhancement could bring weighs heavily against a reasonable and slow application of brain stimulation methods and it is not likely that their use could be delayed. Although these techniques might be a promising tool for treating many disorders, they could also bring serious consequences to individuals as well as to society, which are now very difficult to estimate. Therefore, it is of utmost importance to regulate the use of these techniques to prevent their application by untrained personal and in particular their uncontrolled use. It is the responsibility of neuroscientists, medical doctors, ethicists, sociologists, and philosophers to keep the broad public educated and alert, in order to readily and in time respond to these emerging neuroethical issues.

References

Anjin [pseudonym] (2015). "Neuroengineering – Who else is waiting for DIY instructions on how to do Transcranial Magnetic Stimulation at home to induce savant like states?". On: Reddit. Available at: https://www.reddit.com/r/cogsci/comments/826a7/neuroengineering_who_else_is_waiting_for_diy/? (accessed on December 22, 2015).

Antal, A., Kincses, T. Z., Nitsche, M. A., Paulus, W. (2003). "Modulation of moving phosphine thresholds by transcranial direct current stimulation of V1 in human". In: *Neuropsychologia* 41 (13/2003), pp. 1802–1807. doi: https://doi.org/10.1016/s0028-3932(03)00181-7.

Antal, A., Paulus W. (2013). "Transcranial alternating current stimulation (tACS)". In: *Frontiers in Human Neuroscience* 7:317. doi: https://doi.org/10.3389/fnhum.2013.00317.

Bain, G. H., Lemmon, H., Teunisse, S., Starr, J. M., Fox, H. C., Deary, I. J., et al. (2003). "Quality of life in healthy old age: relationship with childhood IQ, minor psychological symptoms and optimism". In: *Soc Psych Psychyatr Epidemiol* 38 (11/2003), pp. 632–636. doi: https://doi.org/10.1007/s00127-003-0685-5.

Bennabi, D., Pedron, S., Haffen, E., Monnin, J., Peterschmitt, Y., Van Waes, V. (2014). "Transcranial direct current stimulation for memory enhancement: from clinical research to animal models". In: *Front Syst Neurosci* 8:159. doi: https://doi.org/10.3389/fnsys.2014.00159.

Bersani, F. S., Minichino, A., Enticott, P. G., Mazzarini, L., Khan, N., Antonacci, G., et al. (2013). "Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: A comprehensive review". In: *Eur Psychiat* 28 (1/2013), pp. 30–39. doi: https://doi.org/10.1016/j.eurpsy.2012.02.006.

Bostrom, N., Sandberg, A. (2009). "Cognitive enhancement: methods, ethics, regulatory challenges". In: *Sci Eng Ethics* 15 (3/2009), pp. 311–341. doi: https://doi.org/10.1007/s11948-009-9142-5.

Brukamp, K., Gross, D. (2012). "Neuroenhancement – A Controversial Topic in Contemporary Medical Ethics". In: Clark, P. A. (ed.) (2012). *Contemporary Issues in Bioethics*. InTech, pp. 39–50. doi: https://doi.org/10.5772/35001. Available at: http://www.intechopen.com/books/contemporary-issues-in-bioethics (accessed on January 2, 2016).

Chatterje, A. (2004). "Cosmetic neurology. The controversy over enhancing movement, mentation and mood". In: *Neurology* 63 (6/2004), pp. 968–974. doi: https://doi.org/10.1212/01.wnl.0000138438.88589.7c.

Chervyakov, A. V., Chernyavsky, A. Y., Sinitsyn, D. O., Piradov, M. A. (2015). "Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation". In: *Front Hum Neurosci* 9:303. doi: https://doi.org/10.3389/fnhum.2015.00303.

Davis, N. J., Van Koningsbruggen, M. G. (2013). "'Non-invasive' brain stimulation is not non-invasive". In: *Front Syst Neurosci* 7:76. doi: https://doi.org/10.3389/fnsys.2013.00076.

Farah, M. J., Illes, J., Cook-Degen, R., Gardner, H., Kandel, E., King, P., et al. (2004). "Neurocognitive enhancement: what can we do and what should we do?". In: *Nat Rev Neurosci* 5 (5/2004), pp. 421–425. doi: https://doi.org/10.1038/nrn1390.

Farah, M. J. (2015). "The unknowns of cognitive enhancement. Can science and policy catch up with practice?". In: *Science* 350 (6259/2015), pp. 379–380. doi: https://doi.org/10.1126/science.aad5893.

Feng, W., Bowden, M. G., Kautz, S. (2013). "Review of transcranial direct current stimulation in poststroke recovery". In: *Top Stroke Rehab* 20 (1/2013), pp. 68–77. doi: https://doi.org/10.1310/tsr2001-68.

Gendle, M. H., McGrath, M. G. (2012). "Can the 8-ocil Shakti alter subjective emotional experience? A randomized, placebo-controlled study". In: *Percept Motor Skill* 114 (1/2012), pp. 217–235. doi: https://doi.org/10.2466/02.24.pms.114.1.217-235.

Grout, J. (2015). "Scribonius Largus". In: Grout, J. (2015). *Encyclopaedia Romana*. Available at: http://penelope.uchicago.edu/~grout/encyclopaedia_romana/aconite/largus.html (accessed on December 17, 2015).

Hamid, A. I. A, Gail, C., Speck, O., Antal, A., Sabel, B. A. (2015). "Effects of alternating current stimulation on the healthy and diseased brain". In: *Front Neurosci* 9:391. doi: https://doi.org/10.3389/fnins.2015.00391.

Hamilton, R., Messing, S., Chatterjee, A. (2011). "Rethinking the thinking cap. Ethics of neural enhancement using noninvasive brain stimulation". In: *Neurology* 76 (2/2011), pp. 187–193. doi: https://doi.org/10.1212/wnl.0b013e318205d50d.

Husain, M., Mehta, M. A. (2011). "Cognitive enhancement by drugs in health and disease". In: *Trends Cogn Sci* 15 (1/2011), pp. 28–34. doi: https://doi.org/10.1016/j.tics.2010.11.002.

Iuculano, T., Kadosh, R. C. (2013). "The mental cost of cognitive enhancement". In: *J Neurosci* 33 (10/2013), pp. 4482–4486. doi: https://doi.org/10.1523/jneurosci.4927-12.2013.

Kadosh, R. C., Levy, N., O'Shea, J., Shea, N., Savulescu, J. (2012). "The neuroethics of non-invasive brain stimulation". In: *Curr Biol* 22 (4/2012), R108–R111. doi: https://doi.org/10.1016/j.cub.2012.01.013.

Karabanov, A., Zieman, U., Hamada, M., George, M. S., Quartarone, A., Classen, J., et al. (2015). "Consensus Paper: Probing Homeostatic Plasticity of Human Cortex with Non-invasive Transcranial Brain Stimulation". In: *Brain Stim* 8 (5/2015), pp. 993–1006. doi: https://doi.org/10.1016/j.brs.2015.06.017.

Kessler, S. K., Minhas, P., Woods, A. J., Rosen, A., Gorman, C., Bikson, M. (2013). "Dosage Consideration for Transcranial Direct Current Stimulation in Children: A Computational Modeling Study". In: *PLoS One* 8 (9/2013), e76112. doi: https://doi.org/10.1371/journal.pone.0076112.

Krishnan, C., Santos, L., Peterson, M. D., Ethinger, M. (2015). "Safety of noninvasive brain stimulation in children and adolescents". In: *Brain Stimul* 8 (1/2015), pp. 76–87. doi: https://doi.org/10.1016/j.brs.2014.10.012.

Larriviere, D., Williams, M. A., Rizzo, M., Bonnie, R. J. (2009). "Responding to Requests from Adult Patients for Neuroenhancements". In: *Neurology* 73 (17/2009), pp. 1406–1412. doi: https://doi.org/10.1212/wnl.0b013e3181beecfe.

Lee, Y., Lilve, A. J. (2009). "The molecular and cellular biology of enhanced cognition". In: *Nat Rev Neurosci* 10 (2/2009), pp. 126–140. doi: https://doi.org/10.1038/nrn2572.

Limoge, A., Robert, C., Stanley, T. H. (1999). "Transcutaneous cranial electrical stimulation (TCES): A review". In: *Neurosci Biobehav Rev* 23 (4/1999), pp. 529–538. doi: https://doi.org/10.1016/s0149-7634(98)00048-7.

Luber, B., Lisanby, S. H. (2014). "Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS)". In: *Neuroimage* 85 (3/2014), pp. 961–970. doi: https://doi.org/10.1016/j.neuroimage.2013.06.007.

Luedtke, K., Rushton, A., Wright, C., Geiss, B., Juergens, T. P., May, A. (2012). "Transcranial Direct Current Stimulation for the Reduction of Clinical and Experimentally Induced Pain. A Systematic Review and Meta-analysis". *Clin J Pain* 28 (5/2012), pp. 452–461. doi: https://doi.org/10.1097/ajp.0b013e31823853e3.

Maslen, H., Douglas, T., Cohen Kadosh, R., Levy, N., Savulescu, J. (2015). "The regulation of cognitive enhancement devices: refining Maslen et al.'s model". In: *J Law Biosci*, lsv029. doi: https://doi.org/10.1093/jlb/lsv029.

Mondino, M., Bennabi, D., Poulet, E., Galvao, F., Brunelin, J., Haffen, E. (2014). "Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders?". In: *World J Biol Psychia* 15 (4/2014), pp. 261–275. doi: https://doi.org/10.3109/15622975.2013.876514.

Nitsche, M. A., Boggio, P. S., Fregni, F., Pascual-Leone, A. (2009). "Treatment of depression with transcranial direct current stimulation. A review". In: *Exp Neurol* 219 (1/2009), pp. 14–19. doi: https://doi.org/10.1016/j.expneurol.2009.03.038.

Nitsche, M. A., Paulus, W. (2000). "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation". In: *J Physiol* 527 (3/2000), pp. 633–639. doi: https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

Paulus, W. (2011). "Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods". In: *Neuropsych Rehab* 21 (5/2011), pp. 602–617. doi: https://doi.org/10.1080/09602011.2011.557292.

Persinger, M. A., Koren, S. A., St Pierre, L. (2014). "Application of weak, complex magnetic fields that attenuates EAE in rats to human subject with moderately severe multiple sclerosis". In: *J Neurol Neurophysiol* 5 (4/2014). doi: https://doi.org/10.4172/2155-9562.1000213.

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., et al. (2009). "Noninvasive cortical stimulation enhances motor acquisition over multiple days through an effect on consolidation". In: *PNAS* 106 (5/2009), pp. 1590–1595. doi: https://doi.org/10.1073/pnas.0805413106.

Saturnino, G. B., Antunes, A., Thielscher, A. (2015) "On the importance of electrode parameters for shaping electric field patterns generated by tDCS". In: *NeuroImage* 120, pp. 25–35. doi: https://doi.org/10.1016/j.neuroimage.2015.06.067.

Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., et al. (2013). "Long-term Enhancement of Brain Function and Cognition Using Cognitive Training and Brain Stimulation". In: *Curr Biol* 23 (11/2013), pp. 987–992. doi: https://doi.org/10.1016/j.cub.2013.04.045.

Sparing, R., Mottaghy, F. M. (2008). "Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)—From insights into human memory to therapy of its dysfunction". In: *Methods* 44 (4/2008), pp. 329–337. doi: https://doi.org/10.1016/j.ymeth.2007.02.001.

Tsang, E. W., Koren, S. A., Persinger, M. A. (2004). "Electrophysiological and quantitative electroencephalographic measurements after treatment by transcerebral magnetic fields generated by compact disc through a computer sound card: The Shakti treatment". In: *Intern J Neurosci* 114, pp. 1013–1024. doi: https://doi.org/10.1080/00207450490461323.

Van Driel, J., Sligte, I. G., Linders, J., Elport, D., Cohen, M. X. (2015). "Frequency band-specific electrical brain stimulation modulates cognitive control processes". In: *PLoS ONE* 10 (9/2015), e0138984. doi: https://doi.org/10.1371/journal.pone.0138984.

Wagner, T., Valero-Cabre, A., Pascual-Leone, A. (2007). "Noninvasive Human Brain Stimulation". In: *Annu Rev Biomed Eng* 9 (1/2007), pp. 527–565. doi: https://doi.org/10.1146/annurev.bioeng.9.061206.133100.

Witkowski, M., Garcia Cossio, E., Chander, B. S., Braun, C., Birbaumer, N., Robinson, S. E., Soekadar, S. R. (2015). "Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS)". In: *NeuroImage* 140, pp. 89–98. doi: http://dx.doi.org/10.1016/j.neuroimage.2015.10.024.

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., et al. (2015). "A technical guide to tDCS, and related non-invasive brain stimulation tools". In: *Clin Neurophysiol* 8 (2/2015), pp. 412. doi: https://doi.org/10.1016/j.clinph.2015.11.012.

Zaghi, S., Acar, M., Hultgren, B., Boggio, P. S., Fregni, F. (2010). "Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation". In: *Neuroscientist* 16 (3/2010), pp. 285–307.

Zubrinić, D. (2008). "Andrija Štampar introduces public health care in China in 1930s, part 1". On: *Croatian World Network*, available at: http://www.croatia.org/crown/articles/9595/1/Andrija-Stampar-is-the-father-of-the-World-Health-Organization.html (accessed on December 22, 2015).

Abbreviations:

EEG – Electroencephalogram
NIBS – Non-invasive brain stimulation
TES – Transcranial electric stimulation
tACS – Transcranial alternating current stimulation
tCS – Transcranial current stimulation
tDCS – Transcranial direct current stimulation
tRNS – Transcranial random noise stimulation
TMS – Transcranial magnetic stimulation
WHO – World Health Organization

Julija Erhardt, Dubravka Švob Štrac

Nefarmakološki alati za neuropoboljšavanje

Neuroetički problemi

Sažetak

Napredak u neuroznanosti i tehnologiji donio nam je nekoliko metoda s potencijalom nefarmakološkog utjecaja na mozak. Najveći broj tih metoda razvijen je sa svrhom tretiranja poremećaja, ali također imaju pogodne učinke na kogniciju i raspoloženje kod zdravih osoba, te potencijal za korištenje u svrhe poboljšavanja. Dvije kategorije metoda koriste se za tretiranje mozga; metode koje primjenjuju magnetsko polje i metode koje primjenjuju električno strujanje kroz skalp. Razvijeno je nekoliko metoda koje se služe jednim od tih principa, od kojih su najvažnije transkranijalna magnetska stimulacija (TMS) i transkranijalna stimulacija istosmjernom strujom (tDCS). Cilj ovog pregleda je dati kratak pregled različitih aspekata najšire korištenih nefarmakoloških tehnika koje mogu biti korištene u svrhe poboljšavanja te istaknuti najvažnije etičke probleme vezane za sigurnost, utjecaj na osobnost, pravdu te autonomiju upotrebe. Bez obzira na količinu informacija o mehanizmima i oblicima upotrebe metoda, mogući opseg i domet nuspojava i implikacija primjene nisu dovoljno naglašeni. Izvan kliničkih uvjeta uređaji nisu regulirani i ne postoji sustav osiguranja. Nadalje, sveprodiruća tehnologija koja okružuje naše življenje i manjak javnog dijaloga štete razvoju sporog i razumnog postupka implementacije i rezultiraju širenjem i komercijalizacijom njihove upotrebe.

Ključne riječi

neuroetika, neuropoboljšavanje, neinvanzivna stimulacija mozga, transkranijalna magnetna stimulacija (TMS), Shakti-8, transkranijalna stimulacija istosmjernom strujom (tDCS), transkranijalna stimulacija izmjeničnom strujom (tACS), transkranijalna stimulacija nasumičnim šumom (tRNS)

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Nicht pharmakologische Mittel für Neuroverbesserung

Neuroethische Fragen

Zusammenfassung

Die Fortschritte in der Neurowissenschaft und Technologie brachten uns mehrere Methoden, die ein Potenzial zur nicht pharmakologischen Beeinflussung unseres Gehirns haben. Die Mehrheit dieser Methoden ist zum Zweck der Behandlung von Störungen entwickelt, darüber hinaus erzielen sie aber günstige Ergebnisse für die Kognition und Gemütsverfassung bei gesunden Personen und beinhalten das Potenzial für die Verwendung zum Verbesserungszweck. Zwei Kategorien von Verfahren werden zur Behandlung des Gehirns verwendet, Methoden, die ein magnetisches Feld anwenden und jene, die elektrischen Strom durch die Kopfhaut einsetzen. Es wurden verschiedene Methoden entwickelt, die eines dieser Prinzipien zur Behandlung verwenden, wovon sich die transkranielle Magnetstimulation (TMS) und die transkranielle Gleichstromstimulation (tDCS) als bedeutendste erweisen. Die Intention dieses Überblicks ist es, ein kurzes Resümee der verschiedenen Aspekte der meistgebrauchten nicht pharmakologischen Techniken zu geben, die zum Verbesserungszweck verwendet werden können, und die relevantesten ethischen Fragen darzulegen, die in Zusammenhang mit Sicherheit, Einfluss auf den Charakter, Gerechtigkeit und Autonomie ihrer Verwendung stehen. Ungeachtet der Menge an Informationen über die Mechanismen und Handlungsweisen für bestimmte Methoden wurden die mögliche Reichweite und der Umfang ihrer Nebenwirkungen und Implikationen bei deren potenziellen Verwendung zugunsten der Verbesserung ungenügend hervorgehoben. Außerhalb der klinischen Verhältnisse sind diese Geräte nicht reguliert und es besteht kein System an Ort und Stelle, um ihre Sicherheit zu gewährleisten. Die alldurchdringende Technologie, die unser Leben umgibt, und der Mangel an öffentlichem Diskurs, beeinträchtigen zudem gemeinsam eine vernünftige und langsame Annäherung an ihre Implementierung und resultieren in der Ausbreitung und Zunahme ihrer kommerziellen Nutzung.

Schlüsselwörter

Neuroethik, Neuroverbesserung, nicht invasive Hirnstimulation, transkranielle Magnetstimulation (TMS), Shakti-8, transkranielle Gleichstromstimulation (tDCS), transkranielle Wechselstromstimulation (tACS), transkranielle Rauschstromstimulation (tRNS)

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Des moyens non pharmacologiques pour une « neuro-amélioration » (Neuroenhancement)

Problèmes neuroéthiques

Résumé

Les avancées technologiques et en neurosciences ont mis à jour de nombreuses méthodes ayant le potentiel d'avoir une influence sur notre cerveau sans avoir recours à des moyens pharmacologiques. Alors que la plupart de ces méthodes ont été développées dans le but de traiter les maladies, elles ont montré des résultats favorables concernant les capacité cognitives et émotionnelles chez des personnes en bonne santé, mais également du potentiel quant à l'amélioration de certaines caractéristiques non pathologiques. Deux catégories de méthodes sont utilisées pour les traitements sur le cerveau, celles qui se servent du champ magnétique et celles qui appliquent un courant électrique impulsé dans le crâne. Les quelques méthodes développées se servent d'un de ces principes pour le traitement des maladies, les plus importantes étant la stimulation magnétique transcrânienne (TMS) et la stimulation transcrânienne à courant direct (tDCS). Le but de cette recherche est de donner un bref aperçu des différents aspects des techniques non pharmacologiques les plus largement pratiquées qui peuvent être utilisées à des fins d'amélioration de caractéristiques non pathologiques, mais aussi de mettre en lumière les problèmes éthiques liés à la sécurité, à l'influence sur le caractère de la personne, à la justice et à l'autonomie de leur utilisation. Bien qu'une quantité d'informations sur les mécanismes et sur les modes d'action de ces méthodes spécifiques nous ait été fournie, l'étendue et la portée d'éventuels effets secondaires et les implications quant à leur potentiel utilisation pour l'amélioration de nos capacités n'ont pas encore été suffisamment soulignées. Ces dispositifs ne sont pas régulés en dehors du cadre clinique et aucun système n'a été mis en place pour assurer leur sécurité. De plus, la technologie omniprésente qui nous entoure et le manque de dialogue public vont à l'encontre d'une approche raisonnable et lente de leur mise en œuvre, ce qui a pour conséquence d'augmenter leur diffusion et leur utilisation à des fins commerciales.

Mots-clés

neuroéthique, neuroenhancement, stimulation non invasive du cerveau, stimulation magnétique transcrânienne (TMS), Shakti-8, stimulation transcrânienne à courant direct (tDCS), stimulation transcrânienne à courant alternatif (tACS), stimulation sonore aléatoire transcrânienne (tRNS)