CHAPTER

19

The Future Usage and Challenges of Brain Stimulation

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http://dx.doi.org/10.1016/B978-0-12-404704-4.00019-3

INTRODUCTION

The current book starts with an overview of the past, by providing a brief history of how transcranial electrical stimulation has been used to enhance cognition and improve health. The rest of the book discusses current knowledge in the field, and provides an excellent overview of different lines of research, such as those in animals, healthy humans, and patients. The aim of this last chapter is to discuss further directions for research in the field of transcranial electrical stimulation (tES).

Over the different chapters it becomes clear that research using tES has demonstrated improvements in different cognitive and non-cognitive functions, ranging from perception and motor movement to attention, working memory, language, and mathematical abilities. These results show that such improvements are not limited to typical populations but can also affect young adults and the elderly, and neurological and psychiatric patients. These results are indeed promising, but suffer from some limitations that have been discussed in various of these chapters, as well as elsewhere (Pascual-Leone, Horvath, & Robertson, 2012; Rothwell, 2012). Some of these limitations include low sample size, artificial tasks with reduced ecological validity, lack of consistency in the montage that led to the enhancement effects, and need for replication. I will not extend the discussion on these points, as they are rather trivial and are not limited to the current field. Instead I will discuss what I perceive as the directions in which the field of tES should, and hopefully will, go. It was difficult deciding which sections to include in this respect, and I have chosen to limit our discussion to 10 sections. I will conclude the chapter with a brief discussion of the challenges that the field is facing.

NEURODEVELOPMENT

tES is used currently to examine the improvement of cognitive performance, for a brief or long period of time, in young adults and elderly. However, its application in younger populations is sparse. Stimulating the child or adolescent brain is a double-edged sword. On the one hand the child brain is more plastic than the adult brain (Anderson, Spencer-Smith, & Wood, 2011; Gogtay et al., 2004), and therefore stimulation at this stage could lead to remarkable and stronger effects, especially when plastic changes would be desirable due to atypical development. On the other hand, this same reason – that the child brain has a greater degree of plasticity – is a cause for concern; namely, that stimulation may substantially change the balance between different brain regions and brain networks, and might lead to a subsequent impairment of the trained and/or non-trained abilities. It is a dilemma whether one should aim to use tES in the pediatric population, and I have discussed this elsewhere (Krause & Cohen Kadosh, 2013). I think that such a decision should be made by weighing the potential risk versus the potential gain (Maslen, Douglas, Cohen Kadosh, Levy, & Savulescu, 2014). For this reason, I recommend that studies on typically developing children should not be run at this stage. However, studies are desperately needed for those with detrimental atypical development, as the consequences of such development negatively impact such children's current life and future. It is an open question at this stage what type of stimulation, montage, and dose would be optimal in their case, as such knowledge is currently limited even when one aims to stimulate the adult brain. However, further tES experiments in this population, along with parallel research using neuroimaging techniques, computational modeling, and preclinical studies, could provide better understanding of the optimal sites for stimulation as a function of development and cognitive abilities, and stimulation efficacy and risk.

ECOLOGICAL VALIDITY AND TRANSFER

Nowadays, most tES studies (as well as studies in other fields) are run in a controlled laboratory setting and on tasks that have little to do with everyday life activities. This is, of course, clearly warranted at the first stage of exploratory research in order to assess the efficacy of tES on human behavior, and to give greater understanding of the biological and cognitive mechanisms that are affected as a function of tES. However, there is a need to expand this line of research toward more ecological settings and tasks that might be more closely related to everyday life. In this case, the combination of tES with other fields, such as education or neurology, is very promising, and would allow assessment of the effect of tES in a more real-life situation. For example, improvement in learning language or improving SAT/intelligence quotient (IQ) scores would provide a demonstration of the real applicability of tES. Of course, one of the caveats is that such improvement cannot allow us to pinpoint the cognitive function(s) and biological mechanisms that have been affected. My answer for this is that we should not forget what is the ultimate goal: to improve human behavior and life. Of course, a better cognitive and neural understanding can further aid us to reach this goal. However, achieving our goal does not necessarily depend on better mechanistic knowledge. Once this goal is achieved, we can redirect our research focus to identify the reasons (e.g., the relevant cognitive/biological mechanisms). One might argue that we should not use tES without a clear understanding of the mechanistic operation, whether cognitive or biological. However, this is not the case when looking at other fields. For example, MRI scanners are used quite successfully for research and clinical applications based on theories that we still do not have a clear understanding of (such as quantum mechanics). Similarly, scurvy was at one time common among sailors, pirates, and others aboard ships at sea. James Lind, a Scottish surgeon in the Royal Navy, proved that scurvy can be treated with fresh fruits in experiments he described in his 1753 book, *A Treatise of the Scurvy* (Krebs, 2013). It would have been ridiculous to wait until the exact mechanism was revealed (lack of vitamin C), two centuries later, to treat this illness. The final example is even more relevant: the current situation with deep brain stimulation (DBS) is the same, in that mechanisms of action are largely unknown but DBS is used worldwide for treating neurological and psychiatric disorders (Kringelbach, Jenkinson, Owen, & Aziz, 2007). Likewise, I do not see any objection if cognitive abilities can be improved in the first instance by using tES. Rather, I believe that achieving this goal could facilitate research in different fields and allow us to shed light on the potential mechanisms.

Another closely related issue in cognitive enhancement and training is the issue of transfer (Taatgen, 2013). Currently, there is mixed evidence from tES-paired training studies that either found or did not find transfer of tES-training benefits to another task. One of the issues regarding this lack of consistency is the difficulty of selecting appropriate training and transfer tasks, and of identifying which cognitive functions and brain regions are tapped by the training material. In other words, the limitation might not be the limited ability of tES to induce transfer, but rather a suboptimal experimental design. Therefore, this potential limitation that has been put forward in the past is not limited to tES but is a generic problem in the field of rehabilitation and cognitive enhancement (Taatgen, 2013). Indeed, some studies have shown that tES can even further increase the chance of transfer in paradigms that have struggled to show transfer without stimulation (Cappelletti et al., 2013; Looi, Duta, Huber, Nuerk, & Cohen Kadosh, 2013). How such improvement occurs at the neural level is still unknown. Further studies are needed to examine the multifaceted issue of transfer effects, and their possible enhancement using tES. Such knowledge will have important applications for improving human behavior in typical and atypical populations.

THE IMPACT OF tES

Another current caveat for the observed results so far is the issue of impact. Is a tES-induced improvement in performance in the order of tens of milliseconds or few percentage points significant for our everyday life (Pascual-Leone et al., 2012; Walsh, 2013)? We can, of course, suggest events in which a few milliseconds can make a difference, such as car accidents, professional sports, playing a musical instrument, or on the battlefield. Nevertheless, our everyday activities are less affected by such small increments in our behavior. It is important to note that not *all* the findings are at the level of milliseconds – for example, improvements have been shown of 1.25 s in arithmetic problem-solving (Snowball et al., 2013), 3 s in solving logic reasoning tasks (Santarnecchi, Feurra, Galli, Rossi, & Rossi, 2013), and up to 50% average reduction in resting tremor amplitude in patients with Parkinson's disease (Brittain, Probert-Smith, Aziz, & Brown, 2013), enhanced working memory capacity (Looi et al., 2013), or qualitative change in behavior (Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010). However, such effects are currently the exception rather than the rule. The low level of improvement might be attributed to several factors. This might include suboptimal task difficulty, lack of adjunct cognitive training, and infrequent repetitions of brain stimulation. As discussed, most studies nowadays are still at the proof-of-concept stage, and this might hamper the possibility of examining real-life situations in which the significance of the effects could be examined.

So far, tES studies have focused on cognitive tasks that produce quantitative effects, begging the question of what other fields of research might benefit from involvement of tES techniques. Notably, tES studies have mainly neglected fields of research that produce more qualitative effects. One such field that has shown promise is social neuroscience, including moral behavior (Ruff, Ugazio, & Fehr, 2013; M. Lavidor and J. Savulescu, personal communication).

INDIVIDUAL DIFFERENCES

Whether or not the effects prove to be robust in daily life, so far various studies have provided evidence for neuroenhancement due to tES at the behavioral and neural levels. However, one unresolved question, which has important implications for the translation of tES, replication, and neuroethics, is the issue of individual differences. Namely, it is unclear how tES affects brain and behavior as a function of individual differences at these levels. Some research has provided initial answers to this pending question (see, for example, Antal et al., 2010; Tseng et al., 2012). While further research in this direction is definitely needed, one of the issues is that research so far has examined the effect of tES after categorizing the group of subjects rather than investigating parametric changes in phenotype (Tseng et al., 2012) or genotype (Antal et al., 2010). The few studies that have examined the efficacy of tES as a function of individual differences have compared dichotomous variables, such as high vs low attention abilities (Tseng et al., 2012). This "extreme groups approach" is warranted at earlier stages of research to examine possible differences, but subsequently impairs reliability and replication (Preacher, Rucker, MacCallum, & Nicewander, 2005). Instead, future research is needed to see how *variation* in human performance is linked to improvement in cognitive abilities. One view is that those with lower abilities will have more room to improve. However, this is not necessarily the case. For example, in the case of education it has been shown that those with greater cognitive ability will also benefit more from schooling, which is one of the most acceptable methods for cognitive enhancement. If two children with different cognitive abilities in a given topic are entering the same class, it is more likely that the child with the higher ability will maintain his or her superior performance and the gap between the children will further increase (Duncan et al., 2007). If tES leads to improvement in those who are already well off cognitively it will lead to neuroethical problems, as it will increase natural inequality rather than reducing it. Methods of enhancement, such as tES, that could reduce the cognitive inequality due to gaps in biological (e.g., reduced gray matter, or suboptimal brain functions, suboptimal neuronal oscillations) or environmental (e.g., socioeconomic) backgrounds would allow more equal opportunities for effective learning. Such a balance in improvement of cognitive abilities would be an important step toward a fairer and more equal society.

I have focused so far on individual differences at the behavioral level. However, individual differences at the neural level can be used as a target to reduce inequality. This can occur at different levels, from structural and functional differences to genetic and neurochemical differences, such as cortical excitation/inhibition ratio level (e.g., Krause, Márquez-Ruiz, & Cohen Kadosh, 2013; Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013). This will require a better understanding of the connection between behavior and brain as a function of individual differences, and of how we could modify a neural system in order to push it toward an optimal level. In this respect it must be noted that, on the one hand, stimulation of one or more brain regions might be more advantageous to those with low cognitive abilities, and this might be due to differences in the recruitment of these brain regions by this population (e.g., Grabner et al., 2007; Rivera, Reiss, Eckert, & Menon, 2005). On the other hand, it might well be that targeting a different brain region will be more beneficial to those with high cognitive abilities. Such differences in the efficacy of tES might be due to qualitative and quantitative differences in individuals' brain–behavioral relationships, and differences in the usage of strategies to solve a given problem as a function of *a priori* ability (Dowker, Flood, Griffiths, Harriss, & Hook, 1996; Lemaire, 2010; Pesenti, 2005; Pesenti et al., 2001). Therefore, careful experimentation, combined with a better understanding of the brain–behavior relationship and cognitive processes, would allow greater advancement in the efficacy of tES and its effect as a function of individual differences.

COGNITIVE AND NEURAL COST

We aim to improve human behavior and brain functions; however, we usually neglect the fact that such improvement might be associated with cognitive and/or neural cost. The brain receives a fixed supply of oxygen and nutrients, and shifting the balance by increasing or decreasing the levels of excitation and inhibition in a given area of the brain might come at the cost of other brain regions and affect the behavior of other domains (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Krause et al., 2013; Pascual-Leone et al., 2012). This view, which is similar to concerns regarding the use of cognitive enhancing drugs (Greely et al., 2008; Hyman, 2011), has not been examined so far in a thorough fashion, although some evidence has been documented at the behavioral level (Iuculano & Cohen Kadosh, 2013). I would like to note that, while I am focusing here on tES, to the best of my knowledge the same also applies to transcranial magnetic stimulation and DBS. That is, it is currently unknown whether there is any mental cost that is associated with cognitive or physical improvement.

As mentioned earlier, one option is to consider the potential gain versus the potential risk. That is, if someone is impaired in a given cognitive function (e.g., speech production), they might be willing to sacrifice other abilities to some degree in order to regain their impaired function (see Chapter 18). Similarly, some might want to increase their average or above-average cognitive capacities in order to enhance their function at work or improve the results of their study (e.g., improve their exam results by a few points in order to gain acceptance to a prestigious programme at the University of Cambridge). In such cases the usage of tES is subjective, and to some degree could be justified (depending of course how keen one is to study at the University of Cambridge). However, it is not clear who should make the decision regarding whether such usage is warranted, especially in the case of patients or people with reduced cognitive abilities who cannot provide their own consent (Maslen et al., 2014).

In contrast to this view of cognitive and neural cost, another scenario might be that the changes in one brain region will lead to proportional changes in other brain regions, thus meaning that changes will be distributed and therefore relatively negligible. In such a scenario, the brain would have no difficulties in adapting to such changes while maintaining similar levels of behavior in other domains.

It is difficult, however, to attempt to examine the extent of potential cognitive/neural costs of tES. The range of cognitive abilities that can be examined in a given experiment is limited logistically, and this is without taking into account abilities outside the cognitive domain, such as emotional and social skills. One possibility is to guide such research by examining how stimulation changes the stimulated brain region and various brain networks. This could help researchers to narrow down significantly the number of potential behavioral indices, and to employ behavioral tasks that tap the affected brain regions. Combining tES with methods such as resting-state functional magnetic resonance imaging (Keeser et al., 2011; Meinzer et al., 2012, 2013; Polanía, Paulus, & Nitsche, 2012), electroencephalography (Neuling, Rach, & Herrmann, 2013; Zaehle, Rach, & Herrmann, 2010; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011), magnetoencephalography (Soekadar et al., 2013; Venkatakrishnan, Contreras-Vidal, Sandrini, & Cohen, 2011), or near infrared spectroscopy (Snowball et al., 2013) can be excellent candidates for such an approach.

MILITARY USE

It is natural that, when discussing human enhancement, defense forces would be interested in examining the applicability of such tools for improving performance in future battlefields and headquarters (Academy of Medical Sciences, British Academy, Royal Academy of Engineering, and Royal Society, 2012). tES in this respect is no exception, and the number of defense forces investing research money in this field is increasing. These projects could range from enhancing the abilities of snipers and drone operators, to improving sustained attention, social skills, and problem-solving and reasoning.

Collaboration between scientists and the military can cause a level of discomfort to some scientists, who should eventually decide where to draw their own line and decide which projects, if any, it is morally right to engage with from the scientist's perspective. I, of course, will not attempt to serve as a moral compass in this case; this should be a personal decision, being one where there is no clear distinction between right and wrong. However, if consulted, my opinion is that projects that are likely to yield benefits for the wider public should not be dismissed outright. Some projects, such as improving problem-solving and reasoning abilities (in which I am involved) or improving social skills, can be easily translated to everyday life activities and in some cases can save lives (e.g., improving sustained attention of airport traffic controllers or lorry drivers).

SPORT

As a potential enhancement in healthy subjects, tES raises issues familiar to ethicists from discussions of pharmacological interventions (Cohen Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012). Without delving into a long discussion on the neuroethical implications of using tES for cognitive and physical enhancement (Cohen Kadosh et al., 2012; Hamilton, Messing, & Chatterjee, 2011), tES could plausibly be used to improve performance in sports and thus raises ethical questions akin to those surrounding doping in sport (Schermer, 2008). tES has a unique feature that makes this issue more pressing: unlike most pharmaceutical enhancements, currently it is not possible to detect that tES has been used to enhance an individual's cognitive or non-cognitive abilities (Davis, 2013). At present, in professional sport, blood and urine samples are routinely used to establish whether performance enhancers have been used.

A previous study has shown that tES can increase muscle endurance and decrease muscle fatigue in normal subjects (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007). Professional athletes who use tES to decrease muscle fatigue might have an important advantage, especially when there is increased load on their muscles, as in some of the most prestigious sporting events, (e.g., Tour de France, Football World Cup, Olympic Games). Similarly, tES has been shown to improve motion perception (Antal et al., 2004) – an important ability in a wide variety of sports, such as football, basketball, and baseball. For example, a goalkeeper who receives stimulation to area MT+ (also known as visual area V5), an extrastriate cortical area known to mediate motion processing (Born & Bradley, 2005; Pascual-Leone & Walsh, 2001), could exhibit improved performance and make fewer mistakes. Such a method of enhancement might, of course, be enthusiastically endorsed by some sports fans!

Another aspect of tES in sport is its application to improve mental preparation before the game. Currently, mental preparation is moderated mostly by sport psychologists. However, some have suggested that tES might be used to generate that feeling of effortless concentration that characterizes outstanding performance (Adee, 2012). Moreover, in the same way that behavioral intervention alone (compared to behavioral intervention with tES) seems to have limited capacity in improving human performance (Cappelletti et al., 2013; Cohen Kadosh, 2013; Krause & Cohen Kadosh, 2013; Reis, Prichard, & Fritsch, 2014), a similar argument can be made for mental preparation techniques that aim to improve athletic performance.

Although we cannot yet be confident that the findings cited above have ecological validity, they provide a potential field of use that scientists and policymakers should be aware of, and that I anticipate will receive considerable attention in the future (for a similar discussion, see Banissy & Muggleton, 2013; Cohen Kadosh, 2013).

COMBINATION WITH OTHER METHODS

At the moment, most tES studies are run in their purest possible form: that is, stimulating a given brain region to see its effect on behavior or a simple physiological measure (motor-evoked potential). However, combining tES with other methods and fields can enrich the basic understanding of the biological and cognitive mechanisms implicated, and may lead to more efficient protocols for stimulation and subsequent enhancement. Neuroimaging is one such method, as it can offer us insights into changes that are induced by tES from the neurochemical to the functional level (for reviews, see Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Hunter, Coffman, Trumbo, & Clark, 2013; Venkatakrishnan & Sandrini, 2012). However, other methods that are less utilized include genetic expression as a function of tES, the combination of tES with DBS electrode recordings, and the effect of *a priori* anatomical, neural, and neurochemical correlates on the efficacy of tES.

Another combination that has been used, although to date to a very small degree, is that of tES with pharmacological manipulations (see Chapter 6). While most tES studies involve healthy adults and focus on motor tasks, there is room for further combinations to assess how interaction between drugs and tES can modulate and further enhance neuroplasticity and efficacy of training. This issue is related to state-dependency of the neural system, because CNS-acting drugs may change the responsiveness of the brain to electrical intervention, similar to the effect of psychological tasks (Feurra et al., 2013).

OPTIMIZATION

Chapter 4 provides an excellent review of the different ways in which tES can be optimized, by taking into account individual differences in brain anatomy. Others have also suggested that individual differences in brain functions, such as cortical excitability, should be taken into account in tES studies, as they may affect the efficacy of stimulation (Krause et al., 2013). Identifying sources of interindividual variability will allow adjustment of stimulation protocols, potentially leading to prolongation and strengthening of the effects of tES (M. Nitsche, personal communication). Similarly, it will also be vital to develop new stimulation montages to better focus the stimulation and perhaps steer the current to the desired sites as a function of individual subjects' brain anatomy (Tecchio et al., 2013) (M. Bikson and D. Terhune, personal communication). Notably, such approaches are time consuming and currently expensive. Future development of cheap and easy-to-use methods to improve optimization would increase the likelihood of using them outside the laboratory.

The combination of tES with brain–computer interfaces is another direction to further optimize stimulation. For example, coupling behavioral measurements with EEG recording can help to assess neuronal oscillations, and specifically to determine which frequency might serve as the optimal neural marker of performance. This, in turn, can be used to design protocols for transcranial alternating current stimulation (tACS) to entrain those optimal EEG performance markers and thus improve online behavior in the most efficient way.

Another approach to optimization is to target a network of brain regions, rather than a single brain region as is commonly the case with tES. Stimulating a network that is engaged in the cognitive function one would like to improve could allow us the ability to increase the strength between the network's regions and the overall network (G. Ruffini, personal communication).

The effect of tES is assumed to stem largely from cortical brain regions close to the electrodes (see Chapter 4). However, it may be possible to use tES to affect subcortical brain regions. This would greatly increase the applicability of tES to additional cognitive domains, as well as neurological and psychiatric conditions (D. Terhune, personal communication). However, targeting subcortical regions is a challenge that, to date, has barely begun to be tackled. Stimulating cortical brain regions that are remotely connected to those subcortical structures seems to be one potential way to bypass such a challenge (Takano et al., 2011).

HOME USE

This last section is probably the "hot potato," subject to considerable debate in the field and, to some degree, even in this book (see Chapters 3 and 18): should tES eventually be used at home? Some concerns have been demonstrated, with regard to safety and knowledge of stimulation, which could lead to an increased risk when tES is used by amateurs (Bikson, Bestmann, & Edwards, 2013; Fitz & Reiner, 2013; Santarnecchi et al., 2013; see also Chapter 3). Others have expressed their view that the risk is over-exaggerated, along with the implications of the results from tES (Walsh, 2013), but at the same time have neglected several points that challenge their view (Chapter 3). In addition, the latter perspective did not take into account future directions that could lead to results with more ecological validity and that will increase the likelihood of amateur use of tES. In addition, safety studies are still lacking, especially longitudinal studies that examine the changes that have occurred as a result of repeated usage of tES (A. Antal, personal communication).

It is a fact that home use of tES does exist. This is due not only to companies that are making easy money from public enthusiasm, but also to an increasing "do-it-yourself" (DIY) culture of those who build their own machines and try to improve their mental ability (see, for example, this video at YouTube: http://www.youtube.com/watch?v=6V64IXFg9yc).

Independent of the varying views of future home use of tES, scientists might agree that at the moment we are still not ready for this stage; indeed, others have articulated this elsewhere (Bikson et al., 2013; Fitz & Reiner, 2013; Santarnecchi et al., 2013; see also Chapter 3. In face of the growing usage of tES by the public, I would like to suggest that if we cannot beat them we should join them. The idea, of course, is not to market devices for profit, but to engage with home users to ameliorate the current lack of knowledge and potential risk while at the same time providing training and examining the changes that occur to their brains as a function of tES. This could include a longitudinal assessment to examine changes in cognitive and brain functions. Of course, it is hard to find a good control for those subjects, but the effect of frequency of usage, and daily dose, would be able to shed some light on the risk of tES for home use, as well as its potential ecological validity. Such a combination could reduce the risk of home use tES (due to the training that will be provided by scientists), and allow a unique insight into the risk and gain from such use.

CONCLUSIONS

The different sections in this chapter provide a glimpse of the challenges that the field of tES is likely to encounter, and future directions. While I limited us to 10 strands that currently pose a challenge and should be examined in future research, I acknowledge that other lines of research are equally needed, as indicated in the various book chapters. These future directions for upcoming research are exciting, will increase our basic knowledge, and will have important impacts on society. The future appears full of intellectual and experimental stimulation.

Acknowledgments

I would like to thank Michal Lavidor, Julian Savulescu, Michael Nitsche, Marom Bikson, Devin Terhune, Giulio Ruffini, and Andrea Antal for their suggestions.

I am most grateful to Simone Rossi for reviewing this chapter and the many excellent additions to it. I would like to thank the different contributors to this book for their very kind suggestions, and interaction on future directions. Some of these have been included, but others were not due to lack of space. I am grateful for this openness and willingness to share their views. I would like to thank Jackie Thompson for proofreading, and the Wellcome Trust (WT88378) for its support.

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