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MINI-REVIEW

Brain Stimulation for Cognitive Enhancement in the Older Person: State of the Art and Future Directions

Nick J. Davis [1]

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Abstract Advances in medicine and healthcare and better education about healthy living have led to a greater proportion of people living healthily into older age. As the global population ages, it will become necessary to address the societal implications of this demographic change. Successful treatment of physical illnesses means that people are more likely to experience cognitive decline, either naturally through the ageing process or through the onset of dementia and related disorders. This will shift the healthcare burden from physical to cognitive care. In addition, healthy, active people are likely to remain in work, meaning that cognitive performance in the healthy elderly will require monitoring and support. This review will consider the possible role of brain stimulation technology in preserving or enhancing cognitive health in the healthy ageing population, and will discuss the current state of scientific research and the gaps in our knowledge around stimulating the brain of the older person.

Keywords Gerontology · Healthy ageing · Neuromodulation · tDCS · TMS

Introduction

The global population is ageing, as people live healthier lives and as many of the diseases that accumulate in older age are better managed. The consequence of improved success against diseases such as cancer or cardiovascular disease is that people now live healthily for many years beyond the traditional end of the working life. Although the health economics of greater longevity is complex (e.g. Cook 2011; Terraneo 2015), the World Health Organization (2015) recommends that nations prepare for this shift in demographics. The greater proportion of people living longer in retirement results in a greater economic burden on those still working, to fund social securities for the population as a whole. One consequence of this is that retirement ages are being increased in many countries, and the proportion of people opting for early retirement is decreasing (Duggan et al. 2007). In parallel, people may also wish to prolong their working life, to maintain the satisfying experience of fulfilling work or to postpone the feelings of changed identity that often accompany retirement (Wang et al. 2011). There is therefore both an economic need and for many people a personal desire to maintain cognitive health and a productive occupation as people reach their seventies, eighties and beyond.

Here I review the cognitive changes that commonly occur during normal ageing, and the neuroanatomic changes that accompany them. I will also suggest how non-invasive brain stimulation (NIBS, but see Davis and van Koningsbruggen 2013) may show promise in arresting the changes of older age, and will discuss some of the possible pitfalls and ethical barriers that may arise as NIBS is used more widely in the lab or in people's daily lives. I will focus here on healthy ageing, although many of the principles here will inform (and be informed by) advances in treating disorders associated with ageing, such as Parkinson's disease, stroke or dementia.

Several avenues have been attempted as a means of increasing or preserving cognitive health in older adults. Cognitive health has long been associated with physical health, and good cognitive performance in older people is associated with good sleep (Nebes et al. 2009), good hydration (Suhr et al. 2004) and a vitamin-rich diet (Riggs et al.

✉ Nick J. Davis
n.davis@mmu.ac.uk

[1] Department of Psychology, Manchester Metropolitan University, 53 Bonsall Street, Manchester M15 6GX, UK

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1996; Wilkins et al. 2006). Maintaining physical activity also appears to slow cognitive decline (Rosano et al. 2005). All of these are sensible and attainable strategies for maintaining good cognitive performance, and possess a quality of 'naturalness' that make them ethically untroubling compared to means such as pharmacological enhancement (Caviola and Faber 2015). Several pharmacological agents are thought to provide modest benefits to cognitive performance in otherwise healthy people, many of which were originally intended for use in neurological disorders (Franke et al. 2014). For example, modafinil was developed for narcolepsy, and methylphenidate is commonly used to treat attention-deficit hyperactivity disorder. Evidence from places such as college campuses suggests that these agents are in use among non-impaired people (Moore et al. 2014). More recently, it has been suggested that NIBS techniques, and especially transcranial direct current stimulation (tDCS), may also be in use among unimpaired people for cognitive enhancement or for recreational purposes (Jwa 2015).

Whilst the main sources of evidence for wider use of pharmacological or device-based enhancement (including online forums or questionnaires on campuses) tend to favour younger responders, it is likely, if not inevitable, that these methods will become more widespread in older demographics as they become more widely known and as current users get older. The questions addressed here are whether NIBS is likely to be of benefit to older people, and whether there are significant gaps in our knowledge relating to the use of NIBS in the older person.

Cognitive and Neural Changes in Healthy Ageing

Our cognitive performance changes through the lifespan. The changes that occur during childhood, when new skills and abilities emerge seemingly from nowhere, have been studied from the earliest days of psychology. Several strong models exist, such as Piaget's classic four-stage model that describes cognitive development from birth to adolescence (Piaget 1926, 1936). These early changes are remarkably consistent in their timing and in their occurrence in all healthily developing children (Fischer and Silvern 1985). However, the changes that occur towards the end of the lifespan, as cognitive performance declines, are much more subtle, and much more variable across individuals (e.g. Deary et al. 2009; Salthouse 2009).

Important and life-relevant cognitive changes include a slowing of response times (Jordan and Rabbitt 1977), increased response variability associated with a lower awareness of errors (Harty et al. 2013), a narrowing of attentional flexibility in spatial awareness (Castel et al. 2007), decreases in perceptual performance (Stevens 1992; Strouse et al. 1998) and slowing in interpreting emotional information (Sullivan et al. 2007). However, some of these changes may be masked by changes in cognitive strategy (Peters et al. 2007).

In parallel with the changes in cognitive performance, during ageing our brains change in structure and anatomical appearance (Lemaître et al. 2005). Figure 1 compares three anatomical brain scans taken from people in the middle years of life with three taken from people in their 90s. Even at a qualitative level, there are evident differences: in older people, the brain is smaller, and the volume of cerebro-spinal fluid is relatively larger; this is particularly evident when comparing the size of the ventricles. Less obvious is the thinning of the skull, and the reduced amount of white matter, although this may be seen in the narrowing of the commissures between the hemispheres. Most MRI-based studies find no differences between the sexes in neuroanatomic changes (e.g. Allen et al. 2005; Raz et al. 2005), although it is worth noting that post-mortem analyses may be more sensitive to changes such as reductions in fibre bundle volume (e.g. Witelson 1991). Functional imaging studies suggest that the distribution of task-related activity in the brain changes during ageing, with a wider network of brain areas recruited compared to the more discrete activations of the younger brain (e.g. Meinzer et al. 2009). These changes in activation are likely to be strategic, whereby higher-order processing is increased in response to reduced activity in more primary regions of the brain (Cabeza et al. 2004; Park and Reuter-Lorenz 2009; Vallesi et al. 2011).

Non-invasive Stimulation in Enhancing Cognition

NIBS has recently shown promise in enhancing cognitive performance in cognitively healthy people. Various protocols have shown benefits in domains such as working and long-term memory (Javadi and Cheng 2013; Mulquiney et al. 2011), fluid reasoning (Santarnecchi et al. 2013), task switching (Leite et al. 2013), language learning (Flöel et al. 2008), positive mood (Austin et al. 2016) and learning complex sensori-motor tasks (Choe et al. 2016). It is reasonably well established that NIBS offers a modest boost to performance in many tasks. Meta-analyses of the effects of NIBS in cognitive processing support this view, with transcranial magnetic stimulation (TMS) improving most aspects of cognitive or memory function, and tDCS favouring response speeds but with less convincing effects on accuracy (Brunoni and Vanderhasselt 2014; Hill et al. 2016).

Recent reviews of the small number of studies of NIBS in older adults found similar benefits, with generally positive outcomes and good tolerability (Martins et al. 2017; Summers et al. 2016). Positive results include enhanced monitoring of errors (Harty et al. 2014), reduced distractibility in a task (Kim et al. 2012), facilitations in language performance (Fertonani et al. 2014; Meinzer et al. 2014) and improved memory (Berryhill and Jones 2012; Flöel et al. 2012;

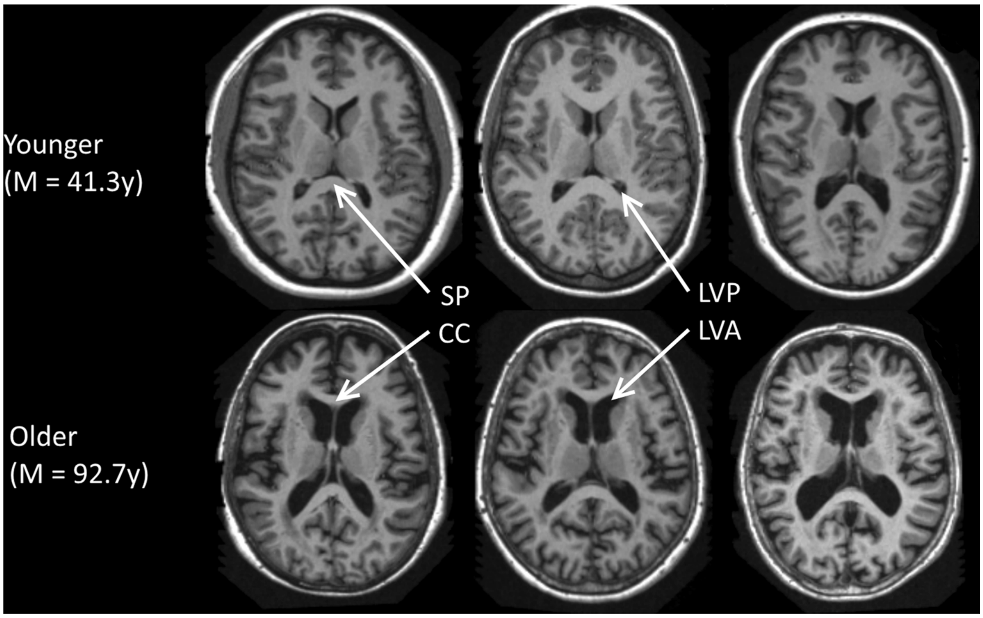

Fig. 1 Comparison of anatomic brain images taken from three women in young middle-age (aged 40, 41 and 43) with images from three healthy, non-demented women (aged 91, 93 and 94). All images were taken from the OASIS repository of brain images (Marcus et al. 2007), using images that were processed and aligned to a horizontal section, with the frontal part (CC) and the splenium (SP) of the corpus callosum evident in all sections. The comparison shows the changes that occur during normal ageing, including the reduction in brain volume and concomitant increase in cerebrospinal fluid, which is especially obvious in the anterior (LVA) and posterior (LVP) parts of the lateral ventricle, the thinning of the bone of the skull and the reduction in white matter

Holland et al. 2011; Manenti et al. 2013). Whilst the current literature is sparse, it would appear that older people show comparable benefits of NIBS to younger people, although there may be important differences in how older people respond (see below). The outlook for the use of NIBS for cognitive enhancement in the older person would appear to be rather positive, with a small but consistent literature pointing to modest gains in function that would seem to at least partially offset the decline of normal ageing, and intriguingly may make neural activity more 'youth-like' (e.g. in terms of functional connectivity patterns: Meinzer et al. 2013).

Of the two common means of modulating brain activity, TMS and tDCS, it seems likely that the latter will be seen more commonly as the field develops. tDCS is a relatively simple and accessible technology, consisting at its most basic level of a battery and a means of regulating current. By contrast, TMS is expensive and demands a more sophisticated level of technical ability to construct and deploy. tDCS can, in principle, be made and used at home (Davis 2016; Jwa 2015). tDCS is thought to be relatively safe, with only a single serious adverse reaction reported (a seizure in an already vulnerable child: Ekici 2015). However, there are likely to be other forms of adverse reactions that are less immediately obvious than a seizure, and therefore less likely to be discussed. One class of adverse effects are already well-known. Participants in tDCS procedures may report headaches, mild burns and other types of skin irritation. These minor effects are probably more common than the published reports would suggest (Brunoni et al. 2011). Relatedly, tDCS may exacerbate existing tendencies to mood changes, leading to treatment-related hypermania or hypomania (Matsumoto and Ugawa 2017). More worryingly, it is known that repeated sessions of tDCS lead to longer-lasting, additive effects. These can often be beneficial, such as when we want to lift mood or enhance learning (Austin et al. 2016; Reis et al. 2009), but the effects of tDCS are not limited to the function of interest. Home- and lab-based users must therefore be careful not to induce long-lasting adverse effects in non-target functions (e.g. Iuculano and Cohen Kadosh 2013).

Key Unknowns and Future Directions

The previous section outlined some of the promising avenues that might be explored in using NIBS for cognitive enhancement in older people. However, it was also clear that there are several unknowns and sources of variance in applying these techniques to older people. Here I will highlight some of the key issues that will need to be addressed in this topic.

Overarching much of this discussion is the practical question of whether NIBS can have any effect in natural settings. All studies cited so far have been lab-based studies, where controlled doses of stimulation have been delivered in a controlled environment, with a carefully controlled outcome measure. How well do lab-based findings translate to people's natural environment? At present, there have been few scientific attempts that have used brain stimulation in the person's home. TMS would be impractical for this use, but two studies have used tDCS with reasonable success (Andrade 2013; Hagenacker et al. 2014). In a less controlled environment, the so-called DIY-tDCS movement has seen people construct and use tDCS devices in their own home. The purposes, protocols and results of at-home users vary widely (Jwa 2015), and harnessing the enthusiasm of this community would be a valuable source of information in designing safe and effective protocols for naturalistic stimulation procedures (Charvet et al. 2015; Davis 2016).

One issue that is particularly relevant for tDCS is that we do not have a principled means of setting dosage, or for producing a given change in performance in a given person (Datta et al. 2012). At present, our best method for setting dosage is to use computational models to predict how the electrical energy will spread through the head from the point of delivery on the scalp. These models have so far been successful in understanding how to target perilesional areas of the stroke-affected brain (Datta et al. 2011), or in determining how best to alleviate chronic pain (Mendonca et al. 2011); however, there are many gaps in our knowledge (Bestmann and Ward 2017). One particular problem is that many existing models use a 'standard' head model, drawn from an MRI scan of a healthy young adult. However, if NIBS protocols are designed around people with this type of head anatomy, they may lead to dangerous concentrations of energy in people with non-standard anatomy such as the very young (Davis 2014) or people with eating disorders (Widdows and Davis 2014). A recent review of the safety of tDCS protocols indicated a wide variation across model heads in the current density on the surface of the brain, given a particular current density at the scalp; the implication is that a head model should be tailored to the individual, or at the very least to the population of interest (Bikson et al. 2016; Fregni et al. 2015). The reason for this uncertainty is that these groups have smaller or thinner skulls than healthy adults. This is illustrated in Fig. 1, where the head anatomy of three younger people is contrasted with that of three older people. The differences mean that the electrically insulating bone layer may offer the brain less protection than might be expected (Ivancich et al. 1992). The loss of bone density and mineralisation in older age is likely to present similar problems when NIBS is used in older people (Blunt et al. 1994). TMS also lacks a comprehensive set of principles for dose-setting, although protocols may at least be designed around individualized motor thresholds (Stokes et al. 2013).

A further source of variability, and possible risk, in brain stimulation is the interaction of stimulation with other treatments that the person may be receiving. As we age, we naturally accumulate conditions that require pharmacological management, such as treatments for blood pressure, high cholesterol or other conditions of later life. Relatively little is known about how the presence of pharmacological agents may affect NIBS, partly because people who are taking psychoactive medications are usually excluded from NIBS experiments on grounds of caution. tDCS and TMS induce changes in neurotransmitter levels in the brain (Stagg et al. 2009; Stagg and Nitsche 2011), so drugs that also manipulate these same mechanisms may interact with NIBS either by cancelling out the effect or by having an additive effect. Since tDCS is known to rely on synaptic mechanisms to produce its longer-lived effects (e.g. Nitsche et al. 2009), it would seem to follow that manipulating neurotransmitter levels would modulate tDCS effects, and indeed there appears to be some evidence of enhanced effect of tDCS with pharmacological support in older people (Prehn et al. 2016). These issues of drug interactions, and related problems of co-occurring conditions as the life course progresses, require careful research to establish clear safety and dosage guidelines. In parallel with these issues, there is the additional complication that individuals may respond to NIBS in different, even opposing, ways. NIBS to the motor cortex is known to be variable across individuals (Wassermann 2002; Wiethoff et al. 2014), and the effects of tDCS of opposing polarities may induce identical effects (Batsikadze et al. 2013). Troublingly, NIBS may induce quantitatively or even qualitatively different effects in the older person (Fujiyama et al. 2014; Heise et al. 2014). Overall, it is clear that considerable research is needed to reduce variability in the response to NIBS, and to understand how these techniques can be used to generate consistent, reliable effects in individual persons.

One problem that older people share with children and with people with eating disorders is the greater possibility of diminished capacity to consent to the procedures of enhancement. All parties in the procedure, including the participant and the person delivering the NIBS, must be certain that the participant has not declined in cognitive function to the point where they may not understand the implications and risks of the procedure. As with many medical treatments delivered to the older person, there are likely to be concerns about whether a person of declining cognitive health can make effective decisions about the intervention (Moye and Marson 2007; Stanley et al. 1984). It will require careful regulation to ensure that people are not coerced into receiving NIBS, nor is it unfairly withheld.

A wider ethical concern is whether we want to live in a society that permits, or even relies upon, widespread cognitive enhancement. Allowing unregulated enhancement presents a number of potential harms (Davis 2017). First, there is the issue that cognitive enhancement may only be available to those who can afford it, leading to, or widening, a divide in health between the richer and the poorer in society (Marmot et al. 2012). Second, by focusing on cognitive performance, we risk losing respect for natural human variation, which is one of the factors that define our humanity (Jordan 1921), and instead narrow the range of acceptable domains of achievement. A third risk is that we lose respect for these very achievements that result from performance under enhancement, just as we are disappointed when athletes are found to have enhanced their performance through use of illicit drugs (Santoni de Sio et al. 2016). Ethical concerns around enhancement raise important questions about the nature and the value of the activities we engage in, and understanding these concerns will be crucial in establishing clear boundaries for the use of enhancement technology in daily life.

Overall, it is evident that there is a wide range of behavioural targets for enhancement, and there are also a number of possible means for generating those enhancements. A key challenge for the near future will be to determine which cognitive faculties are most amenable to enhancement with NIBS, and to establish reliable protocols to deliver those changes. This will be possible only with a coordinated approach of careful experimentation built on solid theoretical foundations and on a good understanding of the neural and anatomical changes of healthy ageing.

Conclusions

It is clear that NIBS holds promise for cognitive enhancement in the older person, although it is not yet clear whether the practical and ethical barriers can be overcome in a way that makes the technology readily accessible to all. The key challenges are as follows:

1. the lack of clear safety and dosage principles
2. the uncertainty regarding the legality and desirability of widespread supranormal enhancement
3. the uncertain efficacy of NIBS in enhancing cognitive performance, when compared to other, more established, techniques such as pharmacological or 'natural' means

None of these barriers is insurmountable, nor is any unique to the question of enhancement in the older person. The solution to the first question of safety and dosage is likely to come from careful, possibly longitudinal, studies that engage with users of NIBS in labs and in their own homes, and from computational studies that explore the physical effects of NIBS on the brain (Davis 2016; de Berker et al. 2013). The second question touches on a wider philosophical debate about human enhancement (e.g. Davis 2017; Savulescu and Bostrom 2009), although society may take the pragmatic position that extending the cognitively healthy phase of the lifespan is desirable. Finally, the third question can only be answered in experimental comparisons of different methods of enhancement, and with suitable control or placebo conditions.

All people have a legitimate desire to experience a long life of physical and cognitive good health. With careful advances in science, and with careful and flexible governance, non-invasive brain stimulation offers hope in preserving cognitive function later in the lifespan.

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Compliance with Ethical Standards

Conflict of Interest The author declares that there is no conflict of interest.

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