Can non-invasive brain stimulation enhance function in the ageing brain?

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Abstract
Advancing age is associated with cognitive and motor performance deficits and a reduced capacity for plasticity. Zimerman and colleagues (2013) have recently shown that non-invasive brain stimulation can enhance behavioural improvements following training on a motor sequence task in older adults. The work is of high clinical importance given the rapidly growing ageing population and the accompanying costs to health systems globally.
A large body of literature suggests that advancing age is associated with cognitive and
motor performance deficits, both of which have a profound impact on older adults’
independence and, as a consequence, their quality of life (reviews Seidler et al. 2010;
Li et al. 2001). Given the rapid increase in the proportion of the population over the
age of 65, it is important to develop interventions to improve motor and cognitive
function in the ageing population.

Evidence from both animal and human studies has shown that advanced ageing is
associated with a reduction in the capacity for plasticity (Foster and Norris 1997;
Landfield et al. 1978; Rogasch et al. 2009; Muller-Dahlhaus et al. 2008; for review
see Burke and Barnes 2006). Experiments in animal studies have shown that at least
some forms of motor learning are mediated by long-term potentiation (LTP) and long-
term depression (LTD) in the motor cortex (Rioult-Pedotti et al. 2000; Rioult-Pedotti
et al. 1998). There is also evidence in humans to suggest that LTP-like processes in
the primary motor cortex (M1) are important in the early stages of motor learning
(Ziemann 2004; Stefan et al. 2006; Rosenkranz et al. 2007). The last decade has seen
many groups investigate the potential of non-invasive brain stimulation (NBS) to
induce plasticity. There is good evidence to suggest that, similar to motor learning,
NBS protocols can induce plasticity via LTP- and LTD- like processes (for review see
Cooke and Bliss 2006). Not surprisingly, this literature has generated excitement
surrounding the potential of NBS to induce behaviourally-important plasticity. In
young adults, there is some evidence to suggest that NBS protocols are effective in
enhancing learning (for example Nitsche et al. 2003; Reis et al. 2009). The capacity
for NBS to enhance learning in older adults might provide substantial clinical benefits
in light of the growing ageing population and associated costs to health systems
globally. Recently, Zimerman and colleagues (2013) investigated the important
question: Can NBS enhance the learning and retention of complex skills, yielding
longer-lasting behavioural improvements, in older adults?

Zimerman and colleagues (2013) examined the effect of anodal transcranial direct
current stimulation (atDCS), a facilitatory protocol that increases cortical excitability
via LTP-like synaptic changes (Nitsche et al. 2008), on learning and retention of a
motor sequence task in young (aged between 22-31 years old) and older adults (aged
between 55-88 years old) (see Zimerman et al. 2013 Fig. 1). The motor sequence task
comprised a 5-element key-pressing sequence to be performed as quickly and as accurately as possible; a task known to engage a large, distributed network of motor areas, including the M1 contralateral to the hand performing the task (Grafton et al. 1995; Penhune and Doyon 2002; Ungerleider et al. 2002). Participants completed 5 blocks of training, each lasting 3 minutes with a 2-minute break between blocks. atDCS or sham stimulation (control condition) was applied with the anode placed over the hand knob of left M1 and the cathode placed over the contralateral supraorbital region. Learning and retention was assessed by measuring the number of correct sequences achieved in each block during the training phase and re-test phase respectively.

As expected, older adults performed worse on the motor task than young adults. This finding is in line with the large body of literature showing age-related deficits in motor performance (for example Grabiner and Enoka 1995; Light and Spirduso 1990; Smith et al. 1999). Zimmerman and colleagues (2013) suggest that the poorer performance across the training blocks of older than younger adults shows significantly reduced learning in older adults. Zimmerman and colleagues (2013) also showed significantly greater behavioural improvements in older adults receiving atDCS than sham during training. Furthermore, when tested 90 minutes and 24 hours after training, performance of the learned skill was significantly greater in older adults who received atDCS than sham during training. Zimmerman and colleagues (2013) suggest that these data show that increasing excitability of M1 (using atDCS) during the training phase of the motor sequence task can increase both learning and retention in older adults.

While the results of Zimmerman and colleagues’ study provide some evidence that atDCS can enhance learning in older adults, two limitations are worth noting. First, it is very difficult to quantify learning differences between two groups when baseline performance is different. While the change in performance across training blocks was significantly smaller for older adults than young adults, the older adults also had a lower baseline performance. As a result, it is not possible to determine the effect of learning independent of baseline performance. Furthermore, in older adults, an absolute difference in baseline performance was evident between the atDCS and sham groups; this small difference in performance at baseline might act as a confound when
assessing differences in learning. While the difference was not statistically significant, a power analysis would be useful to determine the importance, if any, of the absolute difference in this sample. To accurately assess age-related changes in learning, differences in baseline performance between groups could be either eliminated by modifying task difficulty (for example Heuninckx et al. 2005; Wu and Hallett 2005) or controlled for by performing analyses on subgroups of participants with similar baseline performance levels. Second, behavioural improvements during training differed between the two groups and, therefore, it is not possible to distinguish the effect of atDCS on retention independent of learning; the degree of retention might be a function of learning such that those who learn more retain more. Using a task in which there are no in-session learning differences between target groups would allow the investigation of the effect of atDCS on retention, independent of learning.

There is good evidence from animal studies to show that motor learning results in structural changes in M1 (Rioult-Pedotti et al. 2000; Rioult-Pedotti et al. 1998). In humans, studies using transcranial magnetic stimulation (TMS) have provided evidence that motor learning induces LTP-like plasticity in M1 (Ziemann et al. 2004; Stefan et al. 2006; Rosenkranz et al. 2007). In line with this, Zimerman and colleagues (2013) suggested that the greater behavioural improvements evident in older adults who received atDCS (compared to sham) during training is due to facilitation of LTP-like processes in M1, likely mediated by a modulation of GABAergic neurotransmission and an enhancement of NMDA-dependent processes. It is, in fact, possible to test this suggestion: paired-pulse TMS protocols can be used to measure GABAergic and NMDA-dependent processes acting within M1. When a subthreshold TMS stimulus (S1) precedes a suprathreshold TMS stimulus (S2) by 1-6 ms, the amplitude of the motor evoked potential (MEP) elicited by S2 is suppressed due to the activation (by S1) of short-interval intracortical inhibitory (SICI) circuits (Kujirai et al. 1993). When the interval between S1 and S2 is 10-15 ms, the amplitude of the MEP elicited by S2 is facilitated due to the activation (by S1) of intracortical facilitatory (ICF) circuits (Kujirai et al. 1993). Pharmacological studies have shown that SICI and ICF are mediated by GABA \textsubscript{A} receptor and NMDA-dependant processes respectively (Ziemann et al. 1998; Di Lazzaro et al. 2000). Measuring SICI and ICF before and after training of the motor sequence task, accompanied by either atDCS or sham tDCS, would provide knowledge regarding the proposed role of GABAergic
and NMDA-dependent processes in the atDCS-facilitated motor learning in older adults. If modulation of GABAergic and NMDA-dependent processes is involved in the atDCS-facilitated motor learning, we would expect to observe a decrease in SICI and an increase in ICF following training accompanied by atDCS compared to baseline, and compared to training accompanied by sham in older adults.

While Zimerman and colleagues (2013) were interested in testing the possibility of neuroenhancement of learning generally, their use of a motor task to test this hypothesis highlights the important issue of age-related deficits in motor function (for review see Seidler et al. 2010). Visuomotor adaptation, which requires adaptation to external perturbations, is often used to investigate motor function (for review see Krakauer 2009). While both motor sequence learning and visuomotor adaptation engage a large distributed cortical network, there is some evidence to suggest that the cortico-cerebellar network is particularly important in motor adaptation (Smith and Shadmehr 2005; Martin et al. 1996; Maschke et al. 2004). Therefore, the cerebellum might prove an effective target for NBS as a means to improve the ability to adapt to changes in the environment in the ageing population, thereby improving motor function. Indeed, some support for this suggestion comes from work in young adults where atDCS delivered to the cerebellum was shown to enhance performance in the acquisition phase of a visuomotor adaptation task compared to sham (Galea et al. 2011).

In summary, Zimerman and colleagues have provided novel and clinically relevant evidence suggesting that NBS could be used to enhance motor function in the ageing population. This work is of high clinical importance given the rapidly growing ageing population and the accompanying costs to health systems globally. A plausible next step is to further develop NBS protocols and identify new, effective targets for neuroenhancement of the ageing brain that will lead to functional improvements in both the motor and cognitive domains. An equally important next step is to develop a better understanding of the neurophysiological causes of age-related deficits in motor function. The outcome: the development of safe, NBS protocols that can increase independence and quality of life in the ageing population.
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