Review Article • DOI: 10.2478/s13380-013-0104-7 • Translational Neuroscience • 4(1) • 2013 • 20-33

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Translational Neuroscience

USING TRANSCRANIAL ELECTRICAL STIMULATION TO ENHANCE COGNITIVE FUNCTIONS IN THE TYPICAL AND ATYPICAL BRAIN

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Abstract

Transcranial electrical stimulation (TES) includes methods such as transcranial direct current stimulation, transcranial random noise stimulation, and transcranial alternating current stimulation. These methods provide novel ways of enhancing human cognitive abilities for restorative purposes, or for general cognitive enhancement, by modulating neuronal activity. I discuss here the basic principles behind these methods and provide some illustrations of their efficacy in cognitive enhancement in those with typical and atypical brain function. Next, I outline some future directions for research that are have been largely neglected, such as the issue of individual differences, cognitive side effects, the efficacy of TES for use with healthy elderly populations, children with atypical development, and sports. The results observed thus far with TES as well as its future possibilities have significant implications for both basic and translational neuroscience.

Keywords

• Cognitive enhancement • Brain stimulation • TDCS • TRNS • TACS • Development • Neuroethics • Aging

Received 03 December 2012
accepted 13 January 2013

The first associations from the conjunction of "electricity" and "brain stimulation" are probably negative for most people. Indeed, most of the public, are aware of electroconvulsive therapy (ECT), often referred to as "electroshock", and its deleterious effects on cognition (e.g., amnesia) [1]. However, in the new millennium a burst of studies using transcranial electric stimulation (TES) have demonstrated that the delivery of a low current of electricity to well-defined brain regions can positively affect human mental health and well-being in areas such as pain [2], migraines [3] and psychiatric illnesses [4]. The aim of the current paper is to introduce TES methods within the framework of cognitive enhancement, a topic with important implications for translational neuroscience. I further discuss recent advancements, as well as the application of TES in different domains and in different populations, and I end by raising some ideas for future directions that are likely to have a high potential for future use.

The most widely-known method of non-invasive brain stimulation is transcranial magnetic stimulation (TMS). In TMS a magnetic coil is placed above the scalp and delivers magnetic pulses in order to induce action potentials in brain region beneath the coil as well as connected brain regions [5-9]. Although TMS has been shown to be a powerful tool to modulate human performance, mostly by causing 'virtual' impairment [10], I focus here on TES for several reasons. Despite the utility of TMS, relative to TMS, TES is more portable, painless, inexpensive, safer, and potentially has greater long-term efficacy. In addition, TES allows much better control for placebo treatment (sham stimulation). Namely, in contrast to TMS, in most of the cases subjects cannot differentiate between sham stimulation and real TES [11]. This is a fundamental issue in experiments that use single- or double-blind design.

The recent results obtained from TES experiments offer exciting possibilities for the enhancement and treatment of normal or impaired abilities, respectively [12-14]. These characteristics increase the likelihood of future use of TES with different populations, outside of the clinic and laboratory, in the home, office, and in educational institutes.

Meet the TES family

In contrast to some misconceptions, some of which are encouraged by the popular media (http://www.guardian.co.uk/science/2012/jun/03/electrical-brain-stimulation-treatments), it is not a 'shocking' family. In TES, weak electrical currents, usually in the order of 1-2 mA, are applied to the head via electrodes. The electrodes, most frequently at the size of 25-35cm^2, are placed on the scalp above the area that the experimenter is interested in affecting. When the current is applied constantly over a short duration (~20 min) it passes painlessly through the scalp and skull and alters spontaneous neural activity [15]. In what follows I will describe three different forms of stimulation that differ according to the pattern of the current: transcranial direction current stimulation (TDCS), transcranial random noise stimulation (TRNS), and transcranial alternating current stimulation (TACS).

Transcranial direction current stimulation (TDCS)

TDCS, the most well-known and most frequently used type of TES, involves the application of a constant current. Studies on animals and humans have found that the induced changes in tissue excitability vary with current polarity. Anodal stimulation occurs

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where the current exits the electrode and enters the brain, whereas cathodal stimulation occurs where the current exits the brain and re-enters the electrode. Anodal stimulation pushes neural resting membrane potentials closer to the activation threshold and therefore increases tissue excitability [16-18]. The reverse polarity, cathodal stimulation, inhibits cell firing and decreases excitability [16-18]. Most of the studies so far found that anodal stimulation improved human performance, while cathodal stimulation impaired human performance [14,19]. However, some exceptions to that, in which no effect for cathodal stimulation or the opposite pattern (i.e., enhancement rather than impairment), were reported [20-22]. Jacobson et al. [14] have attributed these inconsistencies to several possible mechanisms. The first suggests that the effect of brain stimulation depends on the initial neuronal activation state (state-dependency). In this case, if the area is active in a given task, and TDCS is applied to this region, it will have a differential effect on active neurons that are involved in the given cognitive function vs. neurons that are not involved. In such case anodal stimulation might lead to cognitive enhancement, probably by recruiting additional neurons that by default are not involved in the given cognitive function. In contrast, cathodal stimulation will not be effective as the neurons are already activated in the give cognitive task. The second explanation is the presence of bilateral interactions that support contralateral compensation. For example, in the case of language, cathodal stimulation to Broca's area will not lead to performance impairment, as the contralateral brain region will compensate for the reduction in the stimulated brain region's excitability. However, these explanations are incomplete at the moment, as it seems that the lack of a cathodal effect is presented mainly in some domains (e.g., language), but not other domains that are also subserved by bilateral brain regions (e.g., executive functions) [14]. The third explanation, which has been originally suggested by Antal et al [20], is that cathodal stimulation might act as a source to reduce neuronal noise. Again, it is currently puzzling why such effect would be observed in one task, but not others, and why this is the case only with cathodal but not anodal stimulation [but see ref 21]. Notably, other possible explanations exist, such as variability of strategies that the subject is adapting, and task difficulties (e.g., anodal stimulation is likely to change the performance of a difficult task, while the effect of cathodal stimulation might be less apparent due to a floor effect).

These changes induced by TDCS outlast the stimulation period by ~1 hour after one stimulation session [23]. The long-lasting effects of TDCS are protein synthesis-dependent and are accompanied by several mechanisms including the modifications of intracellular cAMP and calcium levels [24], brain-derived neurotrophic factor [25], and activation of adenosine A1 receptors [26] and therefore share some features with long-term potentiation and long-term depression [27]. Experiments in humans have found that following TDCS there are changes in the local concentration of neurotransmitters GABA and glutamate [28-30], important synaptic mechanisms implementing learning and memory [27,29,31], as well as brain activation as assessed by functional magnetic resonance imaging [e.g., 29,32-34], and electroencephalography [e.g., 35]. While studies have found that the effect of TDCS is locally [32], others have suggested that it affects more distributed networks, rather than only the stimulated brain region [34]. While, most of the TES research has been done using TDCS, it is unclear at the moment what parameters will provide the most optimal combination of results. Factors such as electrode size and type, scalp placement, current intensity, optimal stimulation time, and subject's anatomy have been investigated to some degree [13,36-38], but a large scale, systematic study is required to delineate the role played by these parameters, the interactions between them, and optimize current protocols.

Transcranial random noise stimulation (TRNS)

TRNS is a young form of TES, first employed experimentally in 2008 [39], which involves the application of alternating currents at different frequencies to the scalp. The technique is preferred over TDCS for its higher cutaneous perception threshold [40], making it easier to maintain experimental blinds, and for its oscillatory rather than direct current, which ensures application is polarity (i.e. anodal and cathodal)-independent [41]. TRNS typically involves the generation of 'samples' at a rate of several hundred times per second. These samples are randomly assigned current amplitudes, which are normally distributed around a direct-current component of 0 (i.e., normally distributed with a mean of 0mA). The random fluctuation of these sample currents between positive and negative amplitudes generates the electrical 'noise' that cortical regions of interest are exposed to.

Whereas the mechanisms of TRNS action are less known than TDCS, this technique has been shown enhance cortical excitability. Terney and colleagues increased corticoexcitability by 20-50% while stimulating the primary motor cortex (M1) with TRNS for 10 minutes, and observed an associated improvement in the acquisition and early consolidation of implicit motor learning as tested with a variation on the serial-reaction time task [39]. The group expanded on these findings in an attempt to define a duration threshold for the production of corticoexcitatory effects. They showed that TRNS stimulation lasting just 5 minutes was capable of significantly increasing M1 corticoexcitability [42]. Further work has extended the findings with TRNS to other domains including perceptual learning [43], and arithmetic learning [44]. The effect of TRNS has been suggested to be facilitatory at both electrodes. In addition, it has been shown that compared to anodal TDCS, high-frequency TRNS (100 to 640 Hz) yields even more powerful results [43].

Transcranial alternating current stimulation (TACS)

While in TRNS alternating currents at random frequencies are applied to the scalp, TACS utilizes alternating current in a given frequency range (e.g., alpha (8-14 Hz), beta (14-22 Hz) [45,46]. The most used form of TACS is to affect intrinsic cortical oscillations by applying external electrical frequencies using sinusoidal waves (the intensity constantly varies as a

function of time). For example, in the visual cortex, alpha activity is dominant during eyes-closed or in dark resting conditions. In contrast, higher ranges, such as beta, are dominant in the light. When TACS in the alpha range has been applied to the occipital cortex during dark conditions, it led to the experience of phosphenes, the phenomenology of seeing light without light actually entering the eye. Similar effects have been observed when TACS in the beta range was applied in light conditions [45].

However, it should be noted that other forms of TACS are also possible such as using pulses of unidirectional current in rectangular waves. In such cases, the intensity will be increased rapidly to the desired amplitude, will be held at the peak without any change (as in TDCS), and will drop rapidly to zero [46].

As in TRNS, the underlying mechanisms for TACS are unclear at the moment. However, the application of an alternating current at a certain frequency band to affect intrinsic cortical oscillations is promising, given the range of perceptual [45,47], motor [48], and cognitive phenomena (e.g., learning and memory [49], feature binding [50]) that might be attributed to changes in brain oscillatory activity [51]. However, it is unclear at the moment whether the application of TACS in these domains will enhance cognitive performance or will impair cognitive performance. Moreover, in contrast to the high cutaneous perception threshold for TRNS [40], TACS have a lower cutaneous perception threshold that might lead to a distinction between real and sham stimulation. However, applying different ranges of frequencies as a control to stimulation in a more optimal frequency band can allow a further control in this case [e.g., 45].

Cognitive enhancement in healthy subjects and neurological patients

There are several ways to enhance cognitive abilities, whether for restorative purposes or taking individuals 'beyond the norm', with pharmacological interventions, such as Methylphenidate (Ritalin), Atomoxetine (Strattera), and Modafinil (Provigil) [52], being the most frequently used. However, these drugs lead to diffuse effects at the brain level and their effect is usually for a short-term period. This in turn might increase user-dependency and addiction [52,53]. In this respect TES has important advantages as it seems to maximally affect the brain region beneath the electrode [54], and it has been shown to have effects that can last from up to a few months or a year [22,55,56]. I will now discuss the effects of TES on human cognition with a focus on the populations that have been studied most extensively: healthy adults (cf Table 1), and neurological patients (e.g., stroke patients, Alzheimer patients, cf Table 2). It is beyond the scope of this paper a documentation of all the studies that have yielded cognitive improvement. Rather, I will provide examples for studies that have reported positive results, in different cognitive domains, to demonstrate the applicability of TES to different aspects of human behaviour and cognition.

The effect of TES can be broadly divided into two categories: 1) offline TES, when stimulation has been applied before or after task performance; 2) online TES, in which stimulation has been applied concurrently during task performance. Stimulation and task performance may be completed in a single session or over multiple sessions. Results so far have indicated that the timing of stimulation in respect to task performance may have important effects [57], which might depend on the targeted behaviour. For example, whereas online TES seems to yield the most robust results for learning [13,57], offline TES seems to yield a more powerful results when applied in studies that examined the motor system [for a review see 58].

To assess the improvement induced by TES, in most cases, performance is compared to performance under sham stimulation. Sham stimulation consists of the stimulation of the same regions as in TES, but for a briefer period, such as 15-30 seconds. This stimulation does not alter neuronal excitability [25], but leads to similar sensations over the scalp following habituation of this 'tingling' sensation [11,40]. Thus, it is for the most part indistinguishable from real stimulation.

Whereas the early use of TES focused on vision- or motor-related effects, in recent years studies from different labs have shown the potential of TES to improve different human abilities including working memory, attention, language, mathematics, and decision-making (see Table 1 and Figure 1). A recent meta-analysis [14], noted that in cognitive studies in the domains of attention/perception, language, memory, and executive functions, the mean effect size for anodal stimulation was 0.49, which indicates a medium-to-large effect size.

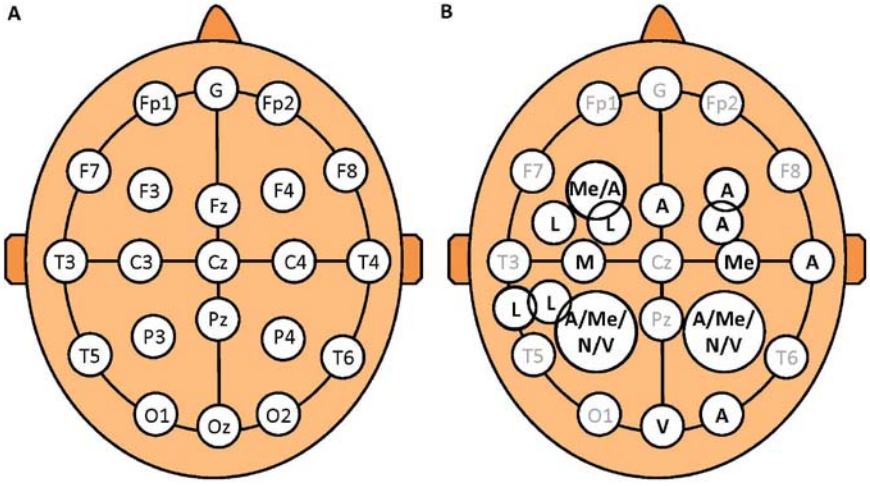

Figure 1. A) Top-view of the international 10-20 EEG reference system. B) Depiction of the findings from Table 1 according to the 10-20 international EEG reference system. Some of the findings did not fall in the exact location and were estimated based on the description in these studies. Some of the circles have been inflated in order to emphasize the abundance of findings in the respective location. Abbreviation: A=Attention; L=Language; M=Motor; Me=Memory; N=Numerical; V=Vision.

Table 1. TES studies on cognitive functions involving normal populations. Rt. = right; lt. = left; RT = reaction time; ACC = accuracy; ATDCS = anodal transcranial direct current stimulation; CTDCS = cathodal transcranial direct current stimulation; (hf-/lf) TRNS = (high-frequency/low-frequency) transcranial random noise stimulation; RALC = rt.-anodal, lt.-cathodal; RCLA = rt.-cathodal, lt.-anodal; WM = working memory; SMA = supplemental motor area; M1 = primary motor cortex; STG= superior temporal gyrus; IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PC = parietal cortex; PPC = posterior parietal cortex; IPL = inferior parietal lobe, SPL = superior parietal lobe; WS = within-subject design; BS = betweensubject design; N/A = detailed information not available.

Authors	N	Mean age (in years)	Sex	Cognitive function	TES	mA	Electrode size	Stimulation sites	Stimulation (min)	Training	Results
Numerical abilities											
Cohen Kadosh et al. [56]	15	range 20-22	N/A	Numerical abilities	RALC, RCLA, sham	1	3x3cm	Lt. and rt. PC (P3, P4)	20	6 consec. days	RALC improved numerical abilities in both tasks RCLA decreased performance Sham in between Stable at 6 month follow-up
Vision											
Fertonani et al. [43]	84	21.7 ± 2.5, 19-30	42f, 42m	Orientation discrimination	Hf/lf-TRNS; ATDCS CTDCS, sham	1.5	16cm^2	Primary visual cortex (V1, 3.5cm above the inion), Cz (additional control site for hf-TRNS)	22		Hf-TRNS to V1 enhanced learning rate compared to ATDCS
Bolognini et al. [104]	20	24, range 20-26	16f, 4m	Multi-sensory visual field exploration	ATDCS, sham	2	7X5cm	Lt. PPS (P3), rt. PPS (P4)	30		Rt. ATDCS improved visual exploration
Terhune et al. [21]	12	21±2	10f,2m	Synaesthetic priming task	ATDCS, CTDCS, sham	1	5X5cm	Stimulation electrode-2 cm above the inion. Reference electrode over the supraorbital area	30		ATDCS decreased synaesthetic experience, CTDCS increased synaesthetic experience
Kanai et al. [45]	8		4m, 4f	Phosphenes detection	TACS	.25-1 at 4-40 Hz	3x4cm (9x6 cm for the reference electrode)	Stimulation electrode-4 cm above the inion. Reference electrode over the vertex	10		In Light: perception of continuously flickering light was most effective at beta frequency range. In dark: alpha frequency range esd the most effective stimulation
Motor											
Nitsche & Paulus [18]	10-19	24.9±3.7-29.9±12.3		Changing in motor evoked-potential	ATDCS, CTDCS	0.2-1	35cm^2	Left M1.-contralateral forehead	1-5		ATDCS increased MEP CTDCS decreased MEP
Reis et al. [55]	36	28.3±1.3-30.8±3	18f, 18m	Sequential visual isometric pinch	ATDCS, CTDCS, sham	1	25cm^2	Left M1-contralateral supraorbital area	20	5 sessions	ATDCS improved task skill acquisition that lasted for 3 months.
Feurra et al. [105]	15	33.3±8.8	8f, 7m	Changing in motor evoked-potential	TACS	1mA at 5 Hz, 10 Hz, 20 Hz, and 40 Hz	7X5cm	Left M1-Pz-right parietal (P4)	1.5		TACS to the M1 at 20Hz (β range) increased MEP
Stagg et al. [29]	12	21-31	6f, 6m	Explicit sequence learning	ATDCS	1	7X5cm	Left M1-contralateral supraorbital area	10		Magnitude of M1 GABA decrease induced by ATDCS correlated positively with both the degree of motor learning and the degree of fMRI signal change within the left M1 during learning.

continued Table 1. TES studies on cognitive functions involving normal populations. Rt. = right; lt. = left; RT = reaction time; ACC = accuracy; ATDCS = anodal transcranial direct current stimulation; CTDCS = cathodal transcranial direct current stimulation; (hf-/lf) TRNS = (high-frequency/low-frequency) transcranial random noise stimulation; RALC = rt.-anodal, lt.-cathodal; RCLA = rt.-cathodal, lt.-anodal; WM = working memory; SMA = supplemental motor area; M1 = primary motor cortex; STG= superior temporal gyrus; IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PC = parietal cortex; PPC = posterior parietal cortex; IPL = inferior parietal lobe, SPL = superior parietal lobe; WS = within-subject design; BS = betweensubject design; N/A = detailed information not available.

Authors	N	Mean age (in years)	Sex	Cognitive function	TES	mA	Electrode size	Stimulation sites	Stimulation (min)	Training	Results
Memory											
Gladwin et al. [69]	14	22 ± 3		Selective attention in WM	ATDCS, sham (WS)	1	7X5cm	Anode lt. DLPFC, cathode rt. orbit	10		ATDCS improved RT in the presence of incorrect distracters
Teo et al. [70]	12	27.23, 2255 ± 9.18	7f, 5m	WM	ATDCS (1mA), ATDCS (2mA), sham	1, 2	35cm^2	Lt. DLPFC (F3)	20	1art	No improvements in ACC but interaction between current strength and RT
Sandrini et al. [71]	27	25 ± 2, 20-30	4f, 5m (per group)	WM	Lt.-anodal-rt.-cathodal, sham (BS)	1.5	7X5cm	PPC (P3 and P4)	13		Interaction stim. condition and task: LARC-TDCS abolished reductions in RT measured in 1-back task; LCRA-TDCS abolished reductions in RT on 2-back task, compared to RCLA-TDCS and sham
Mulquiney et al. [106]	10	29.4 ± 5.8	6f, 4m	WM	ATDCS, hf-TRNS, sham (WS)	1	7X5cm	Lt. DLPFC (F3)	10		ATDCS decreased RT in the 2-back task
Ohn et al. [107]	15	26.5 ± 3.5	10f, 5m	WM	ATDCS, sham (WS)	1	5X5cm	Lt. DlPFC (F3), cathode over contralateral rt. supraorbital area	20		ATDCS enhanced ACC, effect even larger after 30 min.; maintained for at least another 30 minutes
Attention											
Hsu et al. [73]	14	Pre-SMA group: 22.1, range 20-26 M1: 21.79, 18-27	6f, 8m; 6f, 8m (control)	Inhibitory control (addressing ADHD)	ATDCS, CTDCS	1.5	4X4cm	Pre-SMA, superior middle prefrontal (Fz) vs. M1 vs. no-TDCS	10	N/A	ATDCS to Fz improved inhibitory control CTDCS showed a tendency towards reducing inhibitory control
Jacobson et al. [108]	24	26.7 ± 8.7, *control*: 24.2 ± 0.9	7f, 5m, *control:* 7f, 5m	Recognition memory	ATDCS, CTDCS (WS)	1	5X5cm	Rt.-IPL-cathode- lt.-IPS/SPL-anode (P3 + P6)+, rt.-IPL-anode+lt.-IPS/SPL-cathode (P6)	10	N/A	Lt. ATDCS IPS/SPL-rt. CTDCS IPL enhanced recognition memory
Ditye et al. [109]	22	ATDCS 23.58 ± 4.16	ATDCS 7f, 3m; no stimulation 7f, 5m	Behavioural inhibition	ATDCS, no stimulation (BS)	1.5	7X5cm	Rt. IFG (anode between T4-Fz and F8-Cz), cathode lt. orbitofrontal cortex (above lt. eyebrow)	15		ATDCS improved response inhibition
Weiss & Lavidor [110]	30	26.5 ± 5.9, 18-48	20f, 10m	Attention	ATDCS, CTDCS, sham (BS)	1.5	Active 4X4cm, passive 7X5cm	Rt. PPC (P4), lt. supraorbital forehead	15		CTDCS improved flanker processing compared to A-TDCS and sham

continued Table 1. TES studies on cognitive functions involving normal populations. Rt. = right; lt. = left; RT = reaction time; ACC = accuracy; ATDCS = anodal transcranial direct current stimulation; CTDCS = cathodal transcranial direct current stimulation; (hf-/lf) TRNS = (high-frequency/low-frequency) transcranial random noise stimulation; RALC = rt.-anodal, lt.-cathodal; RCLA = rt.-cathodal, lt.-anodal; WM = working memory; SMA = supplemental motor area; M1 = primary motor cortex; STG= superior temporal gyrus; IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PC = parietal cortex; PPC = posterior parietal cortex; IPL = inferior parietal lobe, SPL = superior parietal lobe; WS = within-subject design; BS = betweensubject design; N/A = detailed information not available.

Authors	N	Mean age (in years)	Sex	Cognitive function	TES	mA	Electrode size	Stimulation sites	Stimulation (min)	Training	Results
Dockery et al. [22]	24	24 ± 3.16, 19-32	19f, 5m	Executive planning	ATDCS, CTDCS, sham (WS)	1	35cm^2	Lt. DLPFC (F3), rt. orbit	15		CTDCS improved planning during acquisition and consolidation if preceded by ATDCS ATDCS improved planning in later sessions if preceded by CTDCS persistent performance at 6 and 12 months follow-up (retested under sham)
Bolognini et al. [104]	48	*Exp. 1*: 24 ± 6; *exp. 2*: 22 ± 5; *exp.3*: 25 ± 4	*Exp. 1*; 10f, 6m; *exp. 2*: 9f, 7m; *exp.3*: 15f, 1m	Audio- and visual spatial orienting	*Exp. 1*: ATDCS, *exp. 2*: sham; *exp. 3*: ATDCS to control region	2	35cm^2	A-TDCS to rt. PPC (P4); sham rt. PPC (P4); A-TDCS to rt. V1 (O2); reference to contralateral deltoid muscle	15		ATDCS to rt. PPC improved orienting to both modality-specific and crossmodal task stimuli, particularly the probabilistic audiovisual RSE
Language											
Turkeltaub et al. [61]	23	26.7, 20-50	15f, 10m	Reading efficiency	ATDCS, sham	1.5	5X5cm	Lt. posterior temporal cortex (pTC) (between T7 -TP7); cathode rt. pTC (T8 -TP8)	20		ATDCS improved word reading efficiency in below-average readers
Flöel et al. [60]	19	25.6 ± 2.7, 22-32	9f, 10m	Associative language learning	ATDCS, CTDCS, sham (WS)	1	7X5cm	Lt. posterior peri-sylvian area (Wernicke's area, Cp5), reference on contralateral supraorbital region	20		ATDCS increased ACC and associative learning speed
Holland et al. [32]	10	69, range 62-74	7f, 3m	Speech; naming	ATDCS, sham (WS)	2	7X5cm	Lt. IFG (Broca's area, FC5)	20		ATDCS increased naming speed ATDCS decreased BOLD signal in Broca's area
Cattaneo et al. [72]	10	23.6 ± 3.2		Semantic and phonemic fluency	ATDCS, sham (WS)	2	7X5cm	Anode Broca's area (crossing point between T3-Fz and F7-Cz)	20		ATDCS improved word production in both semantic and phonemic tasks compared to sham
Sparing et al. [111]	15	26.9 ± 3.7	5f, 10m	Picture naming	ATDCS to CP5, CTDCS to CP5; *control*: ATDCS to CP6, sham to CP5		7X5cm	Wernicke's area (CP5), rt. posterior perisylvian region (PPR) (CP6), reference Cz	7		ATDCS over Wernicke's area enhanced picture-naming latency
De Vries et al. [112]	44 + 10 controls	22.6 ± 2.1; *control*: 23.7 ± 2.4	19f, 25m; *control*: 5f, 5m	Syntactic violation detection and rule-based knowledge	ATDCS, sham, *control:* ATDCS over Cz (BS)	1	7X5cm, ref. 10X10cm	Broca's area, ref. rt. Supraorbital region	20		ATDCS to Broca's area improved the detection of syntactic violations

Table 2. TES studies on cognitive functions involving clinical populations. Rt. = rt.; lt. = lt.; RT = reaction time; ACC = accuracy; ATDCS = anodal transcranial direct current stimulation; CTDCS = cathodal transcranial direct current stimulation; (hf-/lf-) TRNS = (high-frequency/low-frequency) transcranial random noise stimulation; RALC = rt.-anodal, lt.-cathodal; RCLA = rt.-cathodal, lt.-anodal; WM = working memory; SMA = supplemental motor area; M1 = primary motor cortex; STG= superior temporal gyrus; IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PC = parietal cortex; PPC = posterior parietal cortex; IPL = inferior parietal lobe, SPL = superior parietal lobe; WS = within-subject design; BS = betweensubject design; N/A = detailed information not available.

Authors	Population	N	Mean age (in years)	Sex	Cognitive function	TES	mA	Electrode size	Stimulation sites	Stimulation (min)	Training	Results
Language												
You et al. [98]	Sub-acute stroke patients with global aphasia	21	67, 48-82	9f, 12m	Speech	ATDCS, CTDCS, sham	2	7X5cm	ATDCS: lt. STG (Wernicke's area, CP5), CTDCS: rt. STG (CP6), sham group: CP5	30	5 times a week for 2 weeks	ATDCS improved: aphasia quotients spontaneous speech CTDCS improved: auditory verbal comprehension
Marangolo et al. [99]	Stroke patients with aphasia	3	N/A	1f, 2m	Speech	ATDCS, sham	1	7X5cm	Lt. IFG (Broca's area)	20	5 consec. days: repetition task	ATDCS improved speech ACC
Fiori et al. [100]	Healthy subjects, stroke patients with aphasia	10 healthy, 3 stroke	Healthy: 55 ± 7.9, 45-70	Healthy: 3f, 7m; patients: 3m	Word retrieval	ATDCS sham (WS)	1	7X5cm	Healthy subjects: TDCS/sham over Wernicke's area (CP5), or TDCS to rt. occipito-parietal area (O2); patients: 5 consec. days ATDCS/sham	20	3 days of training with 6 days in between each/ aphasic patients: 5 consec. days for both ATDCS and sham	ATDCS improved naming ACC and RTs
Fridriksson et al. [64]	Chronic stroke patients with aphasia	8	68.13 ± 10.40, 53-79	N/A	Naming	ATDCS, sham (WS)	1	N/A	Lt. posterior cortex, reference cathode on rt. forehead	20	10 sessions of anomia training (5 consec. days per stimulation condition)	ATDCS improved RT in naming task for trained items (stable at 3 weeks follow-up 75% of patients had stable ACC and RT at 1 and 3 weeks follow-up
Vines et al. [62]	Lt. frontal stroke patients with aphasia	6	56.2, 30-81	6m	Speech fluency	ATDCS, sham (WS)	1.2	16.3cm^2, reference electrode 30cm^2	Rt. posterior IFG (2.5cm posterior to F8)	20	3 consec. days of training, 1 week apart	ATDCS improved speech fluency
Schneider & Hopp [101]	Minimally verbal children with autism	10	9.8 ± 4.4, 6-21	2f, 8m	Syntax acquisition	TDCS	2	5X5cm	Lt. DLPFC (F3), cathode rt. supraorbital region	30	Syntax and vocabulary testing	TDCS improved syntax acquisition from pre- to posttest
Memory												
Ferrucci et al. [102]	Alzheimer patients	10	75.2 ± 7.3	7f, 3m	Word recognition memory and visual attention	ATDCS, CTDCS, sham (WS)	1.5	N/A	Bilateral temporo-parietal areas (P3-T5 and P6-T4)	15	3 days of training per condition (10 days apart); conditions 71 days apart on average	ATDCS: recognition memory ACC improved CTDCS: recognition memory ACC reduced Sham: recognition memory ACC unchanged
Boggio et al. [103]	Alzheimer patients	15	79.05, ± 8.2	7f, 8m	Visual recognition memory	TDCS, sham (WS)	2	35cm^2, deltoid 64cm^2	Temporal lobe (T3, T4), reference rt. deltoid muscle	30	5 days of training per condition	ATDCS improved visual recognition performance Sham: visual recognition reduced Persistent at 4 weeks follow-up

While most of the results found quantitative differences, such as improved reaction times [21,22,29,32,55,59,70-72,104,106,109-111], or accuracy level [21,22,43,55,60,69,73,104,107,108,112], qualitative performance differences that indicate a more advanced mental age have been noted. For example, after 6 days of learning new symbols that indicate numerical information, participants who received anodal stimulation to the right parietal lobe and cathodal stimulation to the left parietal lobe, showed a pattern of performance that matched numerate adults, while those who received sham stimulation or stimulation in the opposite configuration showed a performance that mirrored those with more rudimentary numerical skills, indicating that TDCS could lead to faster mastery of the learned material [59].

As shown in Table 1, some of the studies have observed long-term effects from TES, while some have not examined the longevity of TES, which would be desired from translational neuroscience perspective. Few studies that have examined long-term effects have revealed performance that lasts 3 months [motor skill acquisition, ref 55], 6 months [numerical cognition, ref 56], and 1 year [executive planning, ref 22]. Further details regarding the different cognitive domains/task that were used, as well as the different parameters in each study and a summary of results are presented in Table 1.

In addition, different studies used different electrode sizes, durations of stimulation, and in some cases different stimulation sites to enhance similar cognitive abilities (e.g., working memory). As a result, in some fields, especially those that relate to high-level cognitive functions, as opposed to motor functions, there is no clear consensus of the optimal protocol that needs to be applied in order to enhance cognitive functions [59]. This caveat should be resolved in order for TES to be applied for cognitive enhancement outside of a laboratory setting.

Cognitive enhancement in healthy adults, has important implications for basic science, and also provides a proof of principle for the potential of TES to enhance cognitive abilities. However, to demonstrate the potential of TES as a useful tool for rehabilitation studies, researchers have combined TES and cognitive training in patients (Table 2). These studies include, but are not limited to, memorization of words [60], repeated naming of objects presented in a picture [32], or reading practice [61].

There are important open questions, such as when one would need to apply TES in order to improve the performance of neurological patients. Another question concerns the stimulation site. In some studies stimulation was applied to the contralesional brain region [e.g., 62,63], while in other studies stimulation was applied to the perilesional or lesional brain area [e.g., 64-66]. It is assumed that TES worked in these cases by: 1) reducing the activation in the intact brain structure that inhibits residual functions in the nondamaged tissue nearby the damaged brain region. This could be attributed to rivalry between both hemispheres such as in the case of visuospatial attention [66]. In such cases, cathodal TDCS during cognitive training should lead to improved performance [66]; 2) Compensation by the homologue (contralesional) brain region [63]. This can be achieved by anodal TDCS during cognitive training/rehabilitation [63]. 3) Facilitation of the perilesional brain region using anodal TDCS to improve residual output by the damaged hemisphere [e.g., 64,65]. However, it should be noted that this is not the case in all the studies and one study has found that cathodal TDCS to the damaged brain region improved subsequent performance of the impaired cognitive ability [67].

Currently, it is not clear what the best approach is, and this might depend different factors such as the impaired mental faculty, the time elapsed post stroke, which might have led to more substantial brain reorganisation, including alternation in interhemispheric relationships, and on the neurological damage. Therefore, the right approach should be decided on a patient to patient basis. For example, in some patients the neurological damage might be so substantial leaving little or no intact brain tissue in the region involved in the impaired cognitive function, therefore suggesting that stimulation of the contralesional brain region might be the best way forward [62]. However, we should note that another montage that includes bihemispheric TES, in which anodal TDCS increases excitability of ipsilesional brain regions and cathodal TDCS reduces excitability of the contralesional brain region has also been used [68], although such a montage is currently not employed frequently in the cognitive domain.

As indicated by Table 1-2, stimulation does not need to span over many days, and even short training periods (e.g., 20 min) can significantly improve cognitive performance [32,60,69-72]. However, it is unclear if the neural mechanisms behind single-session effects and multi-sessions effects are the same. In addition, the longevity of single-session and multi-session effects might differ. However, so far this has been examined neither at the behavioural nor at the neural level. Such a line of research is needed, as researchers are becoming more interested in using TES to improve training and skill acquisition in order to provide optimised scaffolding for a better and long-lasting performance afterwards, as opposed to using TES as a device to improve cognitive performance during everyday life.

Other topics that are at the moment also less clear but have important implication for the translational impact of TES are the effect of TES as a function of individual differences and the mental cost(s) posed by TES. Few studies examined the issue of individual differences, whether at the behavioural or at the genetic level, on the effect of TES [73-75], and different neuronal parameters, such as regional cortical excitability and metabolite concentrations are likely to contribute to individual differences. It is clear that a better understanding of the interaction between individual differences and TES is important to improve its efficacy.

As for mental cost(s), while so far most studies have focused their attention on possible physical (e.g., itching) and neurological (e.g., headache) side effects of TES [40,76], the possibility of cognitive side effects due to TES, as well as their persistence, have received little attention [77]. Most of the studies so far have used mainly a single task and assessed the modulation of task performance as a function of stimulation to the target brain area, sham stimulation, and in some cases control regions. The inclusion of additional tasks might be vital to unravel the potential costs that TES

might have on human cognition. Cognitive side effects might not occur for every type of TES, and this might depend on the stimulated brain region, and other parameters such as duration, intensity, and type of stimulation. However, such studies are paramount in order to assess not only the positive effects that TES clearly has on human behaviour, but also the potential side effects, and how these can be avoided by further optimisation of TES protocols. Therefore, while the issue of mental cost(s) is theoretical at this stage, I suggest that future TES studies should not only focus on the issue of cognitive enhancement as has been done thus far. Rather, researchers should devise the best stimulation parameters that will allow cognitive enhancement, without, or when unavoidable, with a tolerable, mental cost. To some degree this issue is comparable to investigations on drugs intake and the monitoring of their potential side effects. In theory, this mental cost might be due to a shift of metabolic consumption and neurochemical modulation in the brain caused by TDCS [25], which changes the respective involvement of different brain areas.

In sum, the current results indicate the exciting potential of TES for cognitive enhancement. This advancement, as any other field of research, generates new questions that will need to be addressed in order to allow a translation from the lab to the real world.

Future directions

The field of TES is moving fast. More labs are incorporating TES as part of their techniques, especially as the method is relatively inexpensive and easy to implement. In addition, biomedical companies are entering into this new emerging field. In this section, I will discuss a few directions for future research that I think are of substantive importance. These are the inclusion of healthy aging on the one end, and children with atypical development on the other end, and the application of TES in sports.

Studies on healthy elderly

Although the study of healthy elderly populations is increasing, including the application of non-invasive brain stimulation to induce plastic changes [for a review see 78], TES is currently applied in a very limited fashion. A search in Pubmed revealed only 12 studies that included the terms "TDCS" and "aging"; of these, only 4 results were experimental papers on healthy elderly samples [79-82]. Similar results are obtained when "aging" is replaced by "elderly". No relevant results were found where TDCS was replaced by TRNS or TACS. While this does not indicate that these references are the only available studies in the field (see for example ref 32), it illustrates a great void in the current literature. Aside from furthering our knowledge of the aging brain in comparison to younger groups [80], there are also translational implications for this research. The healthy elderly are a group that can benefit from TES, as indicated by the limited research findings, and this benefit may be even more substantial the older the person is [82]. If it will appear that TES can improve skill acquisition in elderly, as it has been shown in young adults [13,44], it will provide a route to improve life quality for the increasing number of elderly who due to increasing life expectancy have more time for leisure activity, and need to develop new skills in their generation (e.g., computer use).

Studies on children

The lack of studies on children with atypical development is even more substantial. However, it has a better rationale than not studying the elderly. Specifically, at the moment it is unclear what effects TES might have on the developing brain. On the one hand, it might improve atypical cognitive abilities, such as dyslexia, dyscalculia, dysgraphia, and attentional deficits [83]. On the other hand, it might change the balance or coordination between brain regions and elicit impairments in another cognitive domain, or no improvement in the pre-existing impaired ability.

Some issues pertaining to the application of TES to minors are relatively familiar from other contexts [84], such as the need to obtain valid consent either from a competent adolescent or from the parent/guardian. However, a crucial issue is the possible effect on brain development and the degree to which enhancing some capacities may lead to a deterioration of other capacities. To date, most research on cognitive enhancement using TES has focused on improving average or impaired abilities. However, such enhancement may come at a cost in some cases [85], and this possibility has not received much attention in TES studies [86]. Highly-developed capacities in certain cognitive domains in some individuals are accompanied by reduced functioning in others [87]. However, as discussed earlier the potential cognitive side effects of TES, are at the moment unclear.

If TES does enhance some abilities at a cost to others, then one will need to weigh its costs and benefits. This could mean that TES might in the future become mandatory as a treatment for developmental disorders. Obviously, this raises neuroethical issues that will have to be resolved in collaboration with ethicists [77].

One of the applications in this respect is in the field of education, such as difficulties with literacy and numeracy. Previous studies on adults (Tables 1-2) have shown the potential of TES to improve some components that relate to these cognitive abilities. However, due to the nature of these cognitive skills it is not possible to assess the safety of TES in these domains via standard pre-clinical experimental routes (e.g., animal models). As the mature brain and the developing brain differ in anatomy and function [88-90], data on the effect of TES on the adult brain may not reveal possible side effects of stimulating a developing brain, and might provide little information on efficacy. Further, the atypically developing brain may respond differently from the typically developing brain. Thus, it seems impossible to gather adequate data on efficacy and side effects without testing the specific target population. In addition, whereas TES seems to be safe in adults when proper protocols are followed, it remains unclear whether adverse effects, which do not seem to appear in adults, might occur in younger participants.

It could be argued that in light of this lack of understanding, scientists should not proceed to examine the potential use of TES in children. The issues that I raise in this section are indeed difficult to address. However, I believe that failing to address these issues would deprive a large population of children of potentially

improved psychological abilities, which will have adverse individual and social implications [91].

Sports

As a potential enhancement in healthy subjects, TES raises issues familiar to ethicists from discussions of pharmacological interventions [77]. Without delving into a long discussion on the neuroethical implications of using TES for cognitive and physical enhancement [52,77,92], TES could possibly be used to improve performance in sports and thus raises ethical questions akin to those surrounding doping in sport [93]. 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. For example, in professional sport, blood and urine samples are routinely used to establish whether performance enhancers have been used. A previous study has indicated that TES can increase muscle endurance and decrease muscle fatigue in normal subjects [94]. The potential usage of TES by professional athletes who use TES to decrease muscle fatigue might have an important advantage especially when there is increased load on their muscles in sporting activities (e.g., Tour de France, Football World Cup). Similarly, TES has been shown to improve motion perception [20], 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 [95,96], might exhibit improved performance and make fewer mistakes.

Another aspect is the application of TES to improve mental preparation before the game. Currently, this is moderated mostly by sport psychologists. However, some have suggested that TES might be used to generate that feeling of effortless concentration that characterises outstanding performance [97].

Although this section is at the moment rather speculative (just like the suggestion that we could use TES to enhance cognitive functions was in the previous millennia), and we cannot yet be confident that the findings cited above have ecological validity, they provide a potential field of research and possible use that basic and translational scientists as well as policy makers should be aware of and which I anticipate will receive considerable attention in the future.

Conclusions

TES has been shown to improve a plethora of cognitive abilities in both healthy adults and adults with neurological impairments. However, compared to other non-invasive stimulation methods, such as TMS, it is less studied, less known to the scientists (albeit it has recently received increased attention from the media), and its operating mechanisms are less clear. TES has important characteristics that make it attractive for the purpose of cognitive enhancement, and due to parameters such as portability, comfort, low financial burden, safety, long-term efficacy, and the relative ease of use, it has strong potential to be used as part of a therapeutic intervention or for taking individuals 'beyond the norm'. Although research so far is promising, future studies should expand the current research vertically (optimising parameters, and TES-cognitive training combination, neural mechanisms for TES), and horizontally (individual differences, cognitive side effects, and TES effects on the healthy elderly and atypically developing children). Successful research in these domains will have positive impact on translational neuroscience and, in turn, on public well-being.

Acknowledgements and conflict of interest

I would like to thank Devin B. Terhune for valuable comments, and for Beatrix Krause for helpful with the tables. RCK is supported by the Wellcome Trust (WT88378), and filed a patent for an apparatus for improving and/or maintaining numerical ability.

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