Accepted Manuscript

Title: Enhancing Cognition using Transcranial Electrical Stimulation

Author: Emiliano Santarnecchi Anna-Katharine Brem Erica Levenbaum Todd Thompson Roi Cohen Kadosh Alvaro Pascual-Leone

PII:	S2352-1546(15)00081-9
DOI:	http://dx.doi.org/doi:10.1016/j.cobeha.2015.06.003
Reference:	COBEHA 91

To appear in:

Received date:	8-4-2015
Revised date:	16-6-2015
Accepted date:	17-6-2015

Please cite this article as: E. Santarnecchi, A.-K. Brem, E. Levenbaum, T. Thompson, R.C. Kadosh, A. Pascual-Leone, Enhancing Cognition using Transcranial Electrical Stimulation, *COBEHA* (2015), http://dx.doi.org/10.1016/j.cobeha.2015.06.003

Highlights:

- tES allows to safely modulate brain activity by the means of transcranial electric fields
- tES provides greater anatomical specificity respect to other cognitive enhancer like drugs
- tES shows state and trait-dependency effects
- Regulation about tES application outside laboratory environment are needed

Enhancing Cognition using Transcranial Electrical Stimulation

Emiliano Santarnecchi[1,2,3], Anna-Katharine Brem[1,4], Erica Levenbaum[1], Todd Thompson[1], Roi Cohen Kadosh[4], Alvaro Pascual-Leone[1]

[1]*Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.*
[2] *Brain Investigation and Neuromodulation Laboratory, Department of Medicine, Surgery and Neuroscience, Siena Medical School, Siena, Italy.*
[3] *Siena Robotics and Systems Laboratory, Department of Engineering and Mathematics, University of Siena, Italy.*
[4]*Department of Experimental Psychology, Oxford University, Oxford, United Kingdom.*

Corresponding author: Alvaro Pascual-Leone, MD, PhD
Corresponding author's address: Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.

Corresponding author's phone: +1 617 667 0203
Corresponding author's e-mail address: apleone@bidmc.harvard.edu

Acknowledgement:

This research entitled 'Flexible, Adaptive, and Synergistic Training (FAST)' is supported by the Intelligence Advanced Research Projects Activity (IARPA) via contract#: 2014-13121700007 issued to Honeywell International in the context of the Strengthening Human Adaptive Reasoning and Problem-Solving (SHARP) program. Dr. Pascual-Leone is further supported by the Berenson-Allen Foundation, the Sidney R. Baer Jr. Foundation, grants from the National Institutes of Health (R01HD069776, R01NS073601, R21 MH099196, R21 NS082870, R21 NS085491, R21 HD07616), and Harvard Catalyst | The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health, the Sidney R. Baer Jr. Foundation, the United States Government, the Office of the Director of National Intelligence, or the Intelligence Advanced Research Projects Activity.

Summary

Noninvasive brain stimulation is being widely investigated to understand and modulate human brain function, and offers novel therapeutic approaches to neurologic and psychiatric disorders. Here, we focus on the growing interest in the potential of noninvasive brain stimulation, particularly transcranial Electrical Stimulation (tES), to enhance cognitive abilities in healthy individuals through the modulation of neuronal membrane potentials, specific brain oscillations or the delivery of electrical "noise" to the system. We also emphasize the potential of tailoring tES parameters to individual trait and state characteristics for a personalized-medicine approach. Finally, we address the increasing use of tES by lay people, the ethical issues this raises, and consequently call for appropriate regulation.

The expanding field of neuroenhancement using noninvasive brain stimulation

Is it possible to enhance human cognition and, if so, how? The answer to this question remains unclear, and yet, cognitive enhancement is a rapidly growing field of modern neuroscience, used both for rehabilitative and therapeutic purposes, as well as in attempts to enhance the cognition of healthy young adults. Potential interventions include tailored programs, adopted from the clinical field, e.g. cognitive training, dietary regime, physical training, pharmacological agents, and, most recently, non-invasive brain stimulation (NIBS).

The efficacy of some interventions aimed at improving human cognitive functions has been disputed [2;3]. However, recent evidence demonstrates small, but significant effects for cognitive training (mainly working memory)[4]. Physical activity has also been shown to improve cognitive functions in healthy adolescents and the elderly, and to prevent cognitive decline in the latter [5-7]. Pharmacological agents are being investigated with regards to their potential to enhance cognitive functions [8;9]. Finally, attempts to use NIBS - specifically transcranial electrical stimulation (tES) - to potentiate human cognition date back to the Victorian time [1], but the last ten years have seen an exponential growth of technical progress, turning tES into a promising tools for modulation of neural activity, and thereby possibly enhancing cognitive abilities.

The mechanisms of cognitive enhancement using different approaches likely differ. Partly overlapping and not mutually exclusive neural mechanisms could account for enhancement of cognitive performance using different approaches, and their combination may thus be most effective. One might envision more efficient activation of neural structures recruited by a cognitive task resulting in improved performance on that task. Alternatively, one can postulate that a net increase in more global brain resources would contribute to more wide-spread enhanced abilities. Importantly, facilitation on one cognitive task could happen with or without concomitant costs to other cognitive abilities and functions. Behavioral training probably depends on strengthening neural networks through repeated co-activations, while exercise and pharmacological interventions may work by manipulating available levels of neurotransmitters. tES techniques enable increasing or decreasing activity in specific brain regions and neural networks, induction of paradoxical facilitation by leveraging brain network dynamics, injection of small amounts of noise to maximize signal to noise ratio via stochastic resonance, entrainment of specific oscillatory patterns, and modulation of connectivity and plasticity across brain networks.

The most investigated of tES techniques, transcranial direct current stimulation (tDCS), was re-introduced in the 1990's after having been largely abandoned in the late 1960's [1]. Although its rather non-specific activation of underlying brain areas limits its potential as a diagnostic tool, tDCS has recently been investigated for the treatment of motor, perceptual, mood, and cognitive dysfunctions in patients. Initially, tDCS research with healthy participants was mostly designed as precursor for patient studies. However, following a series of promising results, interest in tDCS to potentially enhance brain function in healthy individuals has been rapidly growing. Technical developments have led to the design and implementation of transcranial alternating stimulation (tACS) and transcranial random noise stimulation (tRNS) (see Figure 1 for a brief explanation of tES techniques), which are thought to engage different neural mechanisms than tDCS and also offer promise to enhance human abilities. It is also possible to combine tDCS with tACS (oscillatory tDCS, or osc-tDCS) adding a DC offset to the sinusoidal AC, therefore possibly exploiting the DC effect on cortical excitability and the AC synchronizing effect on rhythmic neuronal activity. This review will cover recent advances in neuroenhancement in healthy populations using tES, including a brief introduction to currently available techniques, an analysis of the most recent literature and summary of effects on various cognitive domains, a discussion of ethical issues, and finally an overview of potential future directions.

When cognitive training is not enough: new opportunities using tES

Given the assumption that brain training relies on the repeated activation of a specific neurocognitive circuit, which is sustained by well-orchestrated local and inter-regional activations, the idea of boosting such dynamics by acting on their neurophysiological substrate has materialized in the form of a pertinent body of research. Underlying neurophysiological mechanisms of learning and tES are thought to overlap, and their combination is therefore thought to lead to synergistic effects. Neurophysiological mechanisms underlying tES methods are being investigated, with evidence to date suggesting that the effects are due to changes in neural activity in targeted brain areas and networks [10;11]. The mechanism of action of tDCS is thought to be mediated by "membrane polarization", i.e. an externally induced polarization of neuronal tissue with a consequent change in neuronal firing rates/threshold [12; 13]. tACS [15] and tRNS [16] are thought to alter the brain's intrinsic oscillations through frequency-specific entrainment, plasticity, or stochastic resonance resulting in an increase or decrease of the amplitude, coherence or phase of targeted brain rhythms [14]. Osc-tDCS is presumed to simultaneously manipulate both the cortical excitability and the spontaneous brain rhythms. Preliminary studies show positive results of tES in sensorimotor [17], visual [18] and cognitive [19-22] domains, and suggest that these newer methodologies may provide a flexible approach to directly investigate the effects of neural oscillations on behavior.

Combinations of tES with other interventions, e.g. cognitive training, physical activity, or pharmacologic agents, offer the potential to maximize cognitive enhancement. This supports tES as one of the most promising approaches within the cognitive enhancement field: different from other interventions, which indirectly target specific brain activity patterns, e.g., by promoting an unspecific increase in cerebral blood flow and nutrients (e.g. diet and physical training) or neurotransmitters (e.g. drugs, which also carry undesired side effects), tES allows for a more specific stimulation of brain regions responsible for the cognitive process at hand. Finely tuned tES montages and protocols will likely allow the reproduction of patterns of co-activation within a functional network similar as during cognitive training. Furthermore, repeated strengthening of interregional coupling at rest is hypothesized to be a potential primer to increase efficacy of other cognitive enhancement approaches. Finally, even though a healthy dietary regime and physical activity are strong promoters of well-being and should be encouraged, their effects come with an higher level of commitment in terms of dedication and time. tES could allow to achieve similar cognitive effects with portable, easy to use devices which could be used by individuals unable to follow a specific program due to physical or psychological impairments (e.g. elderly or patients with disabilities). Along with practical features (e.g. ease of use, portability, safety) and considering its early stage of development, tES might represent the best tool for non-invasive cognitive enhancement in humans both alone and combined with other interventions. Despite this promising scenario, its still unproved ability to reliably target subcortical regions through both direct targeting (i.e. through specific montages resulting in current reaching its global maxima on specific structures below the cortical mantle) or indirect targeting (by leveraging on cortico-subcortical connectivity patterns), and the lack of robust knowledge about the mechanism of action and neurobiological effects, emphasize the need for caution in interpreting the current available literature as well as advocating for their widespread use. Many questions remain underexplored, including how these effects may arise, whether they might be limited or modified by one's cognitive capacities or reserves, system-inherent limitations and other state- and trait-related factors.

Recent evidence of tES enhancement effects on cognition

Most published studies investigating tES effects on cognitive functions have used tDCS, but tACS, osc-tDCS and tRNS are gaining popularity (Figure 1B). tDCS has been applied in many cognitive domains (including substantial work in working memory, short- and long-term memory as well as speech and language), with the polarity of stimulation and corresponding effects -i.e. cognitive enhancement is thought to be achieved by placing the anode or cathode over the cortical region (or network node) to be respectively increased or decreased in activity [23;24] (see Figure 2-B)- being considered a fixed feature of such kind of intervention, making its application and the definition of experimental protocols a relatively straightforward task. However, recent evidence suggests new scenarios where the interaction between polarity, localization and timing of stimulation might induce unexpected, even counterintuitive results. Interestingly, several studies have reported paradoxical effects, with behavioral improvements induced by cathodal stimulation [25;26], as well as polarity non-specific effects where both anodal and cathodal stimulation seem responsible for a worsening of performance [25;27;28], emphasizing the need for revising current theories and models of tDCS mechanisms of action. It is important to remember that tDCS should not be conceived as a unitary intervention, but rather as a tool capable of altering activity in different brain structures, by increasing or decreasing their excitability, as well as by modifying the signal to noise ratio in the stimulated region. The specific effect is heavily dependent on variables such as stimulation montage and intensity, but also on intrinsic brain features like structural connectivity and the participation of the target region(s) in specific functional network(s).

A recent quantitative meta-analysis reported a lack of significant effect of tDCS on cognitive functioning when single session interventions are examined [29]. The null result in this study can be due to poor congruence between studies, small sample sizes in each cognitive domain (mainly 2-4 studies), and different study populations. Most importantly though, tDCS cannot be treated as a unitary intervention. One should avoid thinking of 'anodal' or 'cathodal' tDCS and instead emphasize the fact that tDCS exposes the brain to a field of current with specific directionality and differential impact on distinct brain structures depending on stimulation parameters and electrode montage. Furthermore, the impact on the distinct brain structures is modulated by their state of activity, and precision in identifying differences between tDCS protocols is critical to relate targeted brain structures with observed behavioral and cognitive effects. This seems to be a more realistic and sound approach that could help explain variability in study outcomes.

A critical appeal of the potential of tACS is that it can be programmed to take into account the very precise rhythms that are crucial for normal brain function. Traditional pharmacological and other treatments, as well as tDCS and other forms of NIBS, are unable at present to address these very precise rhythms, which might be problematic because these rhythms seem to be crucial for normal cognition. However, we lack a mechanistic understanding of how the multiple, interlocking brain rhythms carry out cognitive processing in healthy individuals, and how these processes are impaired in individuals with mental illness. Furthermore, we need more insights into how to best target the stimulation so that it takes advantage of intrinsic connectivity within the brain. Thus, a number of important steps are required to assess the true potential effectiveness of tACS, including the development of computational models of brain activity, as well as brain stimulation algorithms and hardware tools that can precisely modulate these rhythms and so change cognition. Nevertheless, tACS is being applied to enhance working memory and fluid intelligence, as well as attention and motor-imagery [20;21;30;31], while tRNS has shown promising improvement effects in working memory, numerical abilities, and different learning paradigms [19;22;32]. In order to explore behavioral effects whilst promoting more in-depth knowledge of the neurophysiological underpinnings an increasing number of studies combine electrophysiological recording with the stimulation to inform the tES protocols [20;31]. Such experimental designs are likely to become critical for future investigations moving towards individualized interventions.

Due to the still sparse knowledge about underlying neurophysiological effects of tES, it is also necessary to foster the discussion raised in the last years about *state* and *trait* dependency of tES effects, a factor that likely contributes to the observed inhomogeneity in study outcomes. Various studies have highlighted the importance of monitoring individual factors such as gender, age, education, health status, brain physiology, and genetic polymorphisms, as well as keeping track of other possible "modulators" like satiation level, amount and quality of sleep, energy level, mood, and metabolism-related factors [33]. Several studies have demonstrated that the effects of a single-session of tES can vanish in response to behavioral or cognitive priming [34;35], or lead to enhancement or impairment at the behavioral and physiological level due to individual trait [36]. Therefore, current evidence about tES in cognition should be carefully evaluated and when possible future studies should take individual state and trait into consideration.

Our discussion so far has been mainly limited to studies applying a single tES session, but the number of studies applying tES in combination with cognitive and motor training and in multiple sessions on consecutive or distributed days is increasing (Figure 2). Combining neuroplasticity-based effects of training with the additive value of electrical stimulation has proven to lead to larger effects than training alone [19;22;37], also highlighting different interactions between training and stimulation protocols. Given the different mechanisms behind stimulation approaches, these kinds of studies could also indirectly help provide new knowledge about the neurophysiological underpinnings of learning processes themselves, adding even more value to the implementation of tES to study human cognition. However, the impact of repeated tES sessions on the brain is still not entirely clear, with unpredictable plasticity-based effects possible after weeks or months of stimulation. Future studies should deepen our understanding on such long-term effects as these are also important considering safety aspects, and to enable comparison of the effects of tES with those of other cognitive enhancement approaches.

Ethical and social issues

Noninvasive brain stimulation methods, particularly tES, are receiving increasing attention from the media, particularly given the findings on cognitive enhancement in healthy adults. Instructions on how to build your own tES device can be readily found on the internet and a number of companies offer inexpensive consumer devices for various applications such as to improve thinking speed, attention, and gaming performance [38]. In the wake of these developments, concerns are raised that modulating brain functions, especially over sustained periods of time, could have unforeseen and undesirable consequences [39]. A thoughtful and balanced ethical debate is critically needed, and ought to include ethicists, scientists, clinicians, regulatory agencies, industry, patient advocacy groups, and representatives of the public in general. The technology available on the consumer market and its possible use in healthy and vulnerable subjects, such as patients or children, does not appear to be sufficiently or appropriately regulated. Careful assessment of pertinent regulations differentiating between medical and enhancement uses seems needed [40-42].

Considerations of costs and benefits have to inform the ethical dialogue. Cognitive enhancement as such is only valuable if costs are taken into consideration [43]. Cost-benefit interactions may occur at different systemic levels, ranging from neuronal processes to network interactions and behavioral outcomes, lastly reaching the societal level [44]. Furthermore, the timing of benefits and costs may vary, with potentially short-term benefits being offset by longer-term risks. More studies are needed to fully assess the lifespan risk-benefit balance of tES approaches for neuroenhancement across target populations. The question of cognitive inequality can be related to biological or societal differences. At a biological level, individual traits could determine who profits from cognitive enhancement. At a societal level, inequality could originate from limited access to cutting-edge stimulation technology or patented protocols, despite the recent diffusion of do-it-yourself solutions for homemade stimulation.

Future directions

Recent advances in the field of connectomics and mathematical modeling of current flow are opening new opportunities to tailor tES interventions on the basis of structural connectivity and conductivity patterns of the individual brain, helping to explain observed effects as well as improving the targeting of specific brain areas. On the one hand, computational models can simulate the consequences of neurostimulation and serve as a hypothesis-driven tool linking models with stimulation outcomes [45]. Increasing knowledge about brain connectivity patterns will allow for more precise and multiple-target stimulation, as well as targeting subcortical regions by the means of cortico-subcortical connections, as recently demonstrated for transcranial magnetic stimulation protocols [46]. To this end, viewing the brain as an array of interacting structural and functional "networks" is crucial. Gaining information about these networks will become requisite for future tES studies, especially in the case of tACS where the information about frequency and phase of brain oscillations has been demonstrated to be crucial for the modulation of working memory performance [20]. Moreover, the possibility to simultaneously interact with multiple nodes of a network is appealing. So far, limits have been set by available technologies allowing for one or two "active" stimulation sites only. However, recent advances in the devices and the modeling of tES-induced electric fields enable multiple-site stimulation [47] and the possibility to trace complex connectivity patterns, thus orchestrating between and within-network dynamics.

Going forward, the targeted application of tES methods in combination with technologies that have informed the field about the importance of individual differences in the past could further deepen our understanding of such processes, which, in turn, would enable us to design more efficient and tailored cognitive enhancement protocols. This could be achieved by combining tES with individualized current modeling, structural and functional MRI, electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Successful integration of these techniques in addition to a detailed knowledge of genetic and metabolic factors, could not only advance our understanding of how individual brain differences arise, but inform us about how to leverage this knowledge optimally within the context of interventions aimed to enhance human cognition.

Finally, the opportunity to affect ("entrain") brain oscillations by transcranial oscillatory electrical patterns has opened a new era for perturbation-based neuroscience, allowing researchers to causally explore the interaction between brain oscillations and manifested behavior. However, technical challenges need to be addressed and overcome to enable simultaneous stimulation and monitoring of brain activity in the very same location (e.g. amplifiers saturation, presence of stimulation artifacts in the EEG signal, loss of signal of interest when applying notch filters in the case of tACS), as well as reliable gating/triggering of stimulation by ongoing measures of brain activity. Successful advancements in basic science and engineering approaches would for example allow the implementation of closed-loop systems for multifocal, spatially and temporally individualized tES interventions to improve the efficacy of controlled modulation of human cognitive processes.

In conclusion, tES has recently confirmed its role as a powerful tool for cognitive enhancement, with potential benefits for pathological conditions. Recent innovations have led to the design of new tES methods and contributed significantly to the understanding of neurophysiological effects of different tES methods on the brain. Future research will aim to improve cognitive enhancement methods by simultaneously combining a variety of techniques also giving researchers the impression that a more complex and vast scenario is on the horizon. Such complexity just represents a valuable opportunity for the development of finely tuned cognitive enhancement and therapeutic interventions, where tES features, like its portability, will play a fundamental role to bring lab results to a broader public. A future with people wearing portable devices helping them to stay awake during nightshifts or while driving a car, or improving their motor coordination during an intense track and field training session is relentlessly becoming a more and more plausible and socially accepted scenario. Therefore, more attention to the impact of individual difference on the response to tES and an open, academia-based debate about regulations for tES application should hopefully drive the field hereafter.

Figure legends

Figure 1. tES techniques. Current approaches include (A) direct current stimulation (tDCS), alternating current stimulation (tACS), and random noise stimulation (tRNS). While tDCS is thought to influence neuronal firing rates by polarizing membrane potentials in a bimodal manner, tACS has been shown to up- and down-regulate the firing rate without changing its average value, thus affecting neuronal spike timing [48]. tACS generates an alternating current at a specific frequency, with the potential to synchronize or desynchronize activity between targeted brain regions through phase-locking and coherence mechanisms. Given recent theories about neural populations communicating through time-locked oscillations [49], such capability of tACS can be exploited for tailoring individualized interventions aimed at coupling or decoupling activity between specific brain regions. In contrast, tRNS involves the application of alternating currents at random frequencies. Due to its oscillatory, rather than direct current, nature, it has been proposed that tRNS is polarity-independent (i.e., neither anodal nor cathodal; [50]). High-frequency tRNS (from 100Hz to 640 Hz) has been shown to elicit powerful cortical excitability modulations with respect to anodal tDCS, and even longer after-effects [51]. (B) The exponential growth of tES. Literature search was run on Medline database; search parameters were "repetitive Transcranial Magnetic Stimulation", "transcranial Direct Current Stimulation", "transcranial Alternate Current Stimulation", "transcranial Random Noise Stimulation" and their acronyms (rTMS, tDCS, tACS, tRNS).

Figure 2. tDCS and cognition: a snapshot of the available literature. (A) The proportion of studies addressing different cognitive functions and targeting different brain regions of interest (the size of the circles on the brain surface represent the % of studies involving stimulation of the highlighted region). (B) The most investigated functions and stimulation sites, as well as the percentage of studies reporting changes in accuracy and/or reaction times for anodal and cathodal tDCS. Bars refer to the percentage of studies reporting an increase/decrease in accuracy/reaction time respect to the total amount of studies applying anodal or cathodal tDCS (in brackets), regardless of the cognitive function(s) being investigated). (C) An overview of the number of studies testing an online or offline tDCS effect, the corresponding average effect on accuracy and reaction being reported and the proportion of single and multiple session studies. Note: electrodes locations refer to the 10/20 international EEG system. WM=working memory; STM=short-term memory; LTM=long-term memory; ACC=accuracy; RT=reaction time; a-tDCS=anodal tDCS; c-tDCS=cathodal tDCS.

Reference List

1. Guleyupoglu B, Schestatsky P, Edwards D, Fregni F, Bikson M: **Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations**. J.Neurosci.Methods 2013, **219:**297-311.

2. Thompson TW, Waskom ML, Garel KL, Cardenas-Iniguez C, Reynolds GO, Winter R, Chang P, Pollard K, Lala N, Alvarez GA, Gabrieli JD: **Failure of working memory training to enhance cognition or intelligence**. PLoS.One. 2013, **8:**e63614.

3. Redick TS, Shipstead Z, Harrison TL, Hicks KL, Fried DE, Hambrick DZ, Kane MJ, Engle RW: **No evidence of intelligence improvement after working memory training: a randomized, placebo-controlled study**. J.Exp.Psychol.Gen. 2013, **142:**359-379.

4. Au J, Sheehan E, Tsai N, Duncan GJ, Buschkuehl M, Jaeggi SM: **Improving fluid intelligence with training on working memory: a meta-analysis**. Psychon.Bull.Rev. 2014.

5. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L: **Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment**. Cochrane.Database.Syst.Rev. 2008,CD005381.

6. Carvalho A, Rea IM, Parimon T, Cusack BJ: **Physical activity and cognitive function in individuals over 60 years of age: a systematic review**. Clin.Interv.Aging 2014, **9:**661-682.

7. Chang YK, Pan CY, Chen FT, Tsai CL, Huang CC: **Effect of resistance-exercise training on cognitive function in healthy older adults: a review**. J.Aging Phys.Act. 2012, **20:**497-517.

8. Linssen AM, Sambeth A, Vuurman EF, Riedel WJ: **Cognitive effects of methylphenidate and levodopa in healthy volunteers**. Eur.Neuropsychopharmacol. 2014, **24:**200-206.

9. Repantis D, Schlattmann P, Laisney O, Heuser I: **Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review**. Pharmacol.Res. 2010, **62:**187-206.

10. Shafi MM, Westover MB, Fox MD, Pascual-Leone A: **Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging**. Eur.J.Neurosci. 2012, **35:**805-825.

11. Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A: **Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases**. Proc.Natl.Acad.Sci.U.S.A 2014, **111:**E4367-E4375.

12. Stagg CJ, Nitsche MA: **Physiological basis of transcranial direct current stimulation**. Neuroscientist. 2011, **17:**37-53.

13. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M: **Polarization of the human motor cortex through the scalp**. Neuroreport 1998, **9:**2257-2260.

14. Thut G, Miniussi C, Gross J: **The functional importance of rhythmic activity in the brain**. Curr.Biol. 2012, **22:**R658-R663.

15. Herrmann CS, Neuling T, Rach S, Struber D: **Modulation of EEG oscillations via transcranial alternating current stimulation**. Biomed.Tech.(Berl) 2012.

16. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W: **Increasing human brain excitability by transcranial high-frequency random noise stimulation**. J.Neurosci. 2008, **28:**14147-14155.

17. Feurra M, Paulus W, Walsh V, Kanai R: **Frequency specific modulation of human somatosensory cortex**. Front Psychol. 2011, **2:**13.

18. Kanai R, Chaieb L, Antal A, Walsh V, Paulus W: **Frequency-dependent electrical stimulation of the visual cortex**. Curr.Biol. 2008, **18:**1839-1843.

19. Cappelletti M, Gessaroli E, Hithersay R, Mitolo M, Didino D, Kanai R, Cohen Kadosh R, Walsh V: **Transfer of Cognitive Training across Magnitude Dimensions Achieved with Concurrent Brain Stimulation of the Parietal Lobe**. J.Neurosci. 2013, **33:**14899-14907.

    *This study demonstrated how brain stimulation coupled with cognitive training may elicit the transfer of cognitive proficiency to other, non-trained functions. The effect was not observed for cognitive training alone.

20. Polania R, Nitsche MA, Korman C, Batsikadze G, Paulus W: **The importance of timing in segregated theta phase-coupling for cognitive performance**. Curr.Biol. 2012, **22:**1314-1318.
    **A milestone study showing for the first time the opportunity to gather information from electrophysiological signals to guide tACS interventions. First evidence of the possibility to synchronize or desynchronize two brain regions with consequent behavioural effects.

21. Santarnecchi E, Polizzotto NR, Godone M, Giovannelli F, Feurra M, Matzen L, Rossi A, Rossi S: **Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials**. Curr.Biol. 2013, **23:**1449-1453.

    *The first study investigating the effect of tACS on higher order cognition, demonstrating the possibility to transiently enhance fluid intelligence in humans using a single session intervention. It also provided the first evidence of the causal role of gamma oscillations in human cognition.

22. Snowball A, Tachtsidis I, Popescu T, Thompson J, Delazer M, Zamarian L, Zhu T, Cohen KR: **Long-Term Enhancement of Brain Function and Cognition Using Cognitive Training and Brain Stimulation**. Curr.Biol. 2013.

*This study combined 5-day arithmetic training with tRNS of the dorsolateral prefrontal cortex, a key brain area in arithmetic learning, and near infrared spectroscopy. The authors found better arithmetic learning, with superior performance as well as transfer effect for calculation material six months post-training and more efficient brain functions.

23. Jacobson L, Koslowsky M, Lavidor M: **tDCS polarity effects in motor and cognitive domains: a meta-analytical review**. Exp.Brain Res. 2012, **216:**1-10.

24. Nitsche MA, Paulus W: **Transcranial direct current stimulation--update 2011**. Restor.Neurol.Neurosci. 2011, **29:**463-492.

25. Filmer HL, Mattingley JB, Dux PE: **Improved multitasking following prefrontal tDCS**. Cortex 2013, 49, 2845–2852

26. Moos K, Vossel S, Weidner R, Sparing R, Fink GR: **Modulation of top-down control of visual attention by cathodal tDCS over right IPS**. J. Neurosci. 2012, 32, 16360–16368

27. Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F: **Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. J. Cogn. Neurosci. 2008, 20, 1687–1697**

28. Filmer HL, Mattingley JB, Marois R, Dux PE: **Disrupting prefrontal cortex prevents performance gains from sensory-motor training**. J. Neurosci. 2013, 33, 18654–18660

29. Horvath JC, Forte JD, Carter O: **Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS)**. Brain Stimul. 2015.

30. Feurra M, Pasqualetti P, Bianco G, Santarnecchi E, Rossi A, Rossi S: **State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters**. J.Neurosci. 2013, **33:**17483-17489.

*First evidence of the state-dependency of tACS stimulation. It demonstrated dissociation between the effect of alpha and beta frequency stimulation on the motor cortex with regards to the brain state while stimulating.

31. Helfrich RF, Knepper H, Nolte G, Struber D, Rach S, Herrmann CS, Schneider TR, Engel AK: **Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception**. PLoS.Biol. 2014, **12:**e1002031.

32. Saiote C, Polania R, Rosenberger K, Paulus W, Antal A: **High-frequency TRNS reduces BOLD activity during visuomotor learning**. PLoS.One. 2013, **8:**e59669.

33. Krause B, Cohen Kadosh R: **Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation**. Front Syst.Neurosci. 2014, **8:**25.

34. Quartarone A, Morgante F, Bagnato S, Rizzo V, Sant'Angelo A, Aiello E, Reggio E, Battaglia F, Messina C, Girlanda P: **Long lasting effects of transcranial direct current stimulation on motor imagery**. Neuroreport 2004, **15:**1287-1291.

35. Antal A, Terney D, Poreisz C, Paulus W: **Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex**. Eur.J.Neurosci. 2007, **26:**2687-2691.

36. Sarkar A, Dowker A, Cohen Kadosh R: **Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety**. J.Neurosci. 2014, **34:**16605-16610.

37. Prichard G, Weiller C, Fritsch B, Reis J: **Effects of different electrical brain stimulation protocols on subcomponents of motor skill learning**. Brain Stimul. 2014, **7:**532-540.

The authors demonstrated how the combination of training protocols and tES provides more benefits than training alone, at least in the motor learning domain. They also showed how different stimulation protocols, i.e. tDCS and tRNS, differently interact with training.

38. **Neurostimulation: hacking your brain.** The Economist, March 7th 2015

39. Santarnecchi E, Feurra M, Galli G, Rossi A, Rossi S: **Overclock your brain for gaming? Ethical, social and health care risks**. Brain Stimul. 2013, **6:**713-714.

40. Maslen H, Savulescu J, Douglas T, Levy N, Cohen Kadosh R: **Regulation of devices for cognitive enhancement**. Lancet 2013, **382:**938-939.

41. Maslen H, Douglas T, Cohen KR, Levy N, Savulescu J: **The regulation of cognitive enhancement devices: extending the medical model**. J.Law Biosci. 2014, **1:**68-93.

42. Maslen H, Earp BD, Cohen Kadosh R, Savulescu J: **Brain stimulation for treatment and enhancement in children: an ethical analysis**. Front Hum.Neurosci. 2014, **8:**953.

43. Iuculano T, Cohen KR: **The mental cost of cognitive enhancement**. J.Neurosci. 2013, **33:**4482-4486.

*This study provides the first evidence that cognitive enhancement through tES can occur at the expense of other cognitive functions. The double dissociation revealed in this study provides crucial information regarding the benefits and risks of enhancement technologies.

44. Brem AK, Fried PJ, Horvath JC, Robertson EM, Pascual-Leone A: **Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition?** Neuroimage. 2014, **85 Pt 3:**1058-1068.

45. Bestmann S, de Berker AO, Bonaiuto J: **Understanding the behavioural consequences of noninvasive brain stimulation**. Trends Cogn Sci. 2015, **19:**13-20.

46. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, Hermiller MS, Voss JL: **Targeted enhancement of cortical-hippocampal brain networks and associative memory**. Science 2014, **345:**1054-1057.

47. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A: **Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields**. Neuroimage. 2014, **89:**216-225.

48. Reato D, Rahman A, Bikson M, Parra LC: **Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing**. J.Neurosci. 2010, **30:**15067-15079.

49. Fries P: **A mechanism for cognitive dynamics: neuronal communication through neuronal coherence**. Trends Cogn Sci. 2005, **9:**474-480.

50. Miniussi C, Harris JA, Ruzzoli M: **Modelling non-invasive brain stimulation in cognitive neuroscience**. Neurosci.Biobehav.Rev. 2013, **37:**1702-1712.

51. Chaieb L, Paulus W, Antal A: **Evaluating aftereffects of short-duration transcranial random noise stimulation on cortical excitability**. Neural Plast 2011, 2011:105927

Enhancing Cognition using Transcranial Electrical Stimulation

Emiliano Santarnecchi[1,2,3], Anna-Katharine Brem[1,4], Erica Levenbaum[1], Todd Thompson[1], Roi Cohen Kadosh[4], Alvaro Pascual-Leone[1]

[1]*Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.*
[2] *Brain Investigation and Neuromodulation Laboratory, Department of Medicine, Surgery and Neuroscience, Siena Medical School, Siena, Italy.*
[3] *Siena Robotics and Systems Laboratory, Department of Engineering and Mathematics, University of Siena, Italy.*
[4]*Department of Experimental Psychology, Oxford University, Oxford, United Kingdom.*

Financial and Conflict of Interest Disclosures:

Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI). All other authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

Figure 1

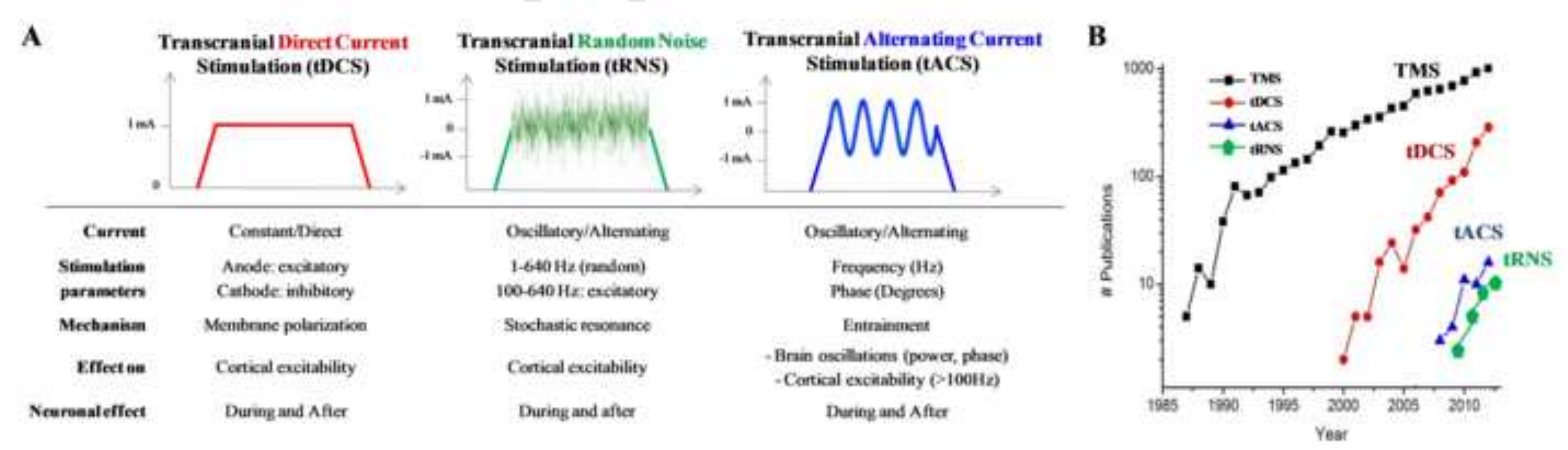
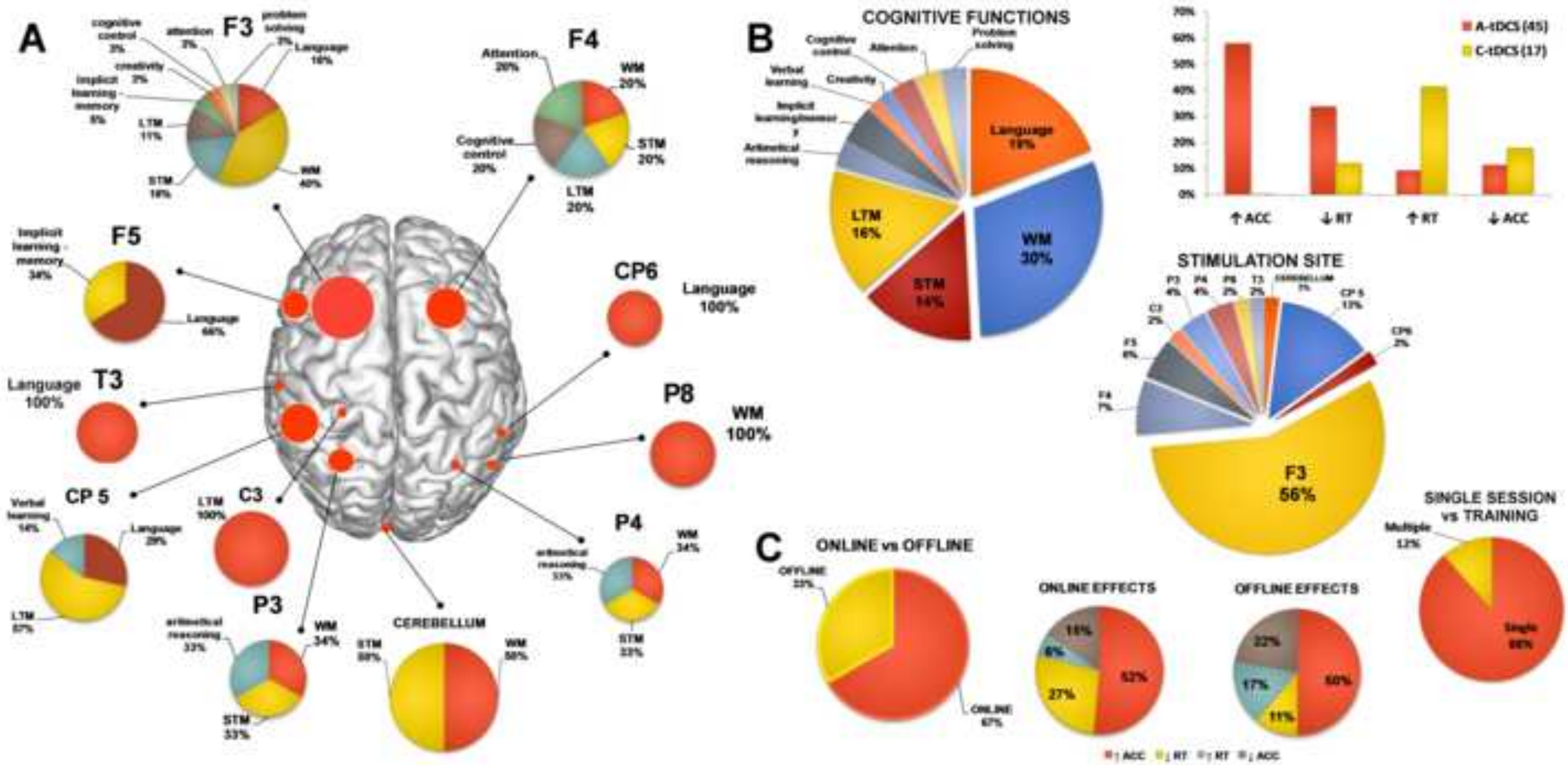

A
Transcranial Direct Current Stimulation (tDCS)
Transcranial Random Noise Stimulation (tRNS)
Transcranial Alternating Current Stimulation (tACS)
1 mA
0
-1 mA
Current
Constant/Direct
Oscillatory/Alternating
Oscillatory/Alternating
Stimulation parameters
Anode: excitatory
Cathode: inhibitory
1-640 Hz (random)
100-640 Hz: excitatory
Frequency (Hz)
Phase (Degrees)
Mechanism
Membrane polarization
Stochastic resonance
Entrainment
Effect on
Cortical excitability
Cortical excitability
- Brain oscillations (power, phase)
- Cortical excitability (>100Hz)
Neuronal effect
During and After
During and after
During and After
B
TMS
tDCS
tACS
tRNS
Publications
1000
100
10
1985
1990
1995
2000
2005
2010
Year

Figure 2


A
F3
F4
F5
CP6
Language
100%
T3
Language
100%
P8
WM
100%
CP 5
C3
P3
P4
CEREBELLUM
B
COGNITIVE FUNCTIONS
Language
19%
WM
30%
LTM
16%
STM
14%
A-tDCS (45)
C-tDCS (17)
STIMULATION SITE
F3
56%
C
ONLINE vs OFFLINE
ONLINE EFFECTS
OFFLINE EFFECTS
SINGLE SESSION
vs TRAINING