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Transcranial Electrical Stimulation in Post-Stroke Cognitive Rehabilitation

Where We Are and Where We Are Going

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Abstract. Cognitive rehabilitation is an important area of neurological rehabilitation, which aims at the treatment of cognitive disorders due to acquired brain damage of different etiology, including stroke. Although the importance of cognitive rehabilitation for stroke survivors is well recognized, available cognitive treatments for neuropsychological disorders, such as spatial neglect, hemianopia, apraxia, and working memory, are overall still unsatisfactory. The growing body of evidence supporting the potential of the transcranial Electrical Stimulation (tES) as tool for interacting with neuroplasticity in the human brain, in turn for enhancing perceptual and cognitive functions, has obvious implications for the translation of this noninvasive brain stimulation technique into clinical settings, in particular for the development of tES as adjuvant tool for cognitive rehabilitation. The present review aims at presenting the current state of art concerning the use of tES for the improvement of post-stroke visual and cognitive deficits (except for aphasia and memory disorders), showing the therapeutic promises of this technique and offering some suggestions for the design of future clinical trials. Although this line of research is still in infancy, as compared to the progresses made in the last years in other neurorehabilitation domains, current findings appear very encouraging, supporting the development of tES for the treatment of post-stroke cognitive impairments.

Keywords: cognitive rehabilitation, stroke, tDCS

Cognitive rehabilitation refers to the rehabilitation of neuropsychological disorders of cognitive functions, including disorders of language, spatial perception, attention, memory, calculation, praxis, and visual perception, which represent frequent consequences of acquired brain damage, in particular of stroke (Stuss, Winocur, & Robertson, 2008). Post-stroke cognitive impairments cause persistent disability for many individuals that results in a loss of independence, disruption in normal activities and social relationships, and they may represent an obstacle to physical rehabilitation; consequently, they represent a major issue for health system and a financial problem for society in terms of need for assistance. Reducing this burden requires the development of effective cognitive rehabilitation strategies. The clinical relevance of post-stroke cognitive rehabilitation is well recognized (Cicerone et al., 2005; Stuss et al., 2008). Nevertheless, the majority of the available treatments seems unsatisfactory: after completing the rehabilitation route, most patients still exhibit some degree of cognitive impairment, showing a little transfer of benefits to daily living (e.g., Bowen, Hazelton, Pollock, & Lincoln, 2013; das Nair & Lincoln, 2007; Pollock et al., 2011; West, Bowen, Hesketh, & Vail, 2008). As consequence, there is a growing need to find out novel

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rehabilitation approaches, or to optimize those available. In this context, transcranial Electrical Stimulation (tES) has attracted the attention of neuropsychologists as potential therapeutic tool for the treatment of post-stroke cognitive deficits (Miniussi & Vallar, 2011).

The clinical interest in tES is supported, first of all, by its feature of being a neuromodulator technique that can noninvasively modulate and interact with neuroplasticity (e.g., Brunoni et al., 2012; Paulus, 2011). Neuroplasticity refers to the adaptive capacity of the central nervous system to continuously acquire new skills and shape its structure and functions in response to environmental demands; it is at the basis of learning in normal conditions, as well as it represents the main mechanism guiding recovery after brain injury (e.g., Nahum, Lee, & Merzenich, 2013; Nudo, 2003; Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Second, an increasing amount of evidence documents the usefulness of tES for improving different cognitive functions in healthy human beings, including language, attention, learning, sensory processing, creativity, decision making, and even social abilities (Cohen Kadosh, 2014; Vallar & Bolognini, 2011).

Starting from this evidence, and considering the promising results obtained in other domains of neurological rehabilitation, such as the treatment of motor disorders and chronic pain (Brunoni et al., 2012), tES is now under investigation as an instrument for promoting the recovery of cognitive impairments in stroke patients. By inducing long-lasting (excitatory or inhibitory) changes in cortical excitability (Paulus, 2011), tES can be used to drive the neural restoration of the impaired cognitive function, to strengthen compensatory mechanisms that may substitute the lost function, and to suppress maladaptive plasticity hampering recovery (Bliss & Cooke, 2011; Fregni & Pascual-Leone, 2007).

So far, language disorders have attracted the greatest effort for the translation of tES in rehabilitation. Instead, the exploitation of tES to treat other post-stroke cognitive impairments is still in its infancy, with clinical evidence limited to a few preliminary, "*proof-of-concept*" studies, primarily exploring short-living effects of a single application of tES in small clinical samples. Clinical trials still lag behind: the effects of multiple tES sessions, their interaction with specific behavioral rehabilitation procedures, and the long-term retaining of performance improvements have been scarcely addressed.

So far, transcranial Direct Current Stimulation (tDCS) has been the main tES method used in cognitive rehabilitation. TDCS consists in the delivery of a homogeneous direct current field of small intensity (≈1–2 mA) directly to the head. The stimulation is delivered transcranially by a battery-driven current stimulator through a pair of electrodes positioned on the scalp. Basically, neurons respond to tDCS by altering their firing rates. In fact, tDCS can induce bidirectional, polarity-dependent changes in cortical excitability: anodal tDCS has been shown to increase cortical excitability (increasing spontaneous neuronal firing rates), while cathodal tDCS has the opposite effect (for reviews of technical and safety aspects of tDCS see: Brunoni et al., 2011, 2012; Miniussi et al., 2008; Nitsche et al., 2008; Paulus, 2011).

The aim of the present review is to offer an overview of the current state of art of the research concerning the use of tDCS in post-stroke cognitive rehabilitation, with the exception of aphasia and memory disorders (see in this issue, the reviews by Crinion et al. and Bartrés-Faz et al.), highlighting its clinical potentiality and discussing the main issues that need to be taken into account for improving this field of research.

TES in Cognitive Rehabilitation: State of Art

Unilateral Spatial Neglect

Unilateral Spatial Neglect (USN) is the most frequent and disabling neuropsychological syndrome caused by lesions to the right hemisphere. USN comprises different, dissociable deficits, but the main clinical feature is the patients' inability to report sensory events occurring in the left side of space, contralateral to the side of the cerebral lesion, and to perform actions in that portion of space (Vallar & Bolognini, 2014). Left USN is recognized as a significant disabling deficit, which may persist chronically and is associated with poor outcome measures on functional activities, in turn posing considerable obstacles to successful rehabilitation (Di Monaco et al., 2011).

The theoretical framework that has guided the use of tES in USN rehabilitation refers to the seminal model of hemispheric competition ("rivalry") originally proposed by Kinsbourne. Accordingly, USN is interpreted as the result of "*imbalance in opponent systems that control for lateral orientation and action*" (Kinsbourne, 1987, pp. 69). Under normal conditions both parietal cortices exert reciprocal inter-hemispheric inhibition. A damage to the right parietal cortex causes a breakdown of such physiological dynamic inhibitory balance between the two hemispheres; the result is a pathological overactivation of the left-hemisphere disinhibition, which aggravates the bias to attend to the right side, and hence to neglect the left side (Hesse, Sparing, & Fink, 2011). In this framework, tDCS has been used with the aim of counteracting such post-stroke inter-hemispheric imbalance, either by up-regulating the excitability of the damaged parietal cortex or by down-regulating the hyperactivation of in the contralesional, intact hemisphere (Hesse et al., 2011; Vallar & Bolognini, 2014).

Sparing and colleagues (2009) tested the value of these two approaches. Ten patients with chronic left USN (time post-onset: ≈2.9 months) due to a right-hemisphere lesion received a single application of anodal tDCS (1 mA, 10 min) to the right posterior parietal cortex (PPC), of cathodal tDCS to the left PPC, and of sham tDCS. Both the inhibitory-cathodal tDCS of the unaffected (left) PPC and the excitatory-anodal tDCS of the affected (right) PPC reduced symptoms of visuospatial neglect, as assessed by means of a visual detection task and a line bisection task. Importantly, the lesion size negatively correlated with the

magnitude of tDCS-induced improvement, in particular following cathodal tDCS of the unaffected hemisphere (Sparing et al., 2009).

Similarly, an improvement in cancellation tasks was obtained in 15 subacute (time post-onset: ≈46 days) patients with left USN, by stimulating the ipsilesional PPC with anodal tDCS (2 mA, 20 min) (Ko, Han, Park, Seo, & Kim, 2008).

More recently, the effects of bi-hemispheric (also called "dual-mode") tDCS over the parietal cortices (1 mA, 20 min; anode over the ipsilesional PPC, cathode over the contralesional PPC) were assessed in 10 chronic stroke patients (time post-onset: ≈27.8 months; Sunwoo et al., 2013). Bi-hemispheric tDCS allows to simultaneously excite one hemisphere and inhibit the other, by applying the anode over a given area of one hemisphere and the cathode over the homologous area of the contralateral hemisphere (e.g., Bolognini et al., 2011; Vines, Cerruti, & Schlaug, 2008). Compared to sham and anodal tDCS of the right PPC, the bi-hemispheric stimulation brought about a greater reduction of the rightward bias in the line bisection task. Instead, no improvement was observed at the star cancellation test.

Then, in a double-blind, sham-controlled, single case study (Brem, Unterburger, Speight, & Jäncke, 2014), the bi-hemispheric parietal tDCS (1 mA, 20 min) was combined with a cognitive therapy for USN (i.e., training of saccades toward the left hemi-space and of visual exploration, reading combined with optokinetic stimulation). A patient with a subacute ischemic stroke of the right posterior cerebral artery (time post-onset: 23 days) suffering from left USN, hemianopia, and hemiparesis underwent daily sessions of the therapy for 4 weeks; at the second week, sham tDCS was added to the therapy, while real tDCS was introduced at the third week. After real tDCS, covert attention allocation toward the left hemi-space (measured through the "Posner paradigm") and alertness significantly improved, while for line bisection and copying only a qualitative improvement was observed, as compared to sham tDCS. Again, star cancellation performance did not vary with tDCS. Improvements in covert attention and alertness were maintained at the follow-up assessments, namely at 1 week and at 3 months after the end of the treatment, whereas improvements in paper-pencil tasks were transient, returning to baseline levels at follow-ups. Activities of daily living (ADLs) improved only at the 3-month follow-up (Brem et al., 2014).

Taken together, current results are very promising, encouraging further investigations of tES for USN rehabilitation. The anodal tDCS over the damaged parietal cortex and the cathodal tDCS of the intact parietal cortex appear both effective for improving neglect symptoms either at standard clinical tests or at experimental tasks; at least for the bisection task, an advantage of the bi-hemispheric stimulation was shown. Noteworthy, hitherto the effects of tDCS were assessed only with respect to extra-personal visuospatial deficits of the USN syndrome, while the chance of modulating even personal neglect, nonvisual (tactile, auditory) disorders, and other deficits frequently associated to this syndrome (e.g., extinction to bilateral stimulation, anosognosia) still needs to be addressed.

Visual Field Loss

Unilateral post-chiasmatic lesions determine a contralesional loss of part of the field of view on the same side in both eyes. Visual field loss greatly affects patient's quality of life, including difficulties in driving, reading, and navigation (Goodwin, 2014). Spontaneous recovery is quite rare and usually incomplete (Zhang, Kedar, Lynn, Newman, & Biousse, 2006). There are three therapeutic approaches for visual field loss: restorative training, optical aids, and compensatory training (Goodwin, 2014). The Vision Restoration Therapy (VRT) is a restorative approach that aims at reducing the visual field loss through repetitive and intensive stimulation of the so-called *transition zone*, an area of residual vision bordering the blind and the intact visual fields, which it is thought to be only partially deafferented, hence reversibly damaged (Kasten, Wüst, Behrens-Baumann, & Sabel, 1998; Sabel & Kasten, 2000). VRT has been shown to lead to an extension of visual field borders of nearly 5° after 6 months of treatment (Kasten, Wüst, Behrens-Baumann, & Sabel, 1998).

A randomized, double-blind, demonstration-of-concept study tested the adjuvant effects of tDCS on the VRT in 12 patients with chronic (time post-onset: ≈30 months) unilateral post-chiasmatic visual field loss (homonymous hemianopia or quadrantanopia) (Plow, Obretenova, Fregni, Pascual-Leone, & Merabet, 2012). During VRT, anodal or sham tDCS (2 mA, 30 min) was delivered over the occipital pole to target both affected and unaffected hemispheres; 1-hr training sessions were carried out three times per week for 3 months. Anodal tDCS induced a greater expansion of the visual field (≈4°), as compared to sham tDCS (namely, VRT alone, visual field expansion ≅0.7°), along with a larger increase in stimulus detection accuracy in the blind hemifield. After the 3-month treatment, patients who received real tDCS showed greater benefits even at vision-related ADLs, in particular visuo-motor activities, while no amelioration was found for quality of life (QOL) measures. The improvement at the ADLs was maintained at the last evaluation, 6 months after the end of the treatment. Intriguingly, only patients stimulated with sham (but not real) tDCS subjectively reported a visual field change (Plow, Obretenova, Fregni, et al., 2012). Such mismatch between changes in objective measures and patients' own subjective impressions of improvement could be due to a placebo effect or, as suggested by the authors, to methodological issues (e.g., small sample size).

Furthermore, anodal tDCS accelerated the recovery of stimulus detection within the first month of VRT, while the shift in the visual field border was only evident after 3 months of treatment (Plow, Obretenova, Jackson, & Merabet, 2012). TDCS-induced improvements in visual field outcomes did not generalize to contrast sensitivity and reading performance, suggesting that the adjuvant use of occipital stimulation is effective in modulating

VRT-specific outcomes, but measures testing the generalizability of the benefits induced by the training (Plow, Obretenova, Jackson, et al., 2012).

In a single case study in a patient with chronic post-stroke hemianopia (time post-onset: ≈72 months), the same research group showed that the visual field expansion by the 3-month VRT plus anodal occipital tDCS was associated to an increase of perilesional occipital activity, around the anode area, as measured with fMRI (Halko et al., 2011).

Finally, a double-blind, sham-controlled study in 12 patients with occipital ischemic lesions (time post-onset: ≈18.4 months) and homonymous visual field defects (hemianopia, quadrantanopia, or paracentral scotoma) showed an increase of visual motion sensitivity in the unaffected hemifield after anodal tDCS (1.5 mA, 20 min) applied over the primary visual cortex on five consecutive days; the improvement was maintained up to 4 weeks, at the time of the last follow-up (Olma et al., 2013). Such amelioration of visual motion perception in the intact hemifield could reflect the reactivation of residual intact neurons in the visual system, which may act as a compensational strategy for damaged visual functions of stroke-related neuronal loss (Olma et al., 2013). However, no clues about the amelioration of visual deficits, nor about the impact of tDCS-induced ipsilesional visual improvement on them, are reported in this work, leaving the clinical relevance of the results uncertain.

In conclusion, tDCS appears a valuable tool for optimizing and increasing the effects of VRT. TDCS not only augments the visual recovery brought about by VRT, but it seems also useful for shortening the duration of this therapy: a visual field expansion emerges when the VRT is reduced by one fourth of its standard duration if tDCS is combined to it. Future research should verify if other visual rehabilitation approaches, as, for instance, training for hemianopic dyslexia or oculomotor exploration, can benefit from concurrent tDCS.

Apraxia

Limb apraxia is a cognitive-motor disorder, usually due to a left-hemisphere lesion, involving a loss or impaired ability to conceptualize or program motor sequences to perform purposeful limb movements, typically with the upper limbs, in the absence of sensory or motor deficits (Heilman & Rothi, 1993). Limb apraxia impairs the ability of managing activities of daily living and has an adverse influence on physical and language therapies (West et al., 2008). Treatments involve both restorative and compensatory approaches, such as the "rehabilitation of gesture execution" method (Smania et al., 2006) or teaching patients internal and external strategies (i.e., oral and written verbalizations) that can compensate the apraxic deficit during execution of everyday activities (Cantagallo, Maini, & Rumiati, 2012).

In a recent double-blind, sham-controlled study in six patients with a left-hemisphere lesion (time post-onset: ≈12.5 months), we have explored the effect of anodal tDCS (2 mA, 10 min) applied over the left PPC, and over the right motor cortex (M1) on ideomotor apraxia (Bolognini et al., 2015). Ideomotor apraxia is characterized by deficits in properly performing tool-use pantomimes and communicative gestures; this impairment is typically identified by asking patients to perform movements on verbal command or to imitate intransitive, symbolic, and nonsymbolic gestures (Barbieri & De Renzi, 1988; Wheaton & Hallett, 2007). Compared to sham tDCS, anodal tDCS of both the contralesional M1 and of the ipsilesional PPC reduced the time required to perform skilled movements with the left, ipsilesional (unimpaired) hand, at the Jebsen Hand Function Test. However, only the left parietal stimulation was able to reduce the planning time required for imitating gestures, and to improve the accuracy of intransitive gesture imitation, at a standard clinical test (see also, Convento, Bolognini, Fusaro, Lollo, & Vallar, 2014). Importantly, the improvement of imitation performance brought about by left parietal tDCS was influenced by the size of the parietal lobe damage: the larger the parietal damage, the smaller the improvement (Bolognini et al., 2015).

A sham-controlled, clinical trial explored the effects of anodal tDCS (Marangolo et al., 2011) of the left inferior frontal cortex (IFC) on the recovery of apraxia of speech, an oral motor speech disorder affecting the ability to translate speech plans into motor plans (Wertz, Lapointe, & Rosenbek, 1984). Three non-fluent aphasic patients with severe apraxia of speech (time post-onset: ≈22 months) were treated; noteworthy, they had a left-hemisphere lesion, but none of them had damage to the IFC where the tDCS anode was positioned. Every patient received five daily sessions of anodal tDCS (20 min, 1 mA) and of sham tDCS, which were delivered during language training for articulatory difficulties. Anodal tDCS augmented the training-induced improvement of articulatory gestures for the correct production of syllables and words, as compared to sham tDCS. At the three follow-up assessments (1 week, 1 and 2 months post-treatment) patients showed retention of the achieved improvement only for anodal tDCS, which did not show any decrement in response accuracy, suggesting a long-term recovery of the patients' articulatory disturbances (Marangolo et al., 2011). Similarly results (Marangolo et al., 2013) were obtained by applying a bi-hemispheric frontal tDCS (anode over the left IFC, and cathode over the right IFC; 20 min, 2 mA) during a language therapy in eight patients with chronic apraxia of speech (time post-onset: ≈29 months).

These studies support the view that apraxic disorders can be improved by stimulating with tDCS the left frontal-parietal network involved in the representation of motor programs and their conversion into motor acts (e.g., Convento et al., 2014; Heilman & Rothi, 1993). The beneficial tDCS effect (nearly a mean 20% of improvement of imitation accuracy) in ideomotor limb apraxia induced by 10 min of stimulation encourages clinical trials testing the long-term effects of multiple tDCS applications (Bolognini et al., 2015).

Dysexecutive Syndrome

Patients with frontal lobe damage usually suffer from the so-called dysexecutive syndrome, which resembles

different cognitive impairments including deficits of working memory, reasoning and problem solving, cognitive flexibility, as well as behavioral disinhibition and general cognitive decline (Elliott, 2003). These impairments all point to a breakdown of a series of coordination processes that takes place in a distributed network of cortical and subcortical frontal structures (Elliott, 2003). Within this network, the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal region (VLPFC) represent core structures for implementing complex cognitive functions; in particular, the DLPFC is crucial for working memory, arousal, and attention, and for behavioral control (D'Esposito et al., 1998; Miller & Cohen, 2001). The neuromodulation of this area was shown to improve working memory in healthy subjects (Fregni et al., 2005) and patients with Parkinson's disease (Boggio et al., 2006).

Jo and colleagues (2009) explored the effect of anodal tDCS (2 mA, 30 min) of the left, contralesional, DLPFC on verbal working memory disorders in 10 patients with a right-hemisphere lesion (time post-onset: ≈2.4 months). Only the Mini-Mental Status Examination, digit and visual span tests were used to screen cognitive functions. Just one application of anodal tDCS improved patients' performance at a working memory task, as compared to sham tDCS (Jo et al., 2009).

Instead, Kang, Baek, Kim, and Paik (2009) explored the usefulness of the anodal stimulation (2 mA, 20 min) of the left DLPFC on attention, which was assessed with a Go/No-Go task. In this study, 10 chronic (time post-onset: ≈18 months) patients with heterogeneous brain lesions (unilateral left- or right-hemisphere lesion, or bilateral), suffering from post-stroke cognitive decline (Mini-Mental Status Examination score $\leq$ 25), were tested. One application of anodal tDCS improved patients' response accuracy in the Go/No-Go task, whereas sham stimulation did not; such improvement emerged 1 hr after tDCS, and it was maintained at the follow-up 3 hrs post-stimulation. Changes in reaction times were comparable for the two stimulations. Unfortunately, the authors did not look for differences in the individual responses to tDCS, notwithstanding the heterogeneity of the brain lesions in their sample.

Bueno, Brunoni, Boggio, Bensenor, and Fregni (2011) reported a marked improvement of mood, as well as of memory and executive functions, after 10 sessions of anodal tDCS (2 mA, 30 min) of the left DLPFC in a single case study. The patient was a 48-year-old woman who suffered from an ischemic stroke affecting the left basal ganglia and the left insula; she presented with a mild right hemiparesis and post-stroke depressive symptoms (including psychomotor retardation, apathy, and malaise), which emerged 3 months after stroke.

The above evidence, together with results from studies in healthy subjects about tDCS effects on other frontal functions, such as on decision-making behavior (Fecteau et al., 2007), planning ability (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009), vigilance (Nelson, McKinley, Golob, Warm, & Parasuraman, 2014), and multitasking performance (Filmer, Mattingley, & Dux, 2013), strongly supports the potential of tDCS for the treatment of post-stroke dysexecutive disorders, as well as for other neurological conditions in which the functioning of the frontal areas is compromised, as, for instance, Traumatic Brain Injury. Given the involvement of the DLPFC in different cognitive and emotional functions, it will be important to further explore whether the stimulation of this area can also affect different clinical outcomes, beyond the specific primary impairment under investigation.

Disorders of Body Representation

Body representation disorders are frequently observed after stroke, and they also required clinical attention in the rehabilitation setting. Although there is no evidence about the use of tES for their treatment, some clues come from the study of Phantom Limb Syndrome (PLS). The amputation of a limb may induce the sensation that the amputated or missing limb is still attached to the body (phantom limb awareness), as well as specific sensory and kinesthetic sensations (phantom sensations), including pain referred to the absent limb (Flor, Nikolajsen, & Jensen, 2006; Hunter, Katz, & Davis, 2003). PLS has been interpreted as the result of the reorganization of the neural network involved in body representation and awareness (Berlucchi & Aglioti, 1997; Flor et al., 2006). While the reorganization of sensorimotor cortical areas plays a major role in the development of phantom limb pain (Flor et al., 2006), the phenomenological experience of having a phantom limb seems to be associated to an abnormally increased excitability of the deafferented PPC, likely due to a release of parietal neurons from inhibitory control (Kew et al., 1994). Support to this hypothesis has been recently provided by using tDCS: the cathodal stimulation (2 mA, 15 min) of this area may induce a short-living (up to 90 min) reduction of the intensity of non-painful phantom sensation, as assessed in a group of seven patients with unilateral lower or upper limb amputation (Bolognini, Olgiati, Maravita, Ferraro, & Fregni, 2013). This evidence not only supports the existence of a relationship between the level of excitability of the PPC and the emergence of phantom sensation, but it also opens up new opportunities for the use of tDCS in disorders of body representation considering that PPC lesions can cause both negative (e.g., disownership of body parts) and positive symptoms (e.g., supernumerary limbs, autoscopic phenomena) related to a derangement of corporeal awareness (e.g., Berlucchi & Aglioti, 1997; Bolognini, Convento, Rossetti, & Merabet, 2013; Vallar & Ronchi, 2009).

Upcoming Directions

Defining the state of art of tES in cognitive rehabilitation, and discussing its efficacy, is quite trivial, considering the paucity of evidence in this field, which is mostly related to studies conducted in small samples of patients, using heterogeneous approaches and different outcome measures. Most importantly, the majority of such works features themselves as pilot experiments, testing the efficacy of a single

application of tDCS, hence not addressing the issue of the long-term maintenance of the cognitive gains, or their generalization to activities of daily living and functional independence. It is evident that future research is needed to determine the clinical relevance of tES in post-stroke cognitive rehabilitation. However, after recognizing these limitations, some considerations can be put forward, also in light of the progresses made in the last years in other neurorehabilitation domains (e.g., Brunoni et al., 2012; Sandrini & Cohen, 2013).

In some studies, the choice of the stimulation mode (e.g., anodal vs. cathodal) and the target area was guided by classical anatomo-functional models of neuropsychological syndromes, such as the model of limb apraxia put forward at the beginning of the 20th century by Liepmann (1977), and the model of "inter-hemispheric rivalry" proposed by Kinsbourne (1987) for USN; in these cases, tES not only has corroborated such neurological, brain-based models of cognitive functions, but it has also highlighted their validity in neurorehabilitation. The choice of the tES protocol has been also based on neuroimaging findings in healthy subjects evidencing that a specific cerebral region is involved in a given cognitive function, hence following modular paradigms, in which complex cognitive functions are thought to be mediated by independent brain areas. Future studies will need to take into account the increasing number of evidence suggesting that most cognitive functions are mediated by widely distributed areas functioning in parallel (Fuster, 2000; Sporns, 2014), as well as recent interpretation of neuropsychological syndromes in terms of a breakdown of functional connectivity in cortical networks (He et al., 2007). In light of this, a challenging advance could be the use of tES to stimulate the connections between areas, rather than a single area, in order to produce changes in brain connectivity that may affect the processing in the impaired cognitive network (Luft, Pereda, Banissy, & Bhattacharya, 2014).

Another important step will be the identification of the factors that may predict the patient's response to tES. For instance, Jung, Lim, Kang, Sohn, and Paik (2011) showed that the severity of the language disorder can foresee responders versus nonresponders to the combined use of tDCS and speech therapy: the minor the language impairment, the greater the benefits by tDCS (Jung et al., 2011). Moreover, it was observed that the time elapsed from stroke is not related to the improvement of apraxic functions brought about by tDCS in chronic patients (Bolognini et al., 2015). Nevertheless, it may play a major role in acute and subacute stages, when the patient's clinical condition is typically more instable. With respect to the lesion profile, while the overall size of the lesion may reduce the behavioral benefit brought about by parietal tDCS in USN (Sparing et al., 2009), it seems that, more than the lesion volume, it is the extension of the damage affecting the area targeted by tDCS that may predict its efficacy. Indeed, apraxic patients with extensive left parietal lesions show a smaller improvement by left parietal tDCS, while the volume of their lesion is less relevant in determining their behavioral outcome (Bolognini et al., 2015).

It is worth mentioning that cognitive rehabilitation is typically driven *by* the characteristics of the neuropsychological symptoms identified by special batteries of tests designed to measure cognitive functioning following brain injury. However, the implementation of tES in cognitive rehabilitation will probably require to go beyond the neuropsychological assessment, looking for neurophysiological markers of either altered cognitive functioning or of functional integrity in the stroke brain; the chance of tracking local and network changes associated with tES enhancement will be also valuable for refining tES protocols (e.g., Romero Lauro et al., 2014; Veniero, Bortoletto, & Miniussi, 2014).

Generalization of the treatment effects represents the key goal of any rehabilitation approach; so far, the transfer of tES improvement of cognitive disorders to activities of daily living has been addressed by few studies (Brem et al., 2014; Plow, Obretenova, Fregni, et al., 2012; Plow, Obretenova, Jackson, et al., 2012). On the other hand, given that tES lacks spatial focality (e.g., Brunoni et al., 2012; Wagner et al., 2007), and considering that a given area may be involved in different cognitive processes, it is advisable to measure not only tES effect on the cognitive deficit under investigation, but also on other related cognitive processes. A few examples follow. We have recently shown that anodal tDCS of the left parietal cortex improves ideomotor apraxic functions, but not phonemic fluency, which also involves left-hemisphere activity (Bolognini et al., 2015). Conversely, a study exploring the effect of the combined use of motor cortex stimulation and bilateral robotic training on hemiparesis found an unexpected improvement of language functions (Hesse et al., 2007); Marangolo and coworkers (2011) showed that the anodal tDCS of the left IFC improved the targeted deficit, namely speech apraxia, but it also increased oral production in two out of three patients, and written naming and word writing under dictation in one patient.

Another critical issue is "when" tES should be used in cognitive rehabilitation. So far, tDCS was primarily used in patients in a chronic stage of illness, and to a lesser extent in subacute patients; for both, its efficacy was overall confirmed as reviewed above. Hypothetically, neuromodulatory approaches may also be useful to strengthen the reorganization of the neural circuits subtending spontaneous recovery, or to prevent the insurgence of maladaptive plastic phenomena, in the acute post-stroke stage.

The issue of the time of the tDCS use in cognitive rehabilitation is also of interest considering the difficulty to engage patients in high demanding cognitive therapies in the acute and subacute phases, as early after stroke there is an important decrease of attentional resources (Loetscher & Lincoln, 2013; Stapleton, Ashburn, & Stack, 2001). An impairment of attention itself may represent a main obstacle for cognitive treatment, even in chronic patients. Hence, the amelioration of attentional abilities should represent a therapeutic priority. In some cases, tES could represent the only affordable way to improve attention, since it does not require an active involvement of the patient in the therapy. Additionally, tES could be used for reducing the time

required for beginning a specific, intensive, cognitive intervention later on, in turn increasing the patient's response to the subsequent training.

On the other hand, evidence from post-stroke motor rehabilitation indicates that tDCS is overall effective in the chronic (more than 3 months from stroke onset) and subacute (less than 3 months from stroke) phases of stroke, while being ineffective in acute patients (within the first 3 days of symptom onset, see for a review, Marquez, van Vliet, McElduff, Lagopoulos, & Parsons, 2015). Given the limited number of studies in neuropsychological research, with the majority of them not controlling for the effect of the time elapsed from stroke on the patients' response to tDCS, any prediction of the clinical (and likely different) utility of tDCS in the different stages of illness (acute, subacute, chronic) remains purely speculative for cognitive rehabilitation.

Finally, most of the current studies have primarily assessed the therapeutic effects of tES delivered alone, without coupling it with any behavioral training. This is of course a necessary starting point for the determination of the area to stimulate, and how to stimulate it (i.e., anodal, cathodal, bi-hemispheric). But it is important to consider that the use of tES as surrogate of cognitive trainings is likely suboptimal, as tES may activate neural circuits in an unspecific way. Rather, the future research should focus on the possibility of coupling tES-specific cognitive training in order to achieve additive clinical improvements (Miniussi & Vallar, 2011). The rationale of this approach, as originally proposed by Bolognini, Pascual-Leone, and Fregni (2009) for motor rehabilitation, is that practice of a cognitive task may be more effective in using the (surviving) neural mechanisms subserving training-dependent plastic changes, if pertinent areas of the cortex are facilitated by neuromodulation. Given that both strategies, learning and cortical stimulation, share similar mechanisms of action for inducing neuroplasticity, their combination might be more beneficial than their use alone (Bolognini et al., 2009). Importantly, this approach implies to know which are the mechanisms activated by the cognitive therapy in order to be able to target, and in turn strengthen, them with tES. Cognitive rehabilitation involves two essential processes: the restoration of functions damaged by stroke, which implies a neuronal reorganization (or plasticity) in a task-specific neuronal architecture that takes place during learning or relearning within a damaged cognitive system, and the development of compensatory strategies to learn how to do things differently when functions cannot be restored to pre-injury level. This last case implies a cognitive reorganization since the patient uses a different set of cognitive processes to perform the same task either because a new cognitive procedure has been learned or because of increased demands on normal cognitive processes (Munoz-Cespedes, Rios-Lago, Paul, & Maestu, 2005; Price, Mummery, Moore, Frackowiak, & Friston, 1999). Obviously, these two processes require a differential use of tES: if the goal is to restore an impaired cognitive function, the plastic processes involved in the recovery of such function should be identified and primed by tES. Instead, cognitive reorganization may require using tES to facilitate the acquisition of a new strategy, likely by stimulating a system spared by the lesion.

Additionally, the combined use of tES and cognitive training requires a careful consideration of dosage parameters, among which current intensity, duration of stimulation, and its timing with respect to the training (Brunoni et al., 2012; Fregni et al., 2015). Indeed, the cognitive effects of tDCS are dependent on the current intensity, and there is evidence for timing-dependent plasticity regulation in the human (motor) cortex (Brunoni et al., 2012). Such factors represent a source of variability and, importantly, may result in a deterioration of performance. Therefore, the long-term effects of multiple applications of tDCS, their interaction with specific learning stages during a cognitive therapy, the optimal parameters of stimulation, including safety issues (Brunoni et al., 2011), still remain to be addressed in cognitive rehabilitation.

Conclusions

The evidence reviewed above fosters a further, in-depth, exploration of tES to confirm the usefulness of this neuromodulatory tool for the treatment of different cognitive impairments in stroke patients. This line of research will not only enrich cognitive therapies, where there is a pressing need for their betterment, but it will also offer novel clues on the plastic changes featuring injured cognitive systems, the mechanisms underpinning their post-stroke recovery, and clues on how to interact with them in order to drive the enhancement of cognitive functioning after brain injury.

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