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Role of tDCS in potentiating poststroke computerized cognitive rehabilitation: Lessons learned from a case study

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ABSTRACT

Cognitive impairment after stroke is quite common and can cause important disability with a relevant impact on quality of life. Cognitive rehabilitation (CR) and related assistive technology may improve functional outcomes. A 30-year-old woman came to our research institute for an intensive CR cycle following a right parieto-temporal stroke. Because the patient was in the chronic phase, we decided to use 3 different rehabilitative protocols: (a) traditional cognitive training (TCT), (b) computerized cognitive training (CCT), and (c) CCT combined with transcranial direct stimulation (CCT plus) with a 2-week interval separating each session. Cognitive and language deficits were investigated using an ad-hoc psychometric battery at baseline (T0), post-TCT (T1), post-CCT (T2), and post-CCT plus (T3). Our patient showed the best neuropsychological improvement, with regard to attention processes and language domain, after T3. Our data showed that CCT plus should be considered a promising tool in the treatment of poststroke neuropsychological deficits.

KEYWORDS

Computerized cognitive training (CCT); transcranial direct current stimulation (tDCS); young stroke

Introduction

Stroke in young adults is not so uncommon and often represents a diagnostic challenge (Bevan, Sharma, & Bradley, 1990; Kikuchi, Tanaka, Murai, & Tancharoen, 2014). Stroke incidence (20/100,000 to 35/100,000 per year in individuals younger than 55 years old) increased during the last few years because of a rise in the prevalence of diabetes, obesity, cardioembolic sources, and drug abuse, as well as the still high prevalence of smoking (Béjot, 2014; Chraa, Louhab, & Kissani, 2014; Ji, Schwamm, Pervez, & Singhal, 2013; Pezzini et al., 2014). Acute ischemic stroke is the most important cause of mortality and disability and remains a serious and significant global health problem (Bevan et al., 1990) that entails significant direct and indirect costs. Cognitive impairment after stroke is quite common and can cause disability with major impacts on quality of life (QoL) and independence (Cumming, Marshall, & Lazar, 2013; Pater, Coshall, Rudd, & Wolfe, 2003; Rasquin, Lodder, & Verhey, 2005; Shim, 2013).

The neuropsychological profile following stroke is mainly characterized by an alteration in executive functions, with less verbal memory impairment (Sachdev, 2004), especially after a right-hemisphere stroke (Gillespie, Bowen, & Foster, 2006; Welte, 1993). Attention is widely considered to be the basis of other cognitive functions (Hyndman & Ashburn, 2003),

because its impairment can reduce cognitive productivity and plays a key role in the rehabilitation process after stroke (Barker-Collo, Feigin, Parag, Lawes, & Senior, 2009). Poststroke language deficits can include aphasia, alexia, agraphia, and acalculia (Sinanović, Mrkonjić, Zukić, Vidović, & Imamović, 2011). Moreover, poststroke depression is estimated to occur in 30% to 35% of patients during the first year, with a negative impact on rehabilitation, QoL, cognitive function, and mortality (Gbiri, Akinpelu, & Odole, 2010; Schulte-Altdorneburg & Berezki, 2014). During the last decade, advances in the care of those who have had a stroke have been made (World Health Organization, 1989), including prevention, acute management, and recovery, with the implementation of some informatics techniques to improve cognitive recovery (Cumming et al., 2013; Kim, 2003; Loetscher & Lincoln, 2013; Majid, Lincoln, & Weyman, 2000; Nair & Lincoln, 2007; Silver, 2014; Westerberg et al., 2007).

Indeed, it is possible to increase the effects of rehabilitative training by means of noninvasive brain stimulation techniques.

Transcranial direct current stimulation (tDCS) is a form of noninvasive cortical stimulation that modulates cortical excitability and performance of the brain at stimulation sites via weak polarizing currents that enhance or reduce neuronal activity by affecting the

resting potential of the neuronal membrane (Nitsche et al., 2008). tDCS has been reported to transiently improve working memory and attention by stimulating the left dorsolateral prefrontal cortex in healthy individuals (Fregni et al., 2005; Nelson, McKinley, Golob, Warm, & Parasuraman 2014) and in patients with Parkinson disease (Boggio et al., 2006) or Alzheimer disease (Ferrucci et al., 2008). Moreover, the potential of tDCS is to optimize cognitive rehabilitation techniques and promote long-term recovery of language (Holland, & Crinion, 2012) and working memory in patients who have had a stroke (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Jo et al., 2009; Miniussi et al., 2008), as shown in recent studies (Kang, Kim, & Paik, 2012; Kang, Kim, Sohn, Cohen, & Paik, 2011; You, Kim, Chun, Jung, & Park, 2011).

Case description

A 30-year-old right-handed woman, affected by post-stroke expressive aphasia with concomitant cognitive deficits, came to our observation clinic for an intensive cycle of rehabilitation. Her psychomotor development was normal and she reported graduating from secondary school. In August 2013, she was hospitalized for sudden onset of language impairment and right hemiparesis. A computed tomography (CT) scan showed a hypodense lesion in the left parieto-temporal region, and blood tests were normal with the exception of an Methylene-tetrahydrofolate reductase (MTHFR) homozygous mutation. The patient was thus treated with antiplatelets (i.e., cardioaspirin, 100 mg) and performed a conventional rehabilitative motor and speech training (i.e., three times a week for 6 months).

The patient came to our neurorehabilitation research center after about 8 months from stroke onset. As the patient was in the poststroke chronic phase, we decided to treat her by using an intensive cognitive rehabilitation protocol, including three different kinds of training:

1. Traditional cognitive training (TCT), based on a face-to-face approach between the therapist and patient using paper-and-pencil tools;
2. Computerized cognitive training (CCT) by means of the Italian platform ERICA, characterized by specific computerized task-oriented exercises with progressive difficulty, regarding five peculiar cognitive domains: attention, spatial cognition, memory, verbal executive function, and nonverbal executive function; and
3. CCT combined with tDCS (CCT plus). In particular, tDCS was delivered by a BrainStim battery-driven stimulator (E.M.S., Bologna, Italy) using a pair of rubber electrodes enclosed in saline-soaked sponges. To stimulate the right superior temporal gyrus (STG), the active electrode (cathode) was

placed horizontally over T8 according to the 10–20 electroencephalogram system. The reference electrode was placed over the left shoulder, because it has been shown that the great interelectrode distance increases brain current density due to a low-current shunt across the scalp (Bikson et al., 2010). A 1 mA direct current with a fade-in/out of 8 s was delivered for 15 min for two sessions separated by 5 min. Current density was below the safety limit of 0.052 mA/cm² (Nitsche et al., 2003). The impedance was controlled by the device itself and kept at <10 kΩ.

A 2-week interval separated each training session that was articulated in five sessions weekly for 8 weeks (for a total of 40 rehabilitative sessions). Experimental conditions were kept equal across the entire rehabilitation protocol; in particular, the tDCS administration was carried out over exact conditions each day.

The patient underwent a neuropsychological and clinical evaluation before (T0) and after each rehabilitative cycle. Neuropsychological status was assessed by a skilled neuropsychologist through a proper battery to investigate cognitive domains such as attention, memory, language, and executive functions. The battery included: (a) the Mini Mental State Examination (MMSE), the Attentive Matrices (AM), Trail-Making Test Parts A and B, and the Rey Auditory Verbal Learning Immediate and Recall (RAVLI, RAVLR). Moreover we used: (b) the Token Test (TT) (De Renzi, Zambolin, & Crisi, 1987), Boston Naming Test (BNT) (Kaplan, 1983), Verbal Fluency Test (VFT), and Semantic Fluency Test (SFT) to assess spontaneous speech, comprehension, and communication skills; and c) the Hamilton Rating Scale for Depression (HRS-D) and Hamilton Rating Scale for Anxiety (HRS-A) to evaluate the presence of depressive symptoms and anxiety.

To assess whether a change in the individual's score (i.e., before and after each intervention) was statistically significant or not (based on how reliable the measure is), we calculated the Reliable Change Index (RCI; Heaton et al., 2001; Jacobson & Truax, 1991; Parsons, Notebaert, Shields, & Guskiewicz, 2009). This tool can assess the statistical significance of a change in an individual's score (i.e., before and after our intervention). It is defined as the change in an individual's score divided by the standard error of the difference (SE_{diff}) for the test being used. The boundary value for statistical significance within the RCI is ≥ 1.96 (1.96 equates to the 95% confidence interval). In other words, the difference between the two scores (pre–post) has to be at least twice the SE_{diff} (i.e., 1.96 times the SE_{diff}) to be significant.

At baseline (T0), the neuropsychological evaluation showed a mild cognitive deficit (MMSE score = 24.3) with a relevant impairment in auditory verbal learning

(RAVLI = 38.7, RAVLR = 8.2), slurred and slow speech, with a delayed response after stimuli presentation and semantic and phonemic paraphasias. The patient also showed a moderate language disorder with alterations in TT (27, 75), difficulties in understanding, inadequate responses to complex verbal commands, and difficulties in denomination (BNT = 36/60) and semantic categorization with a lacking phonetic fluency (SFT = 32, VFT = 25). Moreover, a moderate depression (HRS-D = 17) with a tendency for anxiety (HRS-A = 16) was also noted. After the end of the TCT (T1), we observed a significant improvement in many items (RCI = 2.3) with some exceptions that were ameliorated only after the combined rehabilitative approach (T3; Table 1). In T2, many items further improved (RCI = 2), but the greatest effects were observed after CCT plus (RCI = 2.6). Indeed, language items improved only after CCT plus (T3), as did depression and anxiety scores, memory, and attentive parameters. In more detail, the patient showed the best improvement in global cognitive functioning (MMSE = 30) with regard to auditory verbal learning (RAVLI = 42.7, RAVLR = 10.2), the selective attention process (AM = 72), reduction in paraphasias with better semantic and phonemic fluencies (Letter

Verbal Fluency [LVF] = 28, Semantic Verbal Fluency [SVF] = 37), denomination (BNT = 50), and verbal comprehension (TT = 35.75) after the CCT-plus session (T3).

Discussion

The novelty of our report consists in the possibility to improve cognitive function in a young patient affected by stroke in the chronic phase. We believe that our patient's evident improvement in cognition, mood, and language function may be related to such an intensive personal computer rehabilitation program associated with tDCS (CCT plus). Indeed, the patient had a mild improvement after TCT, when she performed only a traditional treatment, and had a better recovery after CCT, albeit not as evident as after the CCT-plus treatment. Moreover, language skills improved only after tDCS was applied, and thus, we do not believe the improvement was only due to a cumulative treatment effect. Thus, the active combination of tDCS with computerized and more motivating tools may have been more effective in improving neuropsychological functions.

Recovering language networks are dynamic and depend on multiple factors including the location of the lesion and its size, time since injury, intensity and type of the provided intervention, age at the time of injury, and handedness. It is unlikely that in our patient, factors other than the intensive rehabilitative training may have played a role in the cognitive improvement, because the stroke was in the chronic phase (i.e., after 8 months).

Cognition is not a unitary concept and incorporates multiple domains: (a) attention (focusing, shifting, dividing, or sustaining attention on a particular stimulus or task); (b) executive function (planning, organizing thoughts, inhibition, control); (c) visuospatial ability (visual search, drawing, construction); (d) memory (recall and recognition of visual and verbal information); and (e) language (expressive and receptive; Cumming et al., 2013). Reducing the impact of poststroke cognitive impairment is an important goal. Rehabilitation of impaired cognitive functions is considered a standard component of medical care after acquired brain injury. Indeed, much evidence supports the effectiveness of the two major categories of techniques—traditional and computer-assisted—which are widely used in cognitive rehabilitative treatment.

A computer-assisted cognitive rehabilitation (CACR) has been frequently used since it was developed by Glisky, Schacter, and Tulving (1986). De Luca et al. (2014) have suggested that CACR may be a promising methodology to optimize the rehabilitation outcomes following brain injury (vascular or not). Noninvasive brain stimulation has shown its potential to modulate

Table 1. Comparison of psychometric measures at T0, T1, T2, and T3.

Domain	Test	T0	T1	T2	T3
Cognitive status	MMSE	24.3	28	28	30
Memory					
Immediate	RAVLI	38.7	38.7	38.7	42.7
Recall	RAVLR	8.2	8.2	8.2	10.2
Attention process	AM	60	65	68	72
	TMT-A	30	33	33	33
	TMT-B	50	55	60	62
	TMT B-A	20	22	22	22
Language	LVF	25	25	25	28
	SVF	32	32	31	37
	BNT	36	40	41	50
	TT	27,75	28,75	28,75	35,75
Anxiety symptoms	HRS-A	16	15	7	5
Depression symptoms	HRS-D	17	16	8	4
Physical function	SF-36 (QoL)	90	90	100	100
Role limits-physical		90	90	100	100
Bodily pain		90	90	100	100
General health		60	65	85	90
Vitality		15	19	45	70
Social functioning		10	16	50	65
Role limits-emotional		15	15	30	50
Mental health		10	18	22	43

Note. Mean raw data are reported. Bold values refer to significant changes (i.e., the difference between the consecutive scores is at least twice the SEdiff (standard error of the difference; i.e., 1.96 times the SEdiff). MMSE = Mini Mental State Examination; RAVLI = Rey Auditory Verbal Learning Immediate; RAVLR = Rey Auditory Verbal Learning Recall; TMT-A = Trail-Making Test-Part A; TMT-B = Trail-Making Test-Part B; LVF = Letter Verbal Fluency; SVF = Semantic Verbal Fluency; BNT = Boston Naming Test; TT = Token Test; HRS-A = Hamilton Rating Scale for Anxiety; HRS-D = Hamilton Rating Scale for Depression; SF-36 QoL = Short Form-36 Quality of Life Scale. T0: baseline; T1: after traditional treatment; T2: after computerized cognitive training; T3: after combined training.

brain plasticity in humans and it is used to promote poststroke recovery. In recent years, a variety of studies have shown that tDCS had significant effects for the rehabilitation of cognitive functions in patients with brain injury (Miniussi et al., 2008). tDCS has a high potential to be routinely administered in parallel to intensive cognitive or motor training in neurological diseases in the future (Flöel, 2014). Jo et al. (2009) studied the effects of the tDCS in working memory of patients who sustained a stroke and showed an association between the methodology and improvement in working-memory performance. In a pilot study, Park, Seo, Kim, and Ko (2014) found that the combined use of the tDCS with CACR to the prefrontal cortex may provide positive effects in improving cognitive dysfunction for patients with stroke. Our data showed that CCT in addition to the tDCS should be considered as a rehabilitative tool in the treatment of some neuropsychological deficits. It is clear, however, that a multimodal approach to tDCS is required for understanding how different parameters improve the bilateral language networks necessary to enable recovery.

The interhemispheric inhibition model of poststroke language plasticity posits that the activity of right-hemisphere structures may interfere with the compensatory recovery of the left-hemisphere peri-lesional area. Indeed, this approach also led to improved language functions; cathodal-tDCS applied to the right STG was more beneficial than anodal-tDCS applied to the left STG and was more beneficial than sham (You et al., 2011). Thus, we may speculate that our patient's good response to CCT plus TDCS could depend on the site and direction of the stimulation paradigm inducing a better functional plasticity.

Considering the potential benefit of these synergic interventions highlighting the pivotal role of tDCS, further studies taking into consideration large patient populations, long treatment periods, or the combination of different rehabilitation strategies are needed to confirm our promising findings.

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