Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: January 31, 2024

Citation: Zettin M, Varini M, et al., 2024. Combination of Transcranial Direct Current Stimulation and Action Imitation Training in Post-Stroke Aphasia Rehabilitation: Implications from a Single Case Study, Medical Research Archives, [online] 12(2). https://doi.org/10.18103/mra.v12i2.5124

DOI
https://doi.org/10.18103/mra.v12i2.5124

ISSN: 2375-1924

CASE REPORT

Combination of Transcranial Direct Current Stimulation and Action Imitation Training in Post-Stroke Aphasia Rehabilitation: Implications from a Single Case Study.

Marina Zettin[1,2], Matteo Varini[1*], Marta Gai[1], Danilo Dimitri[1,2]

[1] Centro Puzzle, Turin, Italy,
[2] Department of Psychology, University of Turin, Turin, Italy

*Corresponding author: matteo.varini97@gmail.com

ABSTRACT

Background. One of the most used non-invasive brain stimulation (NIBS) techniques in aphasia rehabilitation is Anodal Transcranial Direct Current Stimulation (A-tDCS). Its application is supported by the fact that brain plasticity, when facilitated by language intervention, can be improved by non-invasive brain stimulation. The effects of neuromodulation combined with various language and communication therapies have led to promising results in the rehabilitation of patients presenting with acquired aphasia. An Action Observation Therapy such as IMITAF seems to contribute to improvements in language skills, mainly in naming. This experimental clinical protocol aims to investigate the rehabilitative potential of A-tDCS on perilesional areas, combined with computerized neuropsychological training.

Method. Participant: Mr. V., 66-year old right-handed male, Italian native speaker. The patient suffered an ischemic stroke due to left carotid artery dissection which resulted in right hemiparesis, mixed transcortical aphasia, characterized by non-fluent speech and dysarthric and disfluent speech.

Treatment: The subject underwent unipolar montage stimulation, with anode placed in F5 and intra-cephalic reference on Fp2. For safety reasons, a stimulation intensity of 1.5 mA was applied for 20 minutes once a day in combination with IMITAF level I, which required the subject to repeat bisyllabic words.

Procedure: The stimulation protocol lasted a total of 4 weeks and was divided into 2 different modes. Clinical Training: 40-minute treatments (no.10 sessions) and involved the combined administration of a-tDCS (20-minute online mode) and 40-minute training.

Home-Based Training: 40-minutes trainig carried out at the patient's home, via PC (no. 8 sessions).

Results. Mr. V. completed the protocol treatment sessions without reporting any adverse effects, such as scalp redness, tingling or headache. The results showed an improvement in the auditory/visual comprehension of words/sentences after A-tDCS and Action Observation Therapy, which has maintained one month after treatment.

Conclusions. Together with IMTAF neuropsychological training, the constant and repeated use of A-tDCS, on the perilesional areas, contributed to improvements in language skills thus promoting an overall recovery of communicative skills in an individual with chronic post-stroke non-fluent aphasia.

Introduction

Aphasia is an acquired language disorder resulting from damage to the brain areas responsible for comprehension and production of language. The most common causes of this disorder include vascular lesions, traumatic brain injury and brain tumors[1], with a prevalence of 250,000 cases in the UK and 1 million in the USA[2].

Aphasia can involve different levels of language processing with deficits in both oral and written comprehension and production. Most aphasia patients show some degree of spontaneous recovery within the first two to three months after the event, due to functional neuronal reactivation and reorganization. Recovery occurs in most patients as they move from the acute to the chronic phase of their condition[3].

The most important factors in recovery process are the lesion location and size, aphasia type and severity, the treatment received and the nature of early haemodynamic response[4].

Post-stroke aphasia is typically associated with infarction in the territory of left middle cerebral artery (MCA). Focal cerebral ischemia is caused by disruption of the blood supply to the brain resulting from cerebral artery occlusion. This area of necrosis forms the infarct core, while brain regions with perfusion above the viability threshold may survive if therapeutic intervention restores normal blood flow[5]. These potentially recoverable regions are called 'penumbra'[6]. Restoring blood flow from the penumbra to specific cortical areas of the left hemisphere in aphasic patients can recover specific aspects of language function such as naming and writing[7,8]. While acute hypoperfusion and tissue necrosis first affect circumscribed brain regions and their fiber tract connections, secondary damage or deactivation due to apoptosis, inflammation, neurodegeneration or diaschisis can, however, also affect remote brain areas and can result in a more widespread disruption of the entire functional network even in the non-ischemic hemisphere[9,10]. At the same time, neuroplastic mechanisms can spontaneously activate within a few days or weeks.

Structural and functional connectivity analyses have recently revealed that major language areas in the left hemisphere are part of a richly interconnected network that extends into the right hemisphere[11]. Although damage to specific brain regions and their connections occurs mainly in the left hemisphere, functional magnetic resonance imaging (fMRI) examinations have shown that in some cases language function is shifted to right hemisphere areas[12].

The lesion can cause interhemispheric inhibition disruption, thus releasing activity in regions homologous to the lesion site. Patterns of reorganization in language networks can be observed after acute injury[13].

Right-hemisphere brain activity can be observed beyond the subacute phase and can also coexist with the reactivation of perilesional areas in the left hemisphere[14,15]. The recruitment of perilesional areas may result from the release of corticortical inhibitory inputs (collateral disinhibition) from the infarcted speech areas[16]. Recruitment of homologous language pathways in the right hemisphere is instead believed to occur through transcallosal disinhibition by the left-hemisphere lesion[17,18].

The role of the right hemisphere in language recovery is still unclear and debated, and for years it had been considered dysfunctional. A number of studies have, however, emphasized the potential benefits of its activation after a left-hemisphere lesion[19]. The right hemisphere could thus play a facilitative and adaptive role in the acute and subacute phases, but be maladaptive in the chronic phase, as it would prevent activation of the spared perilesional tissue and contribute to enhanced recovery[20].

The reactivation of perilesional regions in cases of enhanced recovery is not controversial[21,22]. The remaining activations surrounding the peri-infarct cortex have been correlated with therapy-induced language improvement[23]. The perilesional areas in the left hemisphere could therefore be considered as trigger circuits for possible language recovery[24].

In the hierarchical model of compensatory strategies for post-stroke aphasia[20], the right hemisphere areas can only support some language recovery if the essential language areas in the left side are severely damaged.

This model would also be compatible with studies showing links between language improvement and a repositioning of the language network towards perilesional areas, particularly in the left inferior frontal gyrus[25,26].

Based on these data, therapeutic modulation of the activity of the language network should theoretically favor an activity re-positioning in key regions of the left hemisphere for optimal recovery and/or reduce activity in homologous areas of the right hemisphere[21].

Most of the rehabilitation treatments for acquired aphasia are aimed at recovering the impairment through specific exercises addressed to the damaged function.

Cognitive approaches, on the other hand, target solely the patient's impaired language domain. However, there are rehabilitation protocols working indirectly on the language area[27]. In clinical practice, a series of treatments aims at exploiting the activation of a specific neuronal network, namely the mirror neurons.

In this sense, some studies have shown a significant relationship between gestures and the processing of communicative intention[28], and also for the combination of gestures with verbal production as a rehabilitation technique, which can have significant therapeutic effects for the functional recovery of aphasic patients[29]. To date, the observed evidence has led to the development of various rehabilitation techniques such as the 'Observation with Intent To Imitate' (OTI) and the 'Action Observation Therapy' (AOT). These therapeutic behavioral interventions are therefore presented as recovery models rather than compensatory models. The treatments are able to influence brain reorganization, with the aim of recovering damaged motor functions, instead of compensating them through new strategies learning[30]. Looeiyan et al.,[31] devised a revised version of IMITATE, called IMITATE-R, which involves not only the observation of the actors' mouth movements, but also some videos showing finalized hand gestures. IMITATE has been translated into several languages, including Italian. The Italian program built on this model is called IMITAF[32].

Unlike most behavioral treatment strategies for aphasia, non-invasive brain stimulation (NIBS) techniques have been specifically used to remodel language networks plasticity and, as such, are entirely based on post-stroke neural network reorganization models[24].

In transcranial Direct Current Stimulation (tDCS), small currents (usually 1-2 mA) are applied to the scalp for several minutes via two large surface electrodes (usually 5 × 5 cm or 5 × 7 cm). It is believed that the applied currents are insufficient to directly induce action potentials as in Transcranial Magnetic Stimulation (TMS), but would modulate neuronal resting membrane potentials.

Although changes in membrane potentials are transient, tDCS can help strengthen synaptic connections by producing long-lasting effects which persist even after stimulation[33,34]. Prolonged stimulation can in fact result in long-term potentiation (LTP). Brown et al.,[35] described LTP as the strengthening of the neural connection between two simultaneously activating neurons. Similarly, long-term depression (LTD) refers to a lasting decrease in neuronal activation. These two phenomena represent a strengthening and weakening of synaptic connections respectively, which are essential for the acquisition and storage of new information[24].

According to the literature review carried out by Zettin M. et al.,[24,32] the neurostimulation technique would favor a better recovery of the impaired language functions when administered in combination with neurobehavioral treatment (online-tDCS), compared to the sole use of tDCS stimulation. The review also shows a better efficacy of anodal stimulation on the perilesional area (A-tDCS), with intracephalic referral, especially in cases of moderate or chronic damage. For both safety and methodological reasons, tDCS should be administer for no more than 30 minutes per session, 1 to 2 mA, for 5-15 active stimulation sessions[24].

Aims and Objectives

The aim of this experimental protocol report was to investigate the rehabilitation potential of anodal transcranial Direct Current Stimulation (A-tDCS), combined with IMITAF computerized neuropsychological training, in patients with chronic aphasia following brain injury.

It is assumed that the constant and repeated use of A-tDCS on the perilesional areas, combined with neuropsychological training, may lead to improvements in language skills, mainly in naming, and promote an increase in spontaneous language production and a general recovery of communicative skills.

The secondary aim of this protocol was to find out whether the effects of the neurorehabilitation treatment were maintained one month after stimulation; this data would be obtained through a follow-up assessment.

The present Single Case Study involved an initial assessment of language parameters using behavioral rating scales. This was followed by the administration of the rehabilitation protocol by means of tDCS and finally a textual and qualitative behavioral assessment, post-training, and follow-up.

Design

The present experimental clinical protocol falls into the Single Case Study category. This work involved an initial assessment of language parameters using behavioral rating scales. This was followed by the administration of the rehabilitation protocol by means of a-tDCS, and finally a behavioral re-assessment (Figure 1).

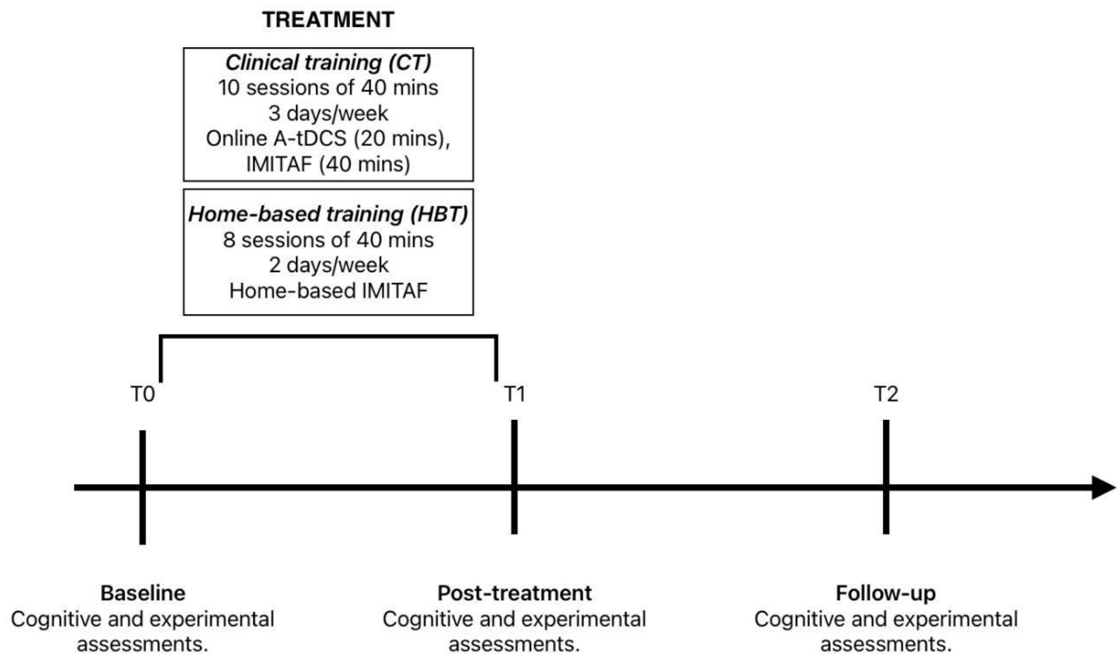


Figure 1. The stimulation protocol lasted a total of 4 weeks and was divided into 2 different modes: Clinical Training (CT) and Home Based Training (HBT). Cognitive and experimental assessments were administered before, after, and 4 weeks after the treatment.

Experimental Clinical Protocol

CASE HISTORY

Mr. V. is a 66-year old right-handed male, native Italian speaker, and with 8 years of schooling. Prior to the traumatic event, he used to work as a small businessman. In September 2018, the patient suffered an ischemic stroke caused by left carotid artery dissection. The ischemic vascular lesion involved the frontal-opercular cortex and basal nuclei, resulting in extensive left thalamo-capsular, occipital and temporo-parietal ischaemic hypodensity, as well as right hemiparesis, mixed transcortical aphasia, characterized by non-fluent and dysfluent speech.

During the first year after the traumatic event, the patient underwent outpatient neurorehabilitation sessions in an Italian hospital. This intervention was aimed at improving the contralateral haemiparesis and the bucco-facial praxic deficit.

On admission to the Puzzle Centre in 2019, one year after the brain injury event, the clinical picture and symptomatology were characterized by:
- severe impairment of oral language encoding, in the absence of written language encoding;
- severe impairment of lexical repetition skill.

Communication was characterized by *conduits d'approche* and dysfunctional mimic-gestural communication efficacy.
Treatments carried out during the rehabilitation period were aimed at improving bucco-facial apraxia, language production and comprehension, implementing mimic-gestural communication efficacy, and monitoring mood.

In 2023, a language assessment was performed with Neuropsychological Examination for Aphasia (ENPA) battery[36] and Aachener Aphasia Test (AAT)[37]. It was not possible to assess performance in lexical decision, repetition and naming tasks. The patient was not able to produce spontaneous language, reading and writing but he was able to perform words and sentences comprehension.

The Test of Attentional Performace (TEA/TAP)[38] and the Attentive Matrices test[39] were also administered, which excluded the presence of attention deficits.

The neurological assessment excluded the presence of mood disorders, hearing or visual impairment. The clinical history excluded episodes of epilepsy, psychosis, major depression, alcohol abuse and/or drug addiction. The patient was not under pharmacological treatment, therefore any interference of a drug with neuromodulatory treatment with A-tDCS was excluded.

The data analyzed in this clinical protocol were collected in accordance with the Declaration of Helsinki. Prior to participation, the patient and the caregiver read and signed an Informed Consent Form.

MATERIALS

Several diagnostic and rehabilitation tools were used for this experimental proposal, and specifically:

- Neuropsychological Examination for Aphasia (ENPA)[36];
- Aachener Aphasia Test (AAT)[37];
- Attentive Matrices[39];
- Test of Attentional Performace (TEA/TAP) [38];
- PC with Pentium I5 processor, Windows 10 operating system and 15 inch screen.
- IMITAF computer software (16 levels), Puzzle Centre Turin, Italy;
- Transcranial direct current stimulation (tDCS HDCstim, Neouronika, Milan, Italy);
- Transcranial Current Stimulation (tDCS).

COMPUTERIZED NEUROPSYCHOLOGICAL TREATMENT ParlaTO

The administration of IMITAF was carried out with the presence of a neuropsychologist, at the rehabilitation centre, or by a trained caregiver, when the training was carried out at home[32]. The treatment can be carried out at home. When used at home, the patient is always supported by a caregiver, who has already been trained in software operation and administration timing. In this case, the caregiver had to ensure that the patient performed the exercise correctly. Any difficulties encountered by the patient and/or caregiver were discussed with the psychologists involved in the study[32]. Mr. V. was assigned IMITAF Level 1, based on the results of the T0 assessment.

The treatment comprised the video presentation of different audiotory-visual tasks, specifically the use of bisyllabic words at the first level. After the viewing and listening phase, the subject was asked to imagine the word or action heard and to repeat it. The facilitator, if necessary, would provide supportive feedback[32].

NEUROREHABILITATION TREATMENT WITH tDCS

The stimulation adopted the HDCstim method (Neouronika, Milan, Italy). The equipment comprised two 35 cm^2 (5 cm × 7 cm) conductive silicone electrodes that were inserted into cellulose sponge pockets moistened with saline and conductive gel to ensure proper electrical conduction. The electrode sizes were chosen to improve the focus of stimulation on the target cortices and to minimize cortical effects under the reference electrode[40]. Based on evidence from the literature review by Zettin et al.[24], the perilesional stimulation area was identified by examining the neurological diagnostic computed tomography (CT) report. The points on the scalp were identified using the International EEG-10/10 system. The use of this system facilitated the daily placement of the electrodes on the scalp and avoided possible positioning errors.

The patient underwent stimulation with monopolar montage (A-tDCS) and intra-cephalic reference, placed on the supraorbital area contralateral to the lesion (Fp2). The stimulation site identified corresponds to the subject's perilesional areas, Brodmann areas 44 and 45, more precisely F5 of the frontal cortex. For safety reasons, a stimulation intensity of 1.5 mA was applied for 20 minutes once a day[24,41](Figure 2).

a)

b)

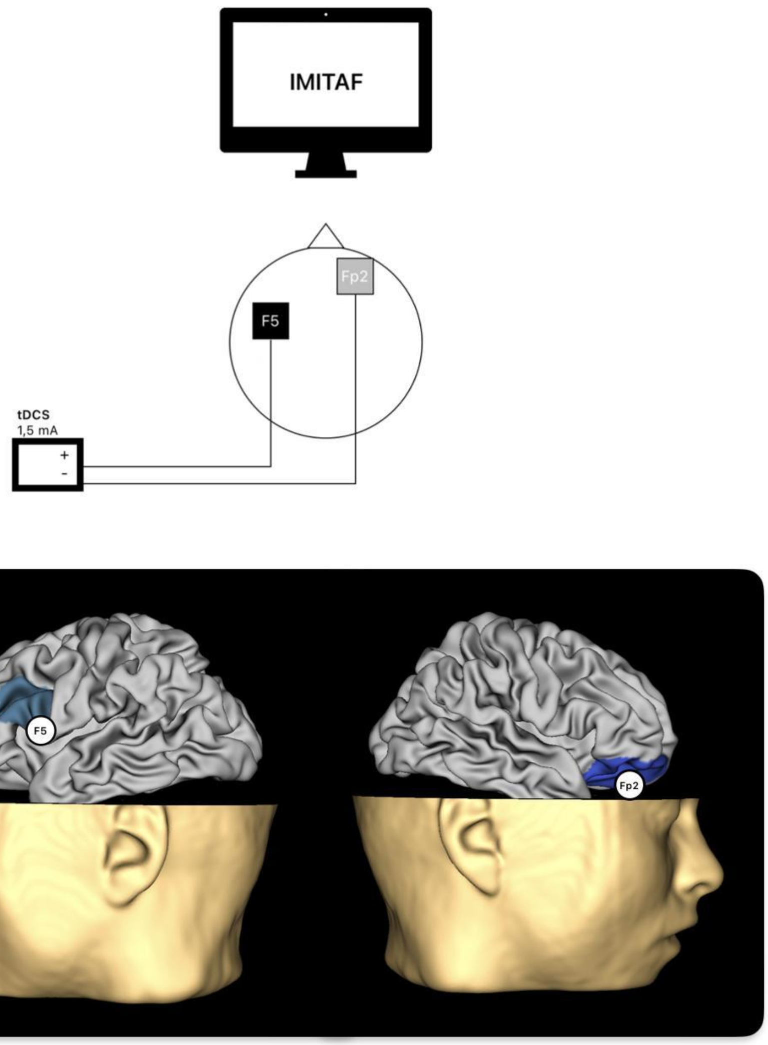


Figure 2. a) Stimulation with monopolar montage (A-tDCS) of perilesional areas (F5). Intra-cephalic reference (Fp2) b) Stimulation sites: F5, frontal lobe premotor cortex area, left hemisphere. Fp2, supraorbital area contralateral to lesion, right hemisphere.

Procedures

STIMULATION PROTOCOL

The stimulation protocol lasted a total of 4 weeks and was divided into 2 different modes (Figure 3):

- **Clinical Training (CT),** which involved 10 treatments carried out at the Puzzle Rehabilitation Centre (Turin, Italy). The treatments were divided into 3 weekly sessions. The tenth session was held on the fourth week. Each session lasted a total of 40 minutes and involved the combined administration of a-tDCS (20-minute online mode) and 40-minute IMITAF training.

- **Home-Based Training (HBT)** made up of 8 treatments carried out at the patient's home. The 8 treatments were divided into 2 weekly sessions spread over the 4 weeks. The total duration of each session was 40 minutes. In this mode, only the IMITAF training was administered to the patient via PC.

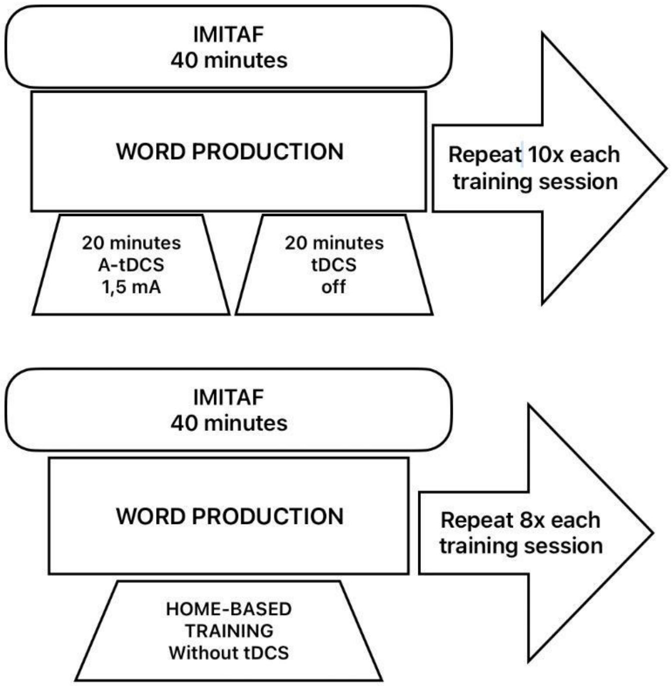


Figure 3. Stimulation protocol with a total duration of 4 weeks, divided into 2 different modes: Clinical Training (CT) and Home-Based Training (HBT).

The stimulation parameters chosen for this experimental design comply with the indications for a safe tDCS use[42,43,44].

During the first therapy sessions, Mr. V. reported itching/burning at the site where the anode was placed. In order to monitor pain/discomfort and adverse effects, a Likert-based rating scale (0 to 10) was created where 0 expressed no discomfort and 10 expressed maximum discomfort. During the first neuromodulatory treatment, the patient reported the highest degree of discomfort, which was equal to 10. To meet this discomfort, the operator administered a film of conductive gel between the skin and the electrode. The itching/burning sensation gradually decreased to level 1.

At each treatment session, the 20-minute tDCS was performed along a 20-minute speech treatment. During this phase, the patient was asked to repeat the words shown on the video in the presence of a caregiver who provided bucco-facial feedback to facilitate the repetition of the target word. The electrodes were then removed and the subject completed the remaining 20 minutes of IMITAF, for a total 40-minute treatment.

A total of 102 high-frequency words were presented. During the training Mr. V. observed and repeated words (*note: words of the Italian repertoire*), such as “Ape”, “Bene”, “Cane”, and words with more complex consonant clusters, such as "“Bravo”, “Corpo”, “Lingua”. The designated facilitator monitored the subject's self-efficacy and motivation.

Results

Mr. V. completed all ten treatment sessions in clinical mode without reporting any adverse effects, such as scalp redness, tingling or headaches.

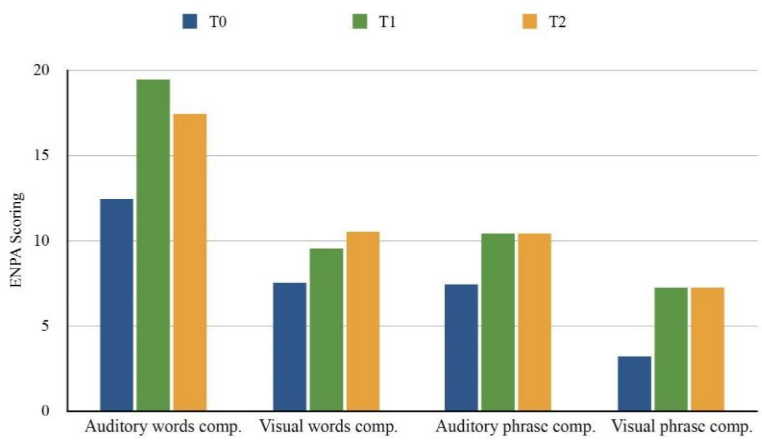
The results of the standardized tests are shown in Graphs 1, and 2. Comparing the raw scores obtained during the baseline assessment (T0) and the post-training assessment (T1), a slight improvement in the auditory/visual words comprehension of or sentences can be seen. In particular, in the ENPA test[36] an improvement of 7 points was observed for auditory words comprehension, 2 points for visual words comprehension, 3 points for auditory sentences comprehension and 4 points for visual sentences comprehension. These scores were maintained at the follow-up assessment (T2), one month after treatment.

The improvement obtained was also reflected in the qualitative analysis of the AAT scores[37], in which an increase in the score from the post-treatment assessment (T1) to the follow-up (T2) of 8 points for listening and reading comprehension was observed.

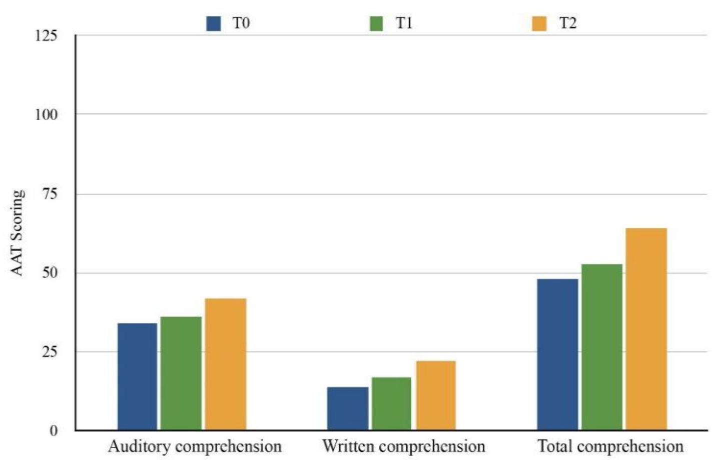
Performance on the Attentive Matrices[39] and the Test of Attentional Performace (TEA/TAP)[38] was examined from pre- to post-treatment to determine whether there was a decrease in performance that could be attributable to the effects of tDCS. Most scores remained stable during the test phases (e.g., TEA/TAP alertness subtest) or increased from pre-treatment (T0) to follow-up (T2) (e.g., Attentive Matrices), thus supporting the idea that prolonged and repeated tDCS was not detrimental to these non-linguistic functions.

Secondary outcomes were identified by qualitative observation of the patient during neurobehavioral training. High-frequency words of the IMITAF Level 1 were considered correct when pronounced in the absence of errors or phoneme substitutions. 244 items were presented, ranging from 13 to 40 items per session. Mr. V. repeated a total of 92 items.

Graph 1



Graph 2



Graphs: Mean task accuracy in three test phases (T0, T1, T2). Neuropsychological Examination for Aphasia (ENPA)36; 2. Aachener Aphasia Test (AAT)37.

Discussion

Results show improvement in auditory/visual comprehension of words/sentences, which maintained one month after treatment (Follow-up, T2). Also in qualitative analysis of scores on the AAT test[37], an increase in score was observed from the post-training assessment (T1) to the follow-up (T2) for listening and reading comprehension. During the training, the patient demonstrated mastery of some high-frequency-use words, such as “Ape”, “Bene”, “Cane”. However, difficulties in reproducing words with more complex consonant clusters persisted, such as “Bravo”, “Corpo”, “Lingua”. In these cases, the operator provided phonological feedback of the target word to encourage continuation of the task and monitor the subject's self-efficacy and motivation. This aspect could have potentially affected performance during treatment sessions. Literature on aphasia behavioral therapy indicates that intervention approaches including both semantic and phonological cues lead to higher performance than interventions which do not implement this approach[45].

However, language performance was not found to be significantly better to make the patient’s language intelligible, but the acquisition of specific high-frequency-use vocabulary generated: increased awareness, increased communicative skills, and consequent improvement in motivation and quality of life. Furthermore, the observed effect of A-tDCS does not seem to depend on engagement of attention or concentration processes. These results suggest that prolonged and repeated tDCS is not detrimental to these non-linguistic functions. Preliminary results and the current data cannot completely rule out the learning, long lasting effect that occurs as a result of repeated application over time due to the involvement of learning mechanisms and plasticity[46].

These results further highlight the potential role of tDCS in modulating and facilitating language performance in individuals presenting with post-stroke aphasia. Online tDCS is based around the idea that cortical activity might increase if the electrical stimulation is paired to specific language tasks[24]. We believe that the improvement induced by tDCS may be due to the method’s ability to trigger adaptive neuroplasticity in neurological patients. Galletta et al.[47] identified four main mechanisms: (1) reactivation of canonical networks that have been partially damaged or rendered dysfunctional by brain injury; (2) recruitment of compensatory networks in mostly contralateral homologous cortical regions; (3) additional recruitment of perilesional areas with suboptimal functioning; and (4) inhibition of ‘maladaptive’ networks[47]. We believe that by using the online A-tDCS paradigm on perilesional areas of stroke patient, we could induce reactivation of canonical networks, additional recruitment of perilesional areas. In addition, considering that spontaneous processes of plastic reorganization after stroke decline rapidly to exhaustion in a few months, the combination of tDCS stimulation, could allow to prolong the timeframe within rehabilitation treatment can be positively administered. Evidence demonstrates that intensive rehabilitation is consistently related with increased therapeutic success[47]. A massive practice for short periods of time, as in the case of IMITAF, may be more effective than longer-lasting but less frequent or intensive practice[32].

Combined treatment of the two techniques would maximize the rehabilitation effect, as tDCS pre-activates damaged neural circuits, making them more responsive to behavioral rehabilitation stimulation through digital devices[24]. Thus, it appears that tDCS does not directly affect performance, but enhances the skills involved in the task performed[48]. It is important to note that tDCS emerges as an extremely promising technique that is both easy to use and free of side effects when used according to the guidelines[42,43,44].

It is acknowledged that these findings are preliminary, and the present data cannot entirely rule out the practice effect. Therefore, future studies should use parallel versions of the same neuropsychological assessments to evaluate cognitive performance pre- and post-stimulation.

Due to the use of a single-case design, the results should be verified in a larger group of participants. Future studies should consider crucial elements, such as the necessity to include large randomized controlled trials to monitor patients' progress over time. However, finding a large homogeneous sample and drawing universal conclusions from the outcome of a study can be complex and often unfeasible. When configuring brain injury treatment, it is important to select the right parameters and stimulation site based on the patient's individual characteristics. Structural imaging from the individual's medical record, such as MRI or CT, can help clinicians better tailor the treatment. Personalised stimulation could therefore optimise the patient's recovery[24]. Thus, our single-case study might pave the way to the application of Online A-tDCS combined with individualized speech therapy in patients with aphasia.

Conclusions

In this experimental clinical protocol, A-tDCS was applied in combination with IMITAF computerized neuropsychological training. The intensive treatment, which specifically works on action, observation and imitation, recalls the principles of AOT. In particular, language is closely interconnected with gestures, based on the "motor theory of speech perception"[49]. Gestures and actions observation can represent a powerful tool in rehabilitation. According to the principles of AOT, observation and imitation of a gesture performed by a third person can promote a faster and more effective recovery of motor impairments[50] and language deficits[30,1]. It is therefore possible to suggest that simple systematic and repeated observation of actions may be an effective alternative therapeutic strategy for word retrieval in aphasic patients[24]. In our single-case study, the behavioral intervention included video presentation of different audiotory/visual tasks using bisyllabic words. After the viewing and listening phase, the subject was asked to imagine the word or action heard and to repeat it[32]. Together with neuropsychological training, the constant and repeated use of A-tDCS, on the perilesional areas, contributed to improvements in language skills, thus promoting an overall recovery of communicative skills in an individual with chronic post-stroke non-fluent aphasia[24]. The use of non-invasive brain stimulation techniques to improve performance through methods such as tDCS represents an attractive prospect. Relatively safe and versatile[42,51], tDCS is increasingly promoted for motor and cognitive improvement in healthy and clinical populations[52,53]. Despite a growing scientific literature, the effects of tDCS remain uncertain[54,55]. In addition to considerable variability in reported effects, studies suggest high inter-individual differences in tDCS response[56,57]. Examinations of technical factors such as electrode placement[58,59], intensities[60,61], and stimulation schedule[62] have not adequately resolved inconsistencies in reported tDCS effects or the wide intra- and inter-individual variability in tDCS response.

Acknowledgments:

Special acknowledgements for this paper are due to Mrs. Eleonora Di Fatta for her valuable assistance in the translation of the text.

References

1. Marangolo P, Caltagirone C. Options to enhance recovery from aphasia by means of non-invasive brain stimulation and action observation therapy. *Expert Review of Neurotherapeutics*. 2013;14(1):75-91. doi:10.1586/14737175.2014.864555
2. Crinion J. Transcranial direct current stimulation as a novel method for enhancing aphasia treatment effects. *European Psychologist*. 2016;21(1):65-77. doi:10.1027/1016-9040/a000254
3. Wade DT, Hewer RL, David R, Enderby P. Aphasia after stroke: natural history and associated deficits. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1986;49(1):11-16. doi:10.1136/jnnp.49.1.11
4. Watila MM, Balarabe SA. Factors predicting post-stroke aphasia recovery. *Journal of the Neurological Sciences*. 2015;352(1-2):12-18. doi:10.1016/j.jns.2015.03.020
5. Hamilton RH. Neuroplasticity in the language system: Reorganization in post-stroke aphasia and in neuromodulation interventions. *Restorative Neurology and Neuroscience*. 2016;34(4):467-471. doi:10.3233/rnn-169002
6. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke*. 1981;12(6):723-725. doi:10.1161/01.str.12.6.723
7. Hillis AE, Wityk RJ, Barker PB, Caramazza A. Neural regions essential for writing verbs. *Nature Neuroscience*. 2002;6(1):19-20. doi:10.1038/nn982
8. Hillis AE, Kleinman JT, Newhart M, et al. Restoring cerebral blood flow reveals neural regions critical for naming. *The Journal of Neuroscience*. 2006;26(31):8069-8073. doi:10.1523/jneurosci.2088-06.2006
9. Carrera E, Jones PS, Morris RS, et al. Is neural activation within the rescued penumbra impeded by selective neuronal loss? *Brain*. 2013;136(6):1816-1829. doi:10.1093/brain/awt112
10. Thiel A, Heiss W. Imaging of microglia activation in stroke. *Stroke*. 2011;42(2):507-512. doi:10.1161/strokeaha.110.598821
11. Turken AU, Dronkers NF. The Neural Architecture of the Language Comprehension Network: Converging Evidence from Lesion and Connectivity Analyses. *Frontiers*. 2011;5. doi:10.3389/fnsys.2011.00001
12. Thompson CK, Ouden DBD. Neuroimaging and recovery of language in aphasia. *Current Neurology and Neuroscience Reports*. 2008;8(6):475-483. doi:10.1007/s11910-008-0076-0
13. Saur D, Lange R, Baumgaertner A, et al. Dynamics of language reorganization after stroke. *Brain*. 2006;129(6):1371-1384. doi:10.1093/brain/awl090
14. Turkeltaub PE, Messing SB, Norise C, Hamilton RH. Are networks for residual language function and recovery consistent across aphasic patients? *Neurology*. 2011;76(20):1726-1734. doi:10.1212/wnl.0b013e31821a44c1
15. Turkeltaub PE, Coslett HB, Thomas A, et al. The right hemisphere is not unitary in its role in aphasia recovery. *Cortex*. 2012;48(9):1179-1186. doi:10.1016/j.cortex.2011.06.010
16. Shimizu T, Hosaki A, Hino T, et al. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. *Brain*. 2002;125(8):1896-1907. doi:10.1093/brain/awf183
17. Thiel A, Habedank B, Herholz K, et al. From the left to the right: How the brain compensates progressive loss of language function. *Brain and Language*. 2006;98(1):57-65. doi:10.1016/j.bandl.2006.01.007
18. Winhuisen L, Thiel A, Schumacher B, et al. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia. *Stroke*. 2005;36(8):1759-1763. doi:10.1161/01.str.0000174487.81126.ef
19. Cheng W, Li Y, Cheng B, et al. Effects of transcranial direct current stimulation over the right hemisphere on naming ability in patients with poststroke aphasia: A meta-analysis. *Journal of Neurolinguistics*. 2021;58:100986. doi:10.1016/j.jneuroling.2021.100986
20. Heiss W, Thiel A. A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language*. 2006;98(1):118-123. doi:10.1016/j.bandl.2006.02.002
21. Torres J, Drebing D, Hamilton RH. TMS and tDCS in post-stroke aphasia: Integrating novel treatment approaches with mechanisms of plasticity. *Restorative Neurology and Neuroscience*. 2013;31(4):501-515. doi:10.3233/rnn-130314
22. Anglade C, Thiel A, Ansaldo AI. The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: A critical review of literature. *Brain Injury*. 2014;28(2):138-145. doi:10.3109/02699052.2013.859734
23. Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *NeuroImage*. 2008;39(4):2038-2046. doi:10.1016/j.neuroimage.2007.10.008

24. Zettin M, Bondesan C, Nada G, Varini M, Dimitri D. Transcranial Direct-Current Stimulation and Behavioral Training, a promising tool for a Tailor-Made Post-stroke Aphasia rehabilitation: A review. *Frontiers in Human Neuroscience*. 2021;15. doi:10.3389/fnhum.2021.742136
25. van Oers, C. A. M. M., Vink, M., van Zandvoort, M. J. E., van der Worp, H. B., de Haan, E. H. F., Kappelle, L. J., Ramsey, N. F., & Dijkhuizen, R. M. (2010). Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. NeuroImage, 49(1), 885–893. https://doi.org/10.1016/j.neuroimage.2009.08.057
26. Marcotte K, Adrover-Roig D, Damien B, et al. Therapy-induced neuroplasticity in chronic aphasia. *Neuropsychologia*. 2012;50(8):1776-1786. doi:10.1016/j.neuropsychologia.2012.04.001
27. Thiel A, Zumbansen A. The pathophysiology of post-stroke aphasia: A network approach. *Restorative Neurology and Neuroscience*. 2016;34(4):507-518. doi:10.3233/rnn-150632
28. Krönke KM, Mueller K, Friederici AD, Obrig H. Learning by doing? The effect of gestures on implicit retrieval of newly acquired words. *Cortex*. 2013;49(9):2553-2568. doi:10.1016/j.cortex.2012.11.016
29. Hanlon RE, Lux WE, Dromerick AW. Global aphasia without hemiparesis: language profiles and lesion distribution. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1999;66(3):365-369. doi:10.1136/jnnp.66.3.365
30. Small SL, Llano DA. Biological approaches to aphasia treatment. *Current Neurology and Neuroscience Reports*. 2009;9(6):443-450. doi:10.1007/s11910-009-0066-x
31. Looeiyan N, Kianfar F, Ghasisin L. The introduction of IMITATE-R and its comparison with the IMITATE treatment method in the naming ability of two Persian speaking aphasic patients. *Neuropsychological Rehabilitation*. 2018;30(4):709-730. doi:10.1080/09602011.2018.1496940
32. Zettin M, Leopizzi M, Galetto V. How does language change after an intensive treatment on imitation? *Neuropsychological Rehabilitation*. 2018;29(9):1332-1358. doi:10.1080/09602011.2017.1406861
33. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *The Neuroscientist*. 2011;17(1):37-53. doi:10.1177/1073858410386614
34. Sacco K, Galetto V, Dimitri D, et al. Concomitant use of transcranial direct current stimulation and Computer-Assisted training for the rehabilitation of attention in traumatic brain injured patients: behavioral and neuroimaging results. *Frontiers in Behavioral Neuroscience*. 2016;10. doi:10.3389/fnbeh.2016.00057
35. Brown RE. Donald O. Hebb and the Organization of Behavior: 17 years in the writing. *Molecular Brain*. 2020;13(1). doi:10.1186/s13041-020-00567-8
36. Capasso, R., & Miceli, G. (2001). *Esame Neuropsicologico per l'Afasia: ENPA* (Vol. 4). Springer Science & Business Media.
37. Luzzatti C, Davidoff J. Impaired retrieval of object-colour knowledge with preserved colour naming. Neuropsychologia. 1994;32(8):933-950. doi:10.1016/0028-3932(94)90044-2
38. Zimmermann P., and Fimm, B. Testbatterie zur Aufmerksamkeitsprüfung (TAP). Würselen: Psytest, 1992.
39. Spinnler H, Tognoni G (1987) Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci suppl 8 to 6: 1–120
40. Nitsche MA, Doemkes S, Karaköse T, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of Neurophysiology*. 2007;97(4):3109-3117. doi:10.1152/jn.01312.2006
41. De Aguiar V, Bastiaanse R, Capasso R, et al. Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs? *Frontiers in Behavioral Neuroscience*. 2015;9. doi:10.3389/fnbeh.2015.00190
42. Bikson M, Grossman P, Thomas C, et al. Safety of transcranial direct current stimulation: Evidence Based Update 2016. *Brain Stimulation*. 2016;9(5):641-661. doi:10.1016/j.brs.2016.06.004
43. Antal A, Alekseichuk I, Bikson M, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*. 2017;128(9):1774-1809. doi:10.1016/j.clinph.2017.06.001
44. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087
45. Brady M, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database of Systematic Reviews. Published online May 16, 2012. doi:10.1002/14651858.cd000425.pub3
46. Filippetti, M., Amico, A. P., Mazzucchelli, M., Perin, C., Cornaggia, C. M., Megna, M. (2021).

Tecniche di stimolazione cerebrale non invasiva: la stimolazione elettrica transcranica. Revisione Narrativa Della Letteratura. Giornale italiano di Medicina Riabilitativa, 36(3), 23-29.

47. Galletta EE, Vogel-Eyny A. Translational treatment of aphasia combining neuromodulation and behavioral intervention for lexical retrieval: implications from a single case study. Frontiers in Human Neuroscience. 2015;9. doi:10.3389/fnhum.2015.00447
48. Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Molecular Psychiatry*. 2019;25(2):397-407. doi:10.1038/s41380-019-0499-9
49. Liberman AM, Mattingly IG. The motor theory of speech perception revised. *Cognition*. 1985;21(1):1-36. doi:10.1016/0010-0277(85)90021-6
50. Ertelt D, Small SL, Solodkin A, et al. Action observation has a positive impact on rehabilitation of motor deficits after stroke. *NeuroImage*. 2007;36:T164-T173. doi:10.1016/j.neuroimage.2007.03.043
51. Matsumoto H, Ugawa Y. Adverse events of tDCS and tACS: A review. *Clinical Neurophysiology Practice*. 2017;2:19-25. doi:10.1016/j.cnp.2016.12.003
52. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*. 2014;85:895-908. doi:10.1016/j.neuroimage.2013.07.083
53. Zhao Q, Wang J, Li Z, Song L, Li X. Effect of anodic transcranial direct current stimulation combined with speech language therapy on nonfluent poststroke aphasia. *Neuromodulation: Technology at the Neural Interface*. 2021;24(5):923-929. doi:10.1111/ner.13337
54. Bonaiuto J, Bestmann S. Understanding the nonlinear physiological and behavioral effects of tDCS through computational neurostimulation. In: *Progress in Brain Research*. ; 2015:75-103. doi:10.1016/bs.pbr.2015.06.013
55. Lee TL, Lee H, Kang N. A meta-analysis showing improved cognitive performance in healthy young adults with transcranial alternating current stimulation. *Npj Science of Learning*. 2023;8(1). doi:10.1038/s41539-022-00152-9
56. Li L, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in Cellular Neuroscience*. 2015;9. doi:10.3389/fncel.2015.00181
57. Vergallito A, Feroldi S, Pisoni A, Lauro LJR. Inter-Individual Variability in TDCS Effects: A narrative review on the contribution of stable, variable, and contextual factors. *Brain Sciences*. 2022;12(5):522. doi:10.3390/brainsci12050522
58. Penolazzi B, Pastore M, Mondini S. Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency. *Behavioural Brain Research*. 2013;248:129-135. doi:10.1016/j.bbr.2013.04.007
59. Filmer HL, Mattingley JB, Dux PE. Modulating brain activity and behaviour with tDCS: Rumours of its death have been greatly exaggerated. *Cortex*. 2020;123:141-151. doi:10.1016/j.cortex.2019.10.006
60. Underwood E. Cadaver study challenges brain stimulation methods. *Science*. 2016;352(6284):397. doi:10.1126/science.352.6284.397
61. Vöröslakos M, Takeuchi Y, Brinyiczki K, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*. 2018;9(1). doi:10.1038/s41467-018-02928-3
62. Katz B, Au J, Buschkuehl M, et al. Individual differences and long-term consequences of TDCS-augmented cognitive training. *Journal of Cognitive Neuroscience*. 2017;29(9):1498-1508. doi:10.1162/jocn_a_01115