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"BEYOND BROCA AND WERNICKE:

NEUROMODULATION IN APHASIA REHABILITATION"

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INTRODUCTION

During the 1990s, a revolutionary process began in the neuroscientific field, which strongly influenced research in neurorehabilitation yielding promising new therapies for improving behavioral and cognitive abilities in persons with neurological damage (Taub et al., 2002). From a modular approach which for decades has assigned each cognitive function (i.e., memory, language, attention) to specific cerebral regions, neuroscience research has moved to a connectionist perspective, “the connectome era” which refers to widely distributed cerebral networks as critical drivers for cognition and behavior (Sutterer & Tranel, 2017).

This paradigm shift has also occurred in aphasia, an acquired language disorder affecting about one-third of people suffering from left-cerebral artery stroke (Rohde et al., 2013). Indeed, advances in neuroimaging have brought new insights to the neural basis of speech and language processing. From the well-known “Wernicke-Lichtheim model” to the current “dual stream model”, the field of language neurobiology has made great strides and is now ready to adopt a modern integrative approach (Gupta & Padma Srivastava, 2020).

This approach reveals that treatment-related brain changes due to language recovery involve not only regions traditionally considered as the “Language areas” but also structures subserving other domains such as the motor cortex (Jirak et al., 2010), the cerebellum (Geva et al., 2021) and the prefrontal regions (Gertel et al., 2020). Thus, in aphasia, from language treatments specifically focused on language protocols, to date, we can plan therapeutic approaches which potentiate these structures to support language recovery.

To improve the effectiveness of aphasia treatments, several researchers have also investigated adjunctive supports in clinical practice. Over the past decade, the most promising results have been reported using non-invasive brain stimulation techniques such as Transcranial Direct Current Stimulation (tDCS) (NIBS; Breining & Sebastian, 2020).

This dissertation aims to further investigate the role of tDCS in aphasia rehabilitation giving me the opportunity to publish three scientific articles during my three years of Ph.D.

The first chapter introduces the traditional theory of language representation referring to the well-known Wernicke-Lichtheim Model which is considered as the synthesis of the major aphasia studies from the late 19th century to the first half of the 20th century. The chapter ends with emphasizing the limitations of this model.

The second chapter outlines the shift from a modular representation of language to the modern concept of large-scale brain networks in the context of neuroimaging studies. Particular emphasis is given to the interaction between the language, the motor, and the executive system.

In the third chapter, tDCS studies in aphasia rehabilitation are reported which starting from the modularity approach to language representation moved to the more recent connectionist approach, thus, applying tDCS over less traditional areas, such as the motor and the prefrontal region.

The fourth chapter includes the three experiments that I carried out during my Ph.D. Following the traditional approach, the first study highlights the effectiveness of tDCS over the left temporo-parietal cortex combined with a language treatment for the recovery of writing abilities in persons with severe agraphia.

In the second experiment, the use of transpinal direct current stimulation (tsDCS) is further investigated. This choice starts from the well-known embodied cognition theory which posits a close interaction between the language and the motor system. Thus, the hypothesis is advanced that different motor regions, such as the motor cortex, the cerebellum, and the spinal cord might act as ancillary structures to support language recovery. In particular, since the stimulation of these structures activates the sensorimotor areas, this would, in turn, facilitate the recovery of those aspects of language characterized by motor properties, such as action verbs and speech articulation.

The last experiment reports a tDCS study which confirms the strong relationships between the language and the executive system. Indeed, executive functions include high-order cognitive abilities such as cognitive flexibility, planning and problem solving which enable humans to achieve goals, to adapt themselves to novel everyday life situations, and to manage social interactions. This highlights the possibility to rely on executive functions to recover functional communication in persons with severe aphasia.

To all persons with aphasia, I have cared for

CHAPTER I

THE LOCALIZATIONIST APPROACH TO LANGUAGE REPRESENTATION

1.1 Definition of aphasia

Aphasia is an acquired language disorder that usually occurs in patients with left-cerebral artery stroke (Basso et al., 2013; Rohde et al., 2013). It impairs the person's ability to make use of language with heterogeneous symptoms varying in their severity and degree of involvement across the different linguistic modalities, including the expression and comprehension of language, reading and writing (Basso, 2003). For example, variations in the severity of expressive impairments may range from the patient's occasional inability to find the correct word to telegraphic and very reduced speech output (Marangolo & Caltagirone, 2014). The presence of aphasia, independently of its degree of severity, always has sudden and long-lasting negative impacts on friendships, social engagements, quality of life, and psychological wellbeing, due to the loss of autonomy in everyday life (Engelter et al., 2006; Mattioli, 2019; Spaccavento et al., 2014).

Stroke is the most common cause of aphasia (in Europe 1 million new cases per year) and its incidence in Italy ranges from 1.8/1.000 to 4.5/1.000 new cases per year, with a prevalence of 6.5/100, which is similar to other high-income countries (Béjot et al., 2016). Incidence of stroke increases with age and is higher in men than in women (mean age at onset 75 years in men and 76.6 years in women), with a peak of incidence in subjects older than 85 (Feigin et al., 2009; Sacco et al., 2011). About 40% of all people who experience a stroke develop aphasia, more frequently in the case of a cardioembolic stroke if thrombolysis is performed (Engelter et al., 2006; Mattioli, 2019). After an initial spontaneous recovery, most notably during the first two to three months following stroke onset, language improvement can occur in response to behavioral interventions. This improvement might also take place in the chronic phase (> six months) (Fama &Turkeltaub, 2014).

Given the great importance of language for human beings, in persons with aphasia full reintegration into family, society and working life might never be achieved. This can lead to a vicious circle whereby communication difficulties are often accompanied by mood disorders, anxiety, and depression, which further worsen the patient's health-related quality of life (Hilari et al., 2003).

1.2 Milestones in the history of aphasia

1.2.1 Broca and Wernicke's contribution

In 1861, Paul Broca (1824-1880), a French physician, presented a detailed report to the Société d'Anthropologie de Paris, in which he described the case of a 51-year-old patient named Louis Victor Leborgne. Leborgne was a Parisian craftsman who had lost the ability to speak at the age of 30 and could only pronounce the syllables "Tan Tan" (Domanski, 2013). Although he lost the ability to speak, he was able to communicate with gestures, despite a paralysis affecting the muscles of his right arm. Even with the loss of speech, Broca was able to ascertain that Leborgne could understand language. The doctor visited the patient six days before his death on 17 April 1861 and he hypothesized that the loss of language was due to a cerebral lesion located in the left hemisphere. After his death, a close examination of the lesion site through autopsy revealed that the area predominantly affected by the brain damage was the third frontal circumvolution of the left hemisphere. After collecting a few additional cases, Broca claimed that a lesion in the third left frontal gyrus results in "*aphemie*", a disturbance in the articulation of words — which impairs the ability to produce voluntary speech. The name proposed by Broca for this speech impairment ("*aphemie*") was not widely accepted in the medical literature, mainly due to the discussion which followed led by the French physician Armand Trousseau (1801–1867). Soon after, the term "*aphasia*" gained the acceptance of the medical world. In 1865, Broca claimed that only the left frontal gyrus was responsible for speech production, thus, he not only established the principle of localization, but he also introduced the notion of hemispheric differences. The latter concept was quickly adopted in the literature and speech began to be interpreted in terms of cerebral dominance (Harris, 1991).

Shortly after Broca published his findings, Carl Wernicke (1848–1905), at the young age of 26, wrote one of the most influential 19th-century monographs on aphasia, *Der*

Aphasische Symptomenkomplex (Wernicke, 1874). He worked in Breslau but visited the Viennese neuropsychiatrist and neuroanatomist Theodor Meynert, who inspired him to study language comprehension deficits (Eling & Whitaker, 2009). After his stay in Vienna, Wernicke studied 10 patients, and post-mortem analyses of the lesions in four of them which led him to affirm that language comprehension is localized in the posterior part of the left superior temporal gyrus, in an area still named Wernicke's area.

In 1874, the Wernicke's model was illustrated from observing patients with fluent speech and severe comprehension difficulties. This model reports a dichotomy of centers for storing the auditory and motor images of words, located at the level of the auditory and motor association areas, and connected by a bundle of fibers running through the arcuate fasciculus. The auditory and motor images of words are independent, but they both represent their lexical phonological representation. Wernicke also hypothesized the existence of a third center, which contains the conceptual representations of words (their meaning), i.e., a network of knowledge that is distributed over a large part of the cortex of both hemispheres and does not constitute a localized center. This network of conceptual knowledge is connected with the auditory and motor lexical representation centers. According to the Wernicke's model (1874), selective lesion of specific areas can lead to different clinical forms:

- The lesion of the auditory pathways, before they reach the auditory-verbal center, results in deafness without aphasia.
- The lesion of the center, which contains the auditory images of words, causes "sensory aphasia" in which words are perceived as indistinct sounds.
- The destruction of the association fibers, which connect the auditory-verbal center with Broca's area, leaves both the articulatory and auditory-verbal images intact; the patient, therefore, does not suffer from a comprehension deficit nor from a deficit of language production, but rather from a deficit in converting the image of a perceived word into the corresponding verbal output, i.e., a repetition deficit. The patient is aware of his errors.
- The lesion of the verbal-motor center causes Broca aphasia, characterized by deficits in production in the absence of comprehension disorders.

- The lesion of the fibers connecting the verbo-motor center to the cranial nerve nuclei involved in articulatory activity gives rise to dysarthria with partially intelligible speech.

The criticisms that have been levelled at Wernicke's model are essentially both theoretical and empirical. Firstly, the author was criticized because in his model he considered language solely in audio-phonatory terms, i.e., in sensory-motor terms, without considering the semantic-conceptual components. Secondly, the model was considered not exhaustive in explaining the wide range of verbal disorders that can be described in people with aphasia (PWA) (Tremblay & Dick, 2016).

1.2.2 Lichtheim and Geschwind's contribution

In 1885, Ludwig Lichtheim published a paper describing a model of language processing stemming from Broca and Wernicke's work. This model named either the Wernicke–Lichtheim or classical model of aphasia were both neuroanatomical and functional, predicting the impact on language due to damage to various brain regions (Lichtheim, 1885). It served as the foundation for classifying the types of aphasia already observed as well as providing a means for predicting aphasia types not yet observed but assumed logically possible based on theoretical considerations. Lichtheim presented the model as a simple diagram identifying three language-related centers within the brain, the neural pathways connecting them, and the possible lesion sites associated with seven distinct types of aphasia. In developing the model, Lichtheim endorsed Wernicke's views that the brain has two main centers in the left hemisphere underpinning language processing. Specifically, Lichtheim assumed that the left superior temporal gyrus (i.e., Wernicke's area) is responsible for decoding speech input and guiding speech production, while the left inferior frontal gyrus (i.e., Broca's area) for storing the motor programs needed to control the vocal apparatus during speech production. Lichtheim specified a third structure — the concept center — as the storage for word concepts. Neural fibers connect the two language centers to the concept center as well as to the peripheral structures responsible for auditory word perception and for controlling the muscle movements involved in speech production. The Wernicke–Lichtheim model has provided generations of clinicians with a framework for classifying different aphasia syndromes.

Characterizations of aphasia syndromes relate to the nature of information flow between the various components of the model. Basic operation of the model for spoken language comprehension begins in Wernicke's area by accessing the phonological properties of words. This information then moves to the concept center to activate the conceptual representations. Finally, the information moves to Broca's area, where grammatical processing takes place and where instructions are held for word pronunciation. For spoken language production, the activation of the concept center stimulates the retrieval of the phonological representations of words in the Wernicke's area, followed by the activation of the corresponding articulatory instructions in Broca's area. The Wernicke–Lichtheim model proposes seven aphasia syndromes (Lichtheim, 1885). Broca's aphasia and Wernicke's aphasia result from lesions to the two main language centers specified in the model.

- In Broca's aphasia, language comprehension remains relatively intact, but the production is characterized by errors in sequencing and coordination that cause articulatory dysfluency.
- In Wernicke's aphasia, comprehension deficits occur along with the production of neologisms and paraphasias.
- The remaining five types of aphasia result from lesions to pathways connecting the language centers, the concept center, or the peripheral structures.
- Conduction aphasia results from a lesion in the fibers connecting Wernicke's and Broca's areas; it is characterized by impairments in repetition.
- Transcortical sensory aphasia results from disruption between Wernicke's and the concept center. Such a lesion causes comprehension deficits, although the ability to repeat remains intact.
- Transcortical motor aphasia — resulting from a lesion between the concept and the Broca's area — again spares repetition skills but is otherwise similar to Broca's aphasia in symptom characteristics.
- Subcortical sensory aphasia stems from a lesion between the auditory periphery and Wernicke's area and leads to auditory agnosia or pure word deafness. Within this aphasia type, a person fails to understand spoken words but does not make errors in word production.

- Subcortical motor aphasia results from a lesion between Broca's area and the peripheral oral musculature and it is alternatively labeled as dysarthria, a motor speech disorder.

Later, during the 20th century, Norman Geschwind (1926-1984), a pioneering American behavioral neurologist, revisited the Wernicke-Lichtheim model for the neuroanatomy of language so that the model is now known as the "Wernicke-Geschwind" model (Geschwind, 1970). Geschwind reinterpreted the functional role of the areas which connect the language centers. In this regard, a prominent role is assigned to the inferior parietal lobe of the left hemisphere, which includes the angular gyrus BA39) and the supramarginal gyrus (BA40). These regions, presenting anatomical connections with the auditory (BA41 and BA42), somesthetic (BA7) and visual (BA18 and BA19) associative cortical areas, constitute cross-modal associative regions in which word sounds are linked to corresponding sensory information. From this point of view, according to Geschwind (1970), aphasic syndromes can be interpreted as the result of lesions in the speech centers and as the product of disconnections between these centers. Overall, the anatomo-functional model of language, built from the study of motor aphasia and sensory aphasia described so far, known today as the Wernicke-Lichtheim-Geschwind model (Schwartz, 1984), is based on the idea that it is possible to anatomically identify Broca's area and Wernicke's area (Schwartz, 1984). This model also assumes strong functional differences among Broca's and Wernicke's area, i.e.: Broca's area is considered crucial for the articulatory planning necessary for speech production, while Wernicke's area is considered crucial for the recognition of speech sounds.

1.3 Classification of aphasia

Since the 19th century, the existence of several aphasic syndromes has been well established. Generally, two main classification criteria have been adopted over time to identify the different forms of aphasia: speech fluency and repetition (Vallar & Papagno, 2018). The speech of PWA may be fluent or non-fluent. Fluent aphasia is characterized by a speech that tends to be abundant, where verbal jargon, i.e., sequences of words that, although existing in the patient's spoken language, give rise to content that lacks logical meaning, can be evidenced. In some cases, the subject may produce the so-called neologistic jargon in which a sequence of non-real words is observed. Substitutions of words belonging to the same semantic category named semantic paraphases (e.g., table-chair), or to different semantic categories named verbal paraphases (table-lion) may often occur. There may also be substitutions, omissions and/or transpositions of phonemes within words, referred to as phonological paraphases (e.g., table-trees), non-real words, referred to as neologisms (e.g., catampus). Perseveration phenomena can also be observed whereby the patient tends to repeat a word or phrase more than once. Prosody, on the other hand, characterized by pauses and variations in intonation, is relatively preserved. Often the fluent PWA are affected by anosognosia, i.e., he/she is unaware of his/her deficit.

In non-fluent aphasia, speech is syntactically poor, expressed with slowness and difficulty if concomitant articulation deficits are present. When the articulatory disorder is pronounced, it can result in a syndrome called "*apraxia of speech*", a motor speech disorder characterized by an impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sounds (Wertz et al., 1991). The syntactic deficit is characterized by agrammatism, which consists of sentences composed mostly of nouns and a few verbs in the infinitive form. Articles, pronouns, and conjunctions may be omitted, resulting in telegraphic language. In both fluent and non-fluent forms, the presence of anomia is always observed: the patient is unable to retrieve the word even though he clearly shows that he is able to activate the corresponding meaning (e.g., zebra: it is an animal, striped, lives in Africa).

In the non-fluent/fluent category, the most frequently reported aphasic syndromes are as follows (Goodglass & Kaplan, 1972):

- Non-fluent Aphasia Syndromes: Broca's aphasia, global aphasia, transcortical motor aphasia and mixed transcortical aphasia.
- Fluent Aphasia Syndromes: Wernicke's aphasia, conduction aphasia, transcortical sensory aphasia, and anomic aphasia

1.3.1 Non-fluent aphasia syndromes

1.3.1.1 Broca's aphasia

It is a prototypical form among non-fluent aphasia syndromes, and it is considered a core deficit of syntactic and/or articulatory skills. Phonological and semantic-lexical abilities are relatively intact. It is characterized by agrammatism and telegraphic language: short and simple sentences, verbs in the infinitive form, elisions of pronouns, articles, auxiliaries, prepositions, lack of concordance between sentence elements. Production and repetition skills are impaired, while comprehension appears mostly functionally preserved but deficient, especially for syntactically complex sentences. Anomic and articulatory errors are frequent. Broca's aphasia may present with concomitant neurological deficits such as partial or total paralysis of the right upper and/or lower limb (hemiparesis), right visual field loss (hemianopsia) and/or possible disturbance of sensation in the right upper and or lower limb (hemianesthesia). The brain area associated with this type of aphasia is the left frontal third circumvolution, and in most patients, the lesion may also extend to the fronto-parietal operculum and insula. Rare cases of Broca's aphasia due to lesions affecting only retrolateral regions of the left hemisphere have also been observed.

1.3.1.2 Global aphasia

It is the most severe form of non-fluent aphasia. Speech is limited to a few stereotyped forms (recurring syllabic fragments), and there is almost always a severe articulatory deficit. All language modalities are affected by global aphasia — speaking, comprehension, reading, and writing. Patients with global aphasia may be able to utter automatic or stereotypic responses (e.g., "yes" and "no") but do so unreliably. As with the other aphasias, global aphasia is most commonly the result of a stroke in the middle cerebral artery that supplies blood to the lateral surface of the left hemisphere of the brain. Not surprisingly, lesions necessary for a persisting, chronic global aphasia are generally quite large and encompass large portions of the left peri-Sylvian region. Global aphasia may present with concomitant neurological deficits, such as partial or total paralysis of the left upper and/or lower limb (hemiparesis), left visual field loss (hemianopsia) and/or possible sensory disturbances of the left upper and/or lower limb (hemianesthesia). In some patients, the condition evolves from global aphasia to other less severe aphasic syndromes, such as Broca's aphasia.

1.3.1.3 Transcortical motor aphasia

Transcortical motor aphasia is sometimes known as dynamic aphasia or anterior isolation syndrome. Functionally, the causal lesion separates the processing of speech from the mechanisms for initiating the action to speak. Patients with transcortical motor aphasia tend to appear mute, or nearly so, and may even have an associated general akinesia, an inability to initiate action. Although transcortical motor aphasia impairs the ability to initiate speech, once such patients begin talking, speech output is typically relatively intact. Comprehension is relatively normal, as is repetition. Prosody, articulation, and grammatical structure remain quite preserved even if verbal output is interrupted by incomplete sentences, verbal paraphasias, or false starts. When asked to say something, or otherwise initiate a response without cues, these patients have a great deal of difficulty in responding. However, performance is characteristically flawless when asked to repeat words, phrases, or sentences. There might be different compromised abilities in word retrieval, with some patients being able to perform well on tasks such as object and verb naming. Verbal output may improve if related to common, repetitious material. The lesions that lead to transcortical motor aphasia are typically found on the mesial surface of the anterior left frontal lobe, near the supplementary motor cortex, or along the lateral aspect of the left frontal lobe; in either case these lesions fall outside of what is traditionally thought of as Broca's area. Presumably, the lesions impinge on an anterior cortical or subcortical site that forms part of a circuit linking the motor speech area with the supplementary motor area and certain limbic structures considered essential for initiating speech and other actions.

1.3.1.4 Mixed transcortical aphasia

Mixed transcortical aphasia, or isolation aphasia, is equivalent to global aphasia with preserved repetition. Patients with this syndrome do not speak unless required, and their verbal output is almost entirely limited to what has been offered by the examiner — a true echolalia. Patients may embellish the output in the form of the completion phenomenon or spontaneous correction of grammatical errors deliberately produced by the examiner. Thus, if told the beginning of a common phrase, the patient may not only repeat what has been said but also continue the phrase to complete it. Comprehension of spoken language is severely disturbed. The ability to repeat, although well preserved compared with all other language features, remains limited and is often below normal. The number of words in a sentence that can be repeated is often limited to three or four. Naming, reading aloud, reading for comprehension, and writing are severely compromised. When a response is elicited, it is often contaminated by paraphasias. Neurological examination reveals variable motor, sensory, and visual field deficits. The lesions producing mixed transcortical aphasia tend to be multifocal or diffuse and include hypoxic insults, large watershed infarctions or a combination of focal watershed and pial infarction, and degenerative processes. The mixed transcortical aphasia syndrome also occurs in thalamic infarction.

1.3.2 Fluent aphasia syndromes

1.3.2.1 Wernicke's aphasia

Wernicke's aphasia is characterized by fluent but relatively meaningless spontaneous speech and repetition and relatively poor comprehension of words, sentences, and conversation. Spoken language may be limited to jargon comprised of either real words, neologisms (nonwords such as "klimorata") or a combination of the two. In contrast to those with Broca's aphasia, individuals with Wernicke's aphasia are typically unaware of the errors. The appropriate melody or intonation may give the impression that the person is speaking another language. Particularly in the acute stage, there is often a severe comprehension impairment, such that the patient may listen to others and respond fluidly with language-like, meaningless utterances for hours, with no apparent inkling that he or she has neither understood anything others have said nor said anything that could be understood by others. Often the person will intermittently include a coherent "social" phrase, such as, "yes, that's right." Written output is typically like spoken output — written words with little or no content, often including nonword letter strings. Reading comprehension is typically no better than spoken comprehension. Repetition is generally like spontaneous speech — fluent jargon. These deficits have been attributed to impaired inhibition of lexical activation, so that the person cannot select the appropriate word, sound, or meaning from competing linguistic units that are also activated. Although such an underlying impairment would account for many of the observed language deficits, it could not easily account for cases with relatively preserved or relatively impaired categories of words, such as animals or tools, or impaired nouns relative to verbs. This collection of deficits is usually caused by neural dysfunction in regions supplied by the inferior division of the left middle cerebral artery (MCA), including Wernicke's area (most of Brodmann area 22, in the posterior, superior temporal gyrus). This hypothesis can account for occasional dissociations between the typical deficits or anomalous lesion sites in patients with Wernicke's aphasia by the fact that there is individual variability in the cerebral vasculature and the areas supplied by particular arteries.

1.3.2.2 Conduction aphasia

Conduction aphasia is another fluent aphasia with speech that contains numerous phonemic paraphasias sometimes produced in a series of increasingly closer approximations of the target (e.g., "splant, plant, plants, pants" for pants — termed "conduit d'approche"), and repetition is poor. It differs from Wernicke's aphasia in that the individuals have relatively good comprehension. They are very aware of their verbal errors and will frequently try to self-correct their mistakes. Conduction aphasia is considered a "disconnection syndrome" caused by a lesion in the arcuate fasciculus, a bundle of nerve fibers that connect Wernicke's and Broca's areas. However, damage to the arcuate fasciculus is not a prerequisite of conduction aphasia. Most available anatomical evidence suggests that this particular aphasia is most often caused by damage to the left superior temporal gyrus and/or the left inferior parietal lobe and to the posterior arcuate fasciculus (Buchsbaum et al., 2011; Fridriksson et al., 2010).

1.3.2.3 Anomic aphasia

Anomic aphasia is also known as amnestic or amnesic aphasia, nominal aphasia, and semantic aphasia. The primary modality of language that is affected is speech production, mostly restricted to the production of names, but it is most easily observed by asking an individual with aphasia to name pictures of objects or actions. Anomia is described by the failure to name or to retrieve names, common and uncommon and proper nouns; auditory comprehension is either unimpaired or only mildly impaired. Anomic aphasia patients manifest a fluent output with pauses while they are searching for a specific word. Speech rate, articulation, and grammar are typically normal. Reading and writing are usually preserved. Anomia is found in all varieties of aphasia; partly for that reason, no specific localization for the causative lesions has been or is likely to be documented.

1.3.2.4 Transcortical sensory aphasia

Transcortical sensory aphasia is an uncommon form of aphasia that may occur when a lesion functionally isolates Wernicke's areas from the rest of the brain, leaving the reception-to-output sufficiently unimpaired that repetition is preserved, but neither speech comprehension nor spontaneous speech remain intact. The simplest way to describe transcortical sensory aphasia is to think of it as a form of Wernicke's aphasia in which the patient exhibits a severe comprehension deficit with preserved repetition. Despite intact articulation, speech repetition might result in paraphasic, neologistic, anomic, and even echolalic articulation. Patients with transcortical sensory aphasia typically tend to be unaware of their impairment. Writing ability is usually disturbed as in patients with Wernicke aphasia.

1.4 Limitations of the localizationist approach to language representation

As reported in the previous paragraphs, despite some contradictory positions, since the end of the 9th century for more than a century, the "localizationist" perspective of language has been hegemonic. As mentioned in the introduction, in the early 1800s, the anatomical-clinical approach was criticized in favor of a holistic approach.

In 1824, Flourens introduced a theory of the brain functions, hypothesizing that the cognitive abilities, including language, are not localized in a specific area of the left hemisphere but involve both hemispheres of the brain (Pearce, 2009). A few years later, Jackson supported Flourens' hypothesis by postulating that language was a function of intelligence and, therefore, more widely distributed in the brain than assumed by the localizationist view (Jackson, 1894). According to this theory, other areas of the brain that are not specifically devoted to language have the ability to take over the functions represented in the damaged areas. Not surprisingly, assuming broader circuits that subserve language function, the detection of language deficit does not necessarily imply the localization of function in a specific area. Scarcely heard by his contemporaries, Jackson was rediscovered in the early 20th century by the so-called "holists", who believed that all areas of the brain were mutually interconnected by nerve fibers. Following this perspective, Karl Lashley (1951) developed the concept of the "equipotentiality" of the cortex: if a brain lesion occurred in a specific area, the network would allow the redistribution of functions to other intact regions.

In an interesting review, Trembley and Dick (2016) examined the main limitations of classical model:

1. The spatial precision of the model is too limited to test a specific hypothesis about brain/behavior relationships.
2. It emphasizes two “language regions”.
3. It focuses on cortical structures and mostly leaves out the subcortical structures and relevant connections.
4. Because of its limited spatial extent and cortical focus, it is not easy to reconcile the model with modern knowledge about the white matter connectivity supporting speech and language function.

Based on this evidence, the authors illustrated the distributed nature of the language connectome, which extends far beyond the single-pathway notion of the arcuate fasciculus connectivity established in Geschwind’s version of the traditional model. In addition, in this review it was reported that there is no consistent anatomical definition of “Broca’s and Wernicke’s Areas”, proposing the need to replace these terms with more precise anatomical definitions (Trembley & Dick, 2016).

Thanks to the scientific progress and observations on human and non-human primates, to date, the classical model of aphasia has been replaced in favor of a modern perspective which considers the language system as part as neural networks largely distributed in the brain (Chang et al., 2015). Modern network-based models are composed of parallel, interconnected streams involving both cortical and subcortical areas. Hickok and Poeppel (2004) have proposed the “dual stream” model, emphasizing that language processing involves the ‘dorsal’ and ‘ventral’ pathways: the ventral stream is largely organized bilaterally from the temporal pole to the basal occipitotemporal cortex, processing vocal signals for comprehension; in contrast, the dorsal stream is strongly dominant in the left hemisphere for production. The function of the dorsal stream is primarily the sensory-motor mapping of sound (Saur et al., 2008). According to the dual-stream model, ventral pathways are bilaterally distributed into both hemispheres, and the major hubs include the superior temporal gyrus (STG), the superior temporal sulcus (STS), the middle and inferior temporal gyri (MTG/ITG), and the anterior temporal lobe (ATL). The ventral stream connects the frontal cortices to the occipital, parietal, and temporal lobes, via long white matter (WM) tracts, including the external capsule (EC), the inferior fronto-occipital fascicle (IFOF), the inferior longitudinal fascicle (ILF), and the uncinate fascicle (UF). On the other hand, the dorsal pathway involves the structures of the left hemisphere in the posterior frontal lobe, posterior dorsal temporal lobe and parietal operculum, including white matter (WM) tracts connecting the frontal lobe to the left temporal and parietal lobes via the arcuate fasciculus (AF) and the anterior and posterior indirect components of the superior longitudinal fasciculus (SLF). Instead of two separate pathways of language function, the dual model supports interconnectivity between different cortical regions through correlated white matter pathways (Nasios et al., 2019).

Although it is worth mentioning the contribution of Pierre Marie and Dejerine concerning the role of the subcortical connection (Lechevalier, 2017), Catani and Ffytche (2005) elaborated the so-called hodotopic theory, according to which cognitive functions are located in cortical epicentres (*topos*= place) interconnected by white matter fibers (*hodos*= pathway). The dynamic organization of white matter tracts (WMTs) and their connections between regions offered a new insight into the connectivity and plasticity of the human brain: it is complex, multimodal and an integrated system of networks (De Benedictis & Duffau, 2011). It is crucial to understand how different brain regions are connected within extensive networks and, simultaneously, to map lesions to white-matter tracts. Whereas previously the focus of researchers was mainly on the cortex, today tractography, a method of investigation based on diffusion tensor imaging (DTI), makes it possible to study the connections between different brain regions in vivo, opening new horizons of interpretation. In this regard, Catani and collaborators (2012) have developed a tractography atlas that maps white matter fibers, allowing precise localization of white matter lesions in association with related symptoms (Catani et al., 2012).

It should be noted that the historical and clinical excursus of aphasia is quite complex. It also includes other cognitive psychology and psycholinguistics models that will not be discussed here, as they dwell less on anatomical explanations.

As we will see in the next chapter, in recent years, neuroimaging studies on healthy and brain-damaged individuals with aphasia have supported this connectionist view (Dronkers & Ludy, 1998; Kertesz et al., 1979; Naeser & Hayears, 1978). Thus, there are no boundaries or brain areas strictly corresponding to the different types of aphasia: most patients present deficits that affect the system as a whole and not specific parts of it.

Indeed, a complex function such as language cannot depend on a specific area of the brain, but on the interaction of several regions that constitute a functional system. This point is also evident from the fact that among patients classified as suffering from the same type of aphasia, there is considerable variability in impairment and performance on the different tasks (Fridriksson et al., 2018a).

CHAPTER II

LANGUAGE AND ITS INTERACTION WITH THE MOTOR SYSTEM AND OTHER COGNITIVE DOMAINS

As described in the previous chapter, for a long time, scholars in the field of aphasia have studied the organization of the human brain to identify the localization of the different aphasia syndromes. The anatomical-clinical correlation method was applied in which the aphasic symptoms were related to the lesioned areas observed *post-mortem* through autopsy of the patient's brain. The links were, therefore, identified using inferential logic:

"if f_a is more affected than function f_b by lesion of area A, ergo area A is the center, focus, domain, or module of the function f_a. If the neurons of area C are more active during function f_c than during function f_d, ergo area C is the center, focus, domain, or module of function f_c" (Fuster, 2000, p. 52).

However, as mentioned in the previous chapter and as we will see later, this method showed its own limitations early on. Today, thanks to a large amount of research in neuroscience, we know that cognitive information and, in particular, language, is represented in interconnected and overlapping neuronal networks which overcome any traditional concepts of modularity (Fuster, 2000, p. 53). In the following paragraphs, first, the concept of neuronal network is reported referring to neuroimaging techniques which allow for the in vivo visualization of the brain area and their corresponding connection bundles. Then, several recent studies are described which, according to the connectionist approach, confirm that the language system is represented beyond the classical language areas, thus, involving the right hemisphere (Gainotti, 2016), the motor cortex (Jirak et al., 2010), the cerebellum (Geva et al., 2021) and the executive system mediated by the prefrontal lobes (Gertel et al., 2020). Finally, some behavioral studies on persons with post-stroke aphasia are reported which highlights the importance of relying on the motor and the executive system to improve different aphasic symptoms.

2.1 Neural networks

The designated name for these networks is large-scale brain networks (Bressler & Menon, 2010). These networks consist of a series of interconnected brain areas, that interact to achieve a defined cognitive action or function. The paradigm of large-scale brain networks takes up the conception and notion of graph theory (Diestel, 2016), where a graph is a structure composed of simple objects, called nodes, and the connections between these nodes are called the arcs (Bressler & Menon, 2010). In the case of large-scale brain networks, the nodes correspond to brain areas, while the arcs correspond to the white-matter bundles that connect the different nodes (Bressler & Menon, 2010). A further division of these brain networks is necessary: one can distinguish between structural and functional networks. "The neuroanatomical structure of large-scale brain networks provides a skeleton of connected brain areas that facilitates signaling along preferred pathways in the service of specific cognitive functions" (Bressler & Menon, 2010, p. 278). The nodes of these networks are connected by long white-matter bundles. The study of these structural connections "is necessary to know which functional interactions are possible" (Bressler & Menon, 2010, p. 281). Large-scale functional networks*,* on the other hand, are composed of "interconnected brain areas [that] interact dynamically in order to perform [...] a specific function" (Bressler & Menon, 2010, p. 281). The different brain areas involved in performing the given action are referred to as functional nodes. The detection of these neuronal networks is possible thanks to sophisticated statistical analyses applied to the latest neuroimaging technologies. What made it possible to overcome the concept of modularity was not only clinical and behavioral evidence or "common sense" (Fuster, 2000, p. 52), but also "technological and methodological advances in the study of the structural and functional connectivity of the brain" (Bressler & Menon, 2010, p. 277).

2.1.1 Neuroimaging techniques

Non-invasive imaging tools such as magnetoencephalography (MEG), electroencephalography (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) are widely used for research purposes. MEG "measures changes in magnetic fields on the surface of the scalp produced by changes in the electrical activity of the brain" (Pinel, 2006, p. 106); similarly, EEG detects the global electrical activity of the brain by returning waves (Pinel, 2006, p. 106). On the other hand, PET uses a radioactive contrast agent — radioactive 2-desoxyglucose (2-DG). Neurons take up this substance because of its structural similarity to glucose, the main energy source of brain cells.

fMRI is an imaging technique that with its broad spectrum of magnetic resonance contrast mechanisms results in the most powerful and flexible imaging tool for the diagnosis of the neural systems (Alexander et al., 2007, p. 316). An application of functional MRI uses BOLD, a hemodynamic contrast tool, i.e., which can assess changes in blood flow. It stands for blood-oxygen-level-dependent*,* a contrast dependent on the oxygen level in the blood. The presence of a BOLD signal during an fMRI is due to the different magnetic properties of oxygenated hemoglobin and deoxygenated hemoglobin (dHB) (Gauthier & Fan, 2019): the former is diamagnetic, that is with magnetization in the opposite direction to the direction of the magnetic field (Mencuccini & Silvestrini, 2010). The second is paramagnetic, the magnetization has the same direction as the magnetic field in which it is located (Mencuccini & Silvestrini, 2010). When the brain performs a task, "active regions consume oxygen to function, leading to a localized increase in dHb. To meet the need for additional oxygen, nearby blood vessels dilate, causing an increase in local blood flow. The inflowing blood is fully oxygenated, thereby diluting the dHb concentration and leading to an increased BOLD signal" (Gauthier & Fan, 2019, p. 116).

Using contrast means such as BOLD allows to infer a correlation between signal enhancement and the underlying neuronal activity, as demonstrated by electrophysiological studies on non-human primates (Logothetis et al., 2001). fMRI can be also applied while the individual is at rest, called resting-state fMRI (rs-fMRI), as opposed to using this technique while the individual is performing a task, to detect the brain areas activated by the task (Bressler & Menon, 2010).

The various tools listed have made great strides in mapping networks. Instruments such as dMRI highlight the brain's structural connectivity by detecting the arcs — the white-matter bundles — that connect nodes. PET and fMRI, on the other hand, allow us to frame the functionality of the brain areas (Bressler & Menon, 2010). Static connectivity is detected by rs-fMRI when no activity occurs during the MRI (Yeo et al., 2011). This fact implies that even during a "resting" state, the central nervous system still exhibits activation patterns (Beckmann et al., 2005).

2.2 Language and neural networks

The neuroimaging methodologies described above have been extensively used also to explain the representation of language in the brain. Indeed, the concept of neural network paved the way to a distributed and no longer modular conception of verbal production and comprehension. Since the 1990s, much evidence has accumulated which refuted the classical Wernicke-Lichtheim model. For example, Dronkers and her colleagues (2007) used MRI to study the preserved brains of two of Broca's original patients and obtained some surprising results: the lesions of both patients extended beyond Broca’s area, involving the deep white matter tracts (Gupta & Padma Srivastava, 2020). Again, studies have found that patients with chronic Broca’s aphasia have lesions in Broca’s area in only 75% of the cases (Dronkers & Baldo, 2010). Indeed, lesions in this brain region often result in a transient mutism which resolves in three to six weeks: “such mutism is undoubtedly an indicator of the contribution of Broca’s area to verbal production, but the rapid recovery of patients suggests that Broca’s area is only one part of a more complex system” (Dronkers et al., 2017, p. 5).

Similarly, the original conception of Wernicke’s aphasia has been questioned. As in the case of Broca’s aphasia, even in the circumstance of a lesion confined to Wernicke’s area, patients present with a transient disturbance that quickly resolves. In the case of persistence of the disorder, lesions can be observed that extend far beyond the region mentioned above (Dronkers & Baldo, 2010). What was thought to be a deficit in language comprehension is actually a difficulty in recovering appropriate phonological representations (Gupta & Padma Srivastava, 2020). Studies on degenerative diseases affecting Wernicke’s area mainly report deficits in verbal short-term memory, whereas comprehension of single words is intact (Gupta & Padma Srivastava, 2020).

Several candidates have been put forward to replace the classical model of language; however, over time, the proposal of Hickock and Poeppel (2000; 2004) has received particular attention. The two authors started from one of Wernicke’s (1874) insights: the language system must interact with a conceptual and articulatory-motor systems (Hickok & Poeppel, 2004). The existence of “an interface with the conceptual system requires no motivation; such an interface is required if we are to comprehend the meaning of the words we hear. The need for an interface with the motor system may at first seem less obvious, but in fact, many areas of language either explicitly or implicitly posit an auditory–motor connection. The simplest demonstration of this comes from development: infants must shape their articulatory gestures in a way that matches the phonetic structure of the language they are exposed to; yet the primary input to this motor learning task is acoustic" (Hickok & Poeppel, 2004, p. 68).

Like the organization of the visual cortex (Hickok & Poeppel, 2000), the two authors have therefore formulated the dual stream model, which subdivides the language network into two pathways: the dorsal pathway and the ventral pathway (Hickok & Poeppel, 2004). The dorsal pathway — also referred to as the "*where*" pathway — connects sounds to their articulatory-motor representations; the ventral pathway — the "*what*" pathway, underlies the understanding of the meaning of the sounds that are perceived (Hickok & Poeppel, 2004). Ergo, the first pathway connects the temporal lobe with the posterior frontal lobe, which is typically associated with the classical model, (Friederici, 2011). This portion of the brain is the seat of the motor cortex (Pinel, 2006), which is imputed to control of body movements; the connection thus allows sensory-motor integration that enables sound mapping for articulation (Nasios et al., 2019). Instead, the ventral pathway connects Broca's area with the temporal lobe, involved in semantic processing (Friederici, 2011). In the first elaboration of this model, Hickock and Poeppel (2004) had estimated which brain areas were involved in the two pathways. The perception of a word activated the superior temporal gyrus bilaterally, even though language was thought to be a strongly lateralized system on the left; from here the bifurcation occurs. Through the ventral pathway, the superior temporal sulcus and the inferior temporal gyrus are reached (Hickock & Poeppel, 2004) On the other hand, the dorsal pathway involved the sylvian-parietal-temporal area, an intermediate region between the temporal and parietal lobe that is involved in the interaction between language and articulation (Hickock & Poeppel, 2004). Inevitably, the two pathways interact with each other in everyday communication (Hickock & Poeppel, 2004). A further important assumption of the dual stream model is the bidirectionality of the brain network:

"In the ventral stream, posterior inferior temporal lobe (pITL) networks mediate the relation between sound and meaning both for perception and production (the involvement need not be symmetrical in perception and production). Similarly, it is hypothesized that sectors of the left STG participate not only in sub-lexical aspects of the perception of speech, but also in sub-lexical aspects of the production of speech (again, perhaps non-symmetrically). In the dorsal stream, it is suggested that temporal–parietal systems can map auditory speech representations onto motor representations (as in verbatim repetition tasks, in which access to a motor-based representation is necessary), as well as map motor speech representations onto auditory speech representations" (Hickock & Poeppel, 2004, p. 73).

The new findings concerning the dual stream model make it possible to reconstruct the activation processes of the brain areas that are part of the network, depending on the tasks performed. Sound perception occurs in the auditory cortex, also located in the superior temporal gyrus (Gupta & Padma Srivastava, 2020). The semantic processing role of the ventral pathway takes place mainly in the temporal lobe. However, there is also the participation of parietal and frontal areas (Binder et al., 2009) through the longitudinal fascicles and the inferior fronto-occipital fascicle (Gupta & Padma Srivastava, 2020). For verbal comprehension, the meaning of words is derived from the middle temporal gyrus, through the longitudinal fascicles. The angular gyrus, pars opercularis and interlobular connections are involved through the inferior fronto-occipital fascicle (Gupta & Padma Srivastava, 2020). The internal semantic system — ventral pathway — communicates with the phoneme retrieval system — dorsal pathway for verbal production. As far as visual stimuli are concerned, they are processed in the occipitotemporal region, and the information is communicated to the ventral and dorsal pathways. The ventral pathway deals with meaning, while the dorsal pathway performs the visual-articulatory conversion (Gupta & Padma Srivastava, 2020).

To date, the dual-flow model has been confirmed through various methodologies, such as DTI (Friederici & Gierhan, 2013) and fMRI (Gupta & Padma Srivastava, 2020). These new tools have also made it possible to expand Hickok and Poeppel's original model. In the ventral pathway, the middle temporal gyrus, the inferior temporal gyrus, and the angular gyrus are included (Gupta & Padma Srivastava, 2020). Structural connectivity studies have identified the involvement of the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus (Gupta & Padma Srivastava, 2020), the external capsule, and the uncinate fasciculus (Nasios et al., 2019). Also, the dorsal pathway includes the supramarginal gyrus and the pars triangularis with the pars opercularis and the precentral gyrus, corresponding to Broca's area (Gupta & Padma Srivastava, 2020) as well as the insula, an area relevant to the voluntary movement (Na et al., 2022). The white-matter bundles supporting this network's connectivity are the arcuate fasciculus and the SLF — superior longitudinal fasciculus (Nasios et al., 2019). The latter has four main components: "SLF I, II, III connect the frontal and parietal cortices. The temporoparietal SLF (SLF-tp) joins the temporal and parietal cortices" (Gupta & Padma Srivastava, 2020, p. S74).

The dual flow model has also been confirmed by studies on PWA. For example, Fridriksson and colleagues (2018a) showed that fluency problems were more strongly associated with damage to the dorsal pathway; conversely, damage to the ventral pathway led to problems in comprehension. Furthermore, the study confirmed the interaction between the two pathways during naming, repetition, and grammar processing tasks (Fridriksson et al., 2018a). The dual stream can also account for the fact that patients with damage to different brain areas have similar communication deficits: such lesions would involve the interaction between the two pathways. Again, this also makes it possible to understand how people with similar damage can present different difficulties in the language domain (Nasios et al., 2019).

Recently, neuroscientific research has gone beyond the anatomical connectivity of the language systems, investigating their functional connectivity (Hertrich et al., 2020). The results of the studies have been surprising, confirming the involvement of areas that were thought to be irrelevant to language processing such as the right hemisphere (Gainotti, 2016), the motor cortex (Jirak et al., 2010) the cerebellum (Geva et al., 2021), and the prefrontal lobes involved in executive functions processing (Gertel et al., 2020).

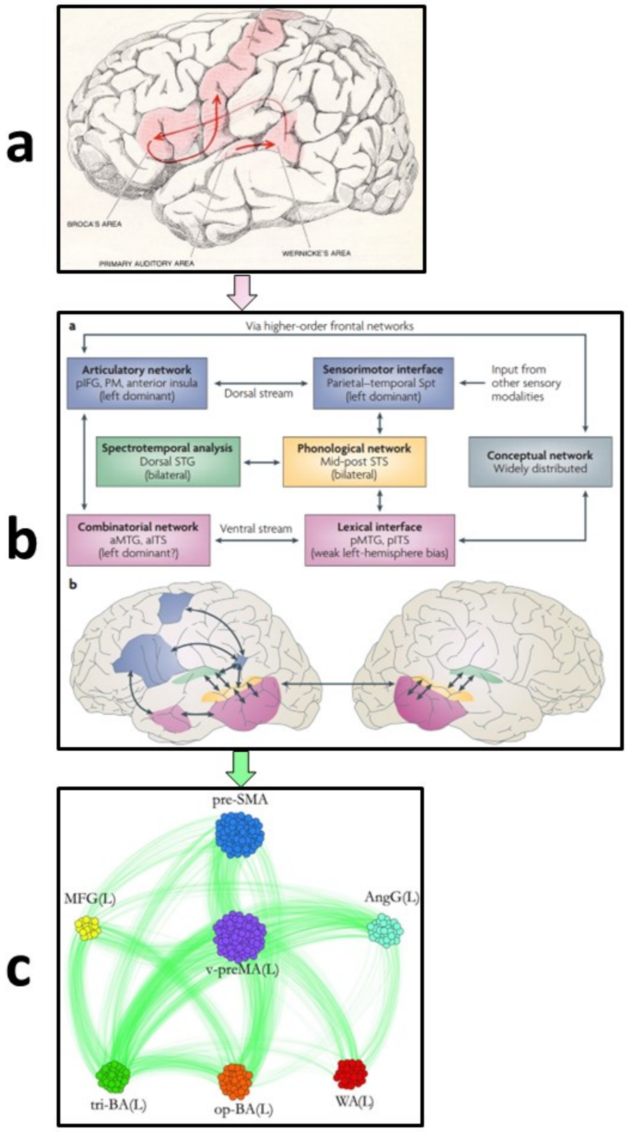

Figure 2.1 Models of language representation. a. classical model. The classical model consists of Broca's area, involved in speech production, and Wernicke's area, involved in auditory speech comprehension. Adapted from DEJERINE Jules, Anatomie des centres nerveux Tome II, Paris, J. Rueff, éditeur, 1901 p.247. **b. dual stream model.** The dual stream model subdivides the language network into two pathways: the dorsal, which connects sounds to their articulatory-motor representations, and the ventral, which underlies the understanding of the meaning of the sounds that are perceived. Adapted from "The Cortical Organization of Speech Processing," by G. Hickok and D. Poeppel, 2007, *Nature Reviews Neuroscience*, *8*, p. 395. Copyright 2007, Nature Publishing Group. **c. connectionist model.** The connectionist model considers the language system as part of a network largely distributed across the brain. Adapted from "Core language brain network for fMRI language task used in clinical applications," by Li Qiongge, et al., 2020, *Network Neuroscience*, *4,* p.139. Copyright 2020, The MIT Press.

2.2.1 The right hemisphere

For years, the Wernicke-Lichtheim model led neuroscientists to believe that language processing was lateralized, represented only the left hemisphere. However, several pieces of evidence have rendered this conception obsolete. Indeed, following a right-hemisphere infarction, 1-13% of right-handed patients suffer from a language disorder; still, the right hemisphere appears to play an essential role in the recovery of language functions in the case of aphasia (Gajardo-Vidal et al., 2018). The involvement of the other half of the brain is also present in the dual stream model (Hickok & Poeppel, 2004): indeed, within this model, language processing takes place in the left and right superior temporal gyrus.

Regarding the role of the right hemisphere in language, multiple lines of research can be found in the literature that investigates this issue. Some authors argue that the right anterior temporal lobe, the seat of the superior temporal gyrus, is linked to higher-level functions (Gainotti, 2016). Indeed, while the left superior temporal gyrus would help in the semantic processing of simple concepts, the right homolog would be responsible for understanding complex and abstract concepts, such as metaphors (Gainotti, 2016). Several studies have shown that individuals with a right hemispheric lesion "suffer from language deficits that selectively affect the semantic-lexical level" (Gainotti, 2016, p. 69).

Another aspect to be considered is the right-hemispheric involvement in the affective component of language. Following a right-hemispheric lesion, some individuals have reported difficulties in modulating their tone of voice, and thus, in affective prosody (Patel et al., 2018). The findings from various research studies also made it possible to formulate the hypothesis of a dual-flow pattern located in the right hemisphere. It has been proposed that the dorsal "*how*" pathway is critical for evaluating prosodic contours and mapping them to subvocal articulation, while the ventral "*what*" pathway […] maps prosody to communicative meaning" (Patel et al., 2018, p. 2). Following Hickock and Poeppel's proposal (2004), research has focused on verbal production and verbal comprehension. The study by Patel and colleagues (2018) has confirmed the difficulty in emotional expression; it also identified that this inability is linked to lesions in the right pars opercularis, the right inferior fronto-occipital fasciculus, the right superior longitudinal fasciculus, and the right uncinate fasciculus, analogous to the structures identified by the dual-flow model.

A final line of research focused on the role of the right hemisphere in language comprehension (Sheppard & Hillis, 2018). For example, the complex study by Gajardo-Vidal and colleagues (2018) attempted to determine the right hemisphere's role using behavioral and neuroimaging methods in both neurotypical and neuroatypical subjects. The results of the study concluded that the activity of the right middle thalamus increases during executive processing, which it is necessary for sentence comprehension. The involvement of the thalamus should not surprise: it is a hub, a nerve center that facilitates the interaction among different structures (Hwang et al., 2021). fMRI studies have shown increased thalamic activity during executive function, memory, and perception tasks and how a lesion in this subcortical structure influences people's performance in multiple domains (Hwang et al., 2021).

2.2.2 The motor system

2.2.2.1 The Embodied Cognition Theory

The Embodied Cognition Theory is a current of thought that also has interested neuroscientists in recent years. The basic idea of this theory is "that most cognitive processes occur through the body's control systems" (Caruana & Borghi, 2013, p. 23). Thus, sensory and motor experiences are linked to higher cognitive functions such as the processes of understanding and producing language (Jirak et al., 2010). These concepts imply that the same sensorimotor areas recruited when we perceive or interact with objects or entities in the world are activated in the act of understanding speech involving those aspects (Jirak et al., 2010; Scorolli, 2014, p. 127). From a neuroscientific point of view, this perspective also implies that the brain areas related to motor actions and language understanding can no longer be seen as independent but rather as working in concert. Areas traditionally regarded as pure motor areas as, e.g., the primary motor or the premotor cortex, as well as areas that have traditionally been assigned to the processing of language, e.g., Broca's or Wernicke's region, are not modularized but instead they provide the linkage to action and language (Jirak et al., 2010, p. 712).

The Embodied Cognition Theory has been supported by numerous studies using different methodologies to investigate the relationship between the language and the motor domain (Jirak et al., 2010). Neuroscientific data have, for example, revealed that during the presentation of verbs related to mouth action (e.g., eating, biting) or limb action (e.g., kicking, pedaling) a neurophysiological response in the corresponding cortical motor areas is enhanced (Buccino & Mezzadri, 2013). Other studies have focused on the relationship between abstract concepts and the motor system. For instance, it was found that the presentation of abstract words which metaphorically refer to concrete aspects recruit the motor system (Scorolli, 2014).

Anatomical connectivity studies have also revealed white-matter bundles connecting the motor area and regions involved in language processing. Diffusion methods have made it possible to identify the frontal aslant tract (FAT), which connects the inferior frontal gyrus — a portion of Broca's area — with different motor areas (Dick et al., 2019). The supplementary motor areas, part of the secondary motor cortex, perform the execution of complex movements (Pinel, 2006) and are linked to the motor execution of language (Dick et al., 2019). Research suggests that the FAT is, in part, responsible of the initiation of verbal production, and, thus, of verbal fluency; thus, its dysfunction might explain stuttering disorder (Dick et al., 2019).

2.2.3 The cerebellum

Traditionally, it was believed that the role of the cerebellum was restricted to movement functions, such as visual-motor coordination or the regulation of muscle tone (Starowicz-Filip et al., 2017). Today, however, its involvement in language is well known. Indeed, cerebellar lesions give rise to language disorders such as ataxic dysarthria and cerebellar mutism (Silveri, 2021). Several authors have also documented the presence of aphasia following cerebellar injury (Silveri et al., 1994; Geva et al., 2021). Accordingly, the cerebellum is strongly connected to the brain via the cerebello-cortical system (Silveri, 2021). The two cerebellar lobes communicate with the brain areas in a crossed manner; that is, the right cerebellum communicates with the left hemisphere and vice versa (Starowicz-Filip et al., 2017). Leiner and colleagues (1991) specifically identified a connection of the right cerebellum with Broca's area, so today we refer to the *"linguistic cerebellum"* to emphasize its role played in language functions (Starowicz-Filip et al., 2017). Some authors believe that

"The cerebellum's role in the regulation of language functions is analogous to its role in motor performance. As in the case of motor functions the cerebellum's role consists of predicting movement direction and preventing dysmetria (underestimation or overestimation of a distance to an object), in the case of language functions it is responsible for the prediction of the final ‘linguistic result’, that is identification and control of potential mistakes before the ready utterance occurs” (Starowicz-Filip et al., 2017, p. 664).

Studies seem to confirm this hypothesis: for example, Friederici (2006) found a higher cerebellar activation during the presentation of sentences with grammatical errors than during grammatically correct sentences.

2.2.4 The executive functions system

The prefrontal cortex is one of the largest areas in humans compared to other species. This portion of the cortex represents the anatomical substrate of executive functions, which play a crucial role in cognition and behavior (Vallar & Papagno, 2007). These functions regulate the processes of planning, organization of actions, memory, attention, and inhibition (Blair, 2017). This grouping is rather heterogeneous, and different tasks recruit different brain areas. In the first section, for example, it was reported that the executive-control network involves the dorsal and ventral pathways of attention (Hutton et al., 2019) and the working memory system (Deldar et al., 2020). Executive functions also play a key role in language processing. Indeed, to communicate effectively, it is necessary to organize our thoughts by selecting the right words from several alternatives and inhibit the tendency to use the same terms; or, to correctly interpret the incoming messages, executive functions processes help us to choose the most coherent interpretation of the perceived speech (Ye & Zhou, 2009).

Studies with different methodologies affirm the importance of executive functions for language. For example, Gertel et al. (2020) investigated the differences between a young and an old brain. They found that older people have stronger connectivity between executive function and language regions, which allows them to compensate for the language difficulties which might cooccur due to cognitive decline.

One of the executive functions components which mostly interacts with the language system is working memory (WM) (Deldar et al., 2020; Makuuchi & Friederici, 2013). Working memory actively maintains and processes information for a short period, prioritizing the retention of task-relevant information over the irrelevant one (Schacter et al., 2009). WM is a function involved in several complex cognitive tasks, such as verbal production and comprehension, reasoning, and decision-making. Indeed,

"Language production initiates with mental planning, which results from environmental, cognitive and emotional contextual factors. Once a message is selected, it needs to be encoded into words with an intended meaning (semantics), and grammatically encoded to provide critical contextual information (i.e., syntactic) […]. This linguistic form goes through a final motor encoding phase to transform the mental process into sounds or written spelling. Every step of language production, from retrieving the mental concept, associating it to the corresponding semantic form, programming, and producing the phonological form, requires WM" (Deldar et al., 2020, p. 17).

2.3 Language and the motor system: behavioral evidence on people with aphasia

In the previous section, the relationship between the motor system and language, as assumed by embodied cognition theorists, was reported. However, the link between these two functions has also been observed in clinical practice. Indeed, it was found that left post-stroke patients with upper limb movement and speech disorders experienced more difficulties in motor and language recovery (Primaßin et al., 2015; Xu et al., 2021) In other words, the concomitance of aphasia and hemiplegia can worsen the patient's prognosis (Fang et al., 2003; Haselbach et al., 2014).

Based on this evidence, several studies have investigated the relationship between language and the motor system. These studies are clinically relevant as a better understanding of the relationship between these two domains would allow alternative or even better rehabilitation practices to be implemented (Primaßin et al., 2015). To explore this association, some authors have focused on motor skills performance in patients with and without aphasia. Xu and colleagues (2021) conducted a study on a large sample of patients with and without aphasia following a stroke (n = 435; aphasia = 214; without aphasia = 221). The instruments used to estimate the subjects' language and motor skills were the Western Aphasia Battery (WAB-R), the Boston Diagnostic Aphasia Examination (BDAE-3), the Fugl-Meyer (FM) scale and the Action Research Arm Test (ARAT). The Western Aphasia Battery (Kertesz, 2007) assesses verbal production, verbal comprehension, repetition, and naming. The index used in this study, called the Aphasia Quotient (AQ), is a weighted summary of scores in these four tasks. The Boston

Diagnostic Aphasia Examination (Goodglass et al., 2001) is an extended examination of the degree of language dysfunction, measured on a scale of one to five. The Fugl-Meyer scale (Fugl-Meyer et al., 1975) assesses the individual's motor performance. In this research, only the functioning of the upper limbs was assessed, considering the ability to perform voluntary movements, coordination of speed and reflexes. Finally, the Action Research Arm Test (Lyle, 1981) is a quantitative test for upper limb function and consists of four subtests: grasping, gripping, squeezing and gross movement. While the FM scale emphasizes the amount of difficulty in performing a task, the ARAT measures the activity during a task (Xu et al., 2021). Statistical analyses revealed a significant correlation between the AQ index and the ARAT ($r = 0.62$; $p < 0.001$) and between the AQ index and the FM scale ($r = 0.70$; $p < 0.001$). To identify which function was most predictive of the relationship between language and the motor system, hierarchical linear regression was performed, where the independent variables were the subtests of the Western Aphasia Battery, and the dependent variables were the motor scales. Only spontaneous verbal production significantly predicted the ARAT ($R^2 = 0.42$; $p < 0.001$) and the FM performance ($R^2 = 0.51$; $p < 0.001$).

To confirm the predictive role of language in motor recovery, Gialanella et al. (2011) used a sample of 156 subjects undergoing motor and language rehabilitation. In the sample, 105 were persons with aphasia. The participants' motor and language skills were assessed through the AAT, the NIHSS, the Fugl-Meyer scale, the Trunk Control Test (TCT), and the Functional Independence Measure (FIM). The Aachener Aphasie Test (Luzzati et al., 1996) assesses the individual's language abilities through six indicators: spontaneous production, token test, repetition, written production, naming, and comprehension. The National Institutes of Health Stroke Scale (Brott et al., 1989) measures the severity of the cerebral infarction. As in the previous study, the Fugl-Meyer scale was administered to assess the individual's motor performance (Gialanella, 2011). The Trunk Control Test (Collin & Wade, 1990) is a questionnaire to measure trunk mobility. The Functional Independence Measure (Keith et al., 1987) estimates the person's needs for assistance in daily activities. Statistical analyses concluded that persons with aphasia compared to persons without aphasia had lower scores on the motor subscales of the FIM ($p < 0.001$), the TCT scale ($p < 0.003$), the NIHSS ($p < 0.001$), and the Fugl-Meyer ($p < 0.002$). Despite this, in the regression model, the AAT size, in contrast with previous studies, was not significantly predictive, (Gialanella, 2011). Hybbinette and co-workers (2021) conducted a study on the recovery of articulatory disorders in persons with aphasia. The research design provided for the first measurements to be taken within four months from the onset of symptoms, while the follow-up was administered at six months from the onset. The aim of the study was to investigate if the recovery of these symptoms were or were not related to the recovery of other impairments over six months. These were estimated through the Apraxia of Speech Rating Scale (ASRS), the Neurolinguistic Aphasia Examination (A-NING), the Boston Naming Test (BNT), the measurement of Non-Verbal Oral Apraxia (NVOA) and the Fugl-Meyer (FM) scale. The Apraxia of Speech Rating Scale (Strand et al., 2014) is an excellent indicator on the presence and severity of apraxia; the Neurolinguistic Aphasia Examination (Lindström & Werner, 1995) assesses seven language skills to determine the type and severity of aphasia. The Boston Naming Test (Kaplan et al., 2001) was used to detect the patients' naming abilities; the Fugl-Meyer scale was used to assess only the upper limbs disorders. Despite the initial 70 participants, only 15 underwent the second assessment. Interestingly and in line with the hypothesis of a relationship between the language and the motor domains, results showed that the improvement in the FM scale at follow-up was significantly correlated with A-NING ($r = 0.72$; $p = 0.03$), ASRS ($r = -0.57$; $p = 0.003$), NVOA ($r = 0.69$; $p = 0.004$) and BNT ($r = 0.80$; $p < 0.001$; Hybbinette et al., 2021).

Some other studies investigated the impact of a motor rehabilitation program on language outcomes. Harnish and colleagues (2014) conducted a pre-post study to measure the effects of six weeks of motor rehabilitation on five participants with language and motor difficulties measured through the WAB and the FM scale. After the intervention, an overall increase in both scales' scores was reported in three out of five patients. Despite the low external validity of the study, due to the low number of participants, these results are promising as they suggest possible alternative interventions for language recovery. Similarly, in the study by Primaßin and colleagues (2015), while two out of four patients benefited from motor rehabilitation, an increase in verbal scores was observed only in one patient. Finally, Ginex and his colleagues (2017) investigated the role of motor recovery in PWA taking cognitive aspects into account. Again, the research design was pre-post: the first measurement occurred on admission; the second, after discharge, following motor and language rehabilitation. The instruments used were the AAT (Walter et al., 1983), the FIM (Keith et al., 1987) and the Raven's colored progressive matrices (CPM) (Basso et al., 1987). The AAT was used to measure the type and severity of aphasia, while the motor scale of the FIM were considered separately in the final analyses. The CPM was used to assess the abstract reasoning abilities of the individuals. Indeed, being a non-verbal test, it is particularly suitable for language difficulties (Basso et al., 1987). The analysis of the scores measured at the time of admission showed a correlation between the FIM motor scale, the token test ($p = 0.002$), the comprehension test ($p = 0.001$), the naming scale ($p = 0.001$), as well as the score at the Raven's matrices ($p = 0.002$). At discharge, a positive correlation was observed between the FIM and the naming test ($p = 0.02$), the FIM and the comprehension test ($p = 0.021$) and the FIM and the CPM test ($p = 0.001$). A correlation between the scores at the CPM with the token test, the naming test, and the comprehension test was also found (all $p = 0.001$). A further analysis identified which factor was predictive of the dependent variable measured by the FIM motor scale score at the discharge time. The multiple regression model identified the dependent variables in the token test and in the motor scale scores at admission (Ginex et al., 2017).

In line with the assumption that the motor system can support language recovery, Marangolo and co-workers' study (2010) investigated whether observing gestures might have a role in promoting long-lasting improvement of lexical deficits in PWA. To do this, six individuals with aphasia were asked to observe, for two consecutive weeks, the therapist executing different everyday actions. After observing each action, they had to produce the corresponding verb. In any presentation, the therapist provided a verbal cue. Results showed increased verb production in the four subjects whose verb retrieval deficits arose from lexical deficits. On the contrary, the two patients with severe semantic disorders did not benefit from the treatment. In agreement with the hypothesis of an interaction between the motor and the language domain (Marangolo et al., 2010), the authors speculated that in those four patients, action observation has activated in the semantic system the sensory-motor features of the action, which have reinforced verb lexical retrieval. Indeed, damage to the semantic system prevented the two remaining patients from correctly producing the verb (Marangolo et al., 2010). In a subsequent study, Marangolo and colleagues (2012) found that observing actions which belong to one's experiential motor repertoire exerts a more significant influence on the recovery of verbs than observing unfamiliar actions. According to the above hypothesis, the authors speculated that the observed familiar action facilitates verb retrieval because its sensory-motor features are recognized at the semantic level. On the contrary, actions which do not belong to the motor repertoire of the observer cannot make use of this matching process (Buccino et al., 2004; Marangolo et al., 2012; Shimada, 2009).

In line with the above studies, to date, several lines of evidence have suggested that the sensorimotor cortex takes part in language processing, at least when speech is translated into sensorimotor actions, such as in the production of verbs denoting actions (Marangolo et al., 2010, 2012; Pulvermüller et al., 2005; Rizzolatti et al., 2009). Consistent with this hypothesis, Gili et al. (2017) investigated through rsfMRI in a group of ten chronic persons with aphasia, the impact on functional connectivity of an action-observation treatment. Two different conditions were considered: 1) actions embedded in real daily life contexts (e.g., the station) 2) actions embedded in pantomimed daily life contexts (e.g., the shop). Results showed that only actions embedded in real contexts exerted significant functional connectivity changes in the right hemisphere and, in particular, in the sensorimotor areas such as the right premotor cortex and the right medial temporal area. These changes were positively correlated not only with the retrieval of action verbs but also of nouns and sentences. Thus, observing action in familiar contexts activates in the observer the sensorimotor properties of the action which, in turn, improves verb actions retrieval. Since verbs play a key role in sentence construction, this improvement resulted in significant changes also in nouns and sentences production (Gili et al., 2017). This improvement was not present in the pantomime condition. This last result suggests that the motor-language system does not simply understand actions, but it actively participates in understanding action intention. Indeed, the authors speculated that if this system was only involved in action understanding (the "what" of an action), a similar response should have been observed also in the absence of context (Gili et al., 2017). Considering the above evidence, it is worth highlighting the importance of the motor system's role in the recovery of specific aspects of language.

2.4 Language and the executive system: behavioral evidence on people with aphasia

The hypothesis of a strong relationship between the language and the executive functions system, reported in the previous section, has also influenced the way in which language treatments can be programmed in clinical practice. Indeed, it is not uncommon to detect cognitive difficulties in patients with an aphasic disorder (LaCroix et al., 2021), and a large body of research attests that executive functions play a considerable role in the prognosis of aphasia (Schumacher et al., 2019). One aspect that has been mainly investigated is the relationship between attention and language abilities. The study by LaCroix et al. (2021) compared the performance of PWA and healthy subjects in attention tasks. The 42 participants, 22 of whom had chronic aphasia assessed by the Boston Diagnostic Aphasia Examination, underwent the Attention Network Test (Fan et al., 2002). This computerized test measures the speed and accuracy of reaction to a stimulus. Prior to exposure to the stimulus, visual cues are presented to speed participant's responses and to select the right button. The results of this study are interesting. Indeed, although no differences in accuracy were found between the two groups ($p = 0.49$), the control group performed significantly faster than the PWA group ($p < 0.001$). Thus, they suggest the role played by language in attentional control (LaCroix et al., 2021). Lee et al. (2020) performed similar research but with different instruments. The aim of the study was to determine the presence of attentional deficits in chronic aphasia as well as their relationship with language scales scores. They used the revised version of the Western Aphasia Battery and the Conners' Continuous Performance Test II. The revised version of the WAB (Kertesz, 2007) provided general estimates of language performance across several indices. The Conners' Continuous Performance Test II (Conners, 2000) measures sustained attention and the ability to shift attention. Participants are presented with a series of visually presented stimuli: participants must press the space bar when they see any letter of the alphabet except the letter "X". Indices of response omissions, time dedicated to find the stimulus and response time were measured (Lee et al., 2020). The study involved 114 PWA and confirmed the expected results: between 20.2% and 48.2% of the sample had difficulties in one of the indices of the attention task; statistical analysis also revealed a worse overall performance in the case of severe aphasia compared to subjects with a less severe aphasic disorder (Lee et al., 2020). A further study using the Test of Everyday Attention (Robertson et al., 1996) confirmed the above results showing a significant correlation between divided attention and improved language skills (Lambon Ralph et al., 2010).

Simic and colleagues (2019) were interested in the predictive role of executive control in the recovery of PWA. They, therefore, conducted a systematic review to identify research findings in the literature. Of the 15 studies, 11 (73%) confirmed that good executive control, measured before language rehabilitation, correlates to better linguistic and functional treatment outcomes. Two studies found no effect, and two others unexpectedly found an opposite effect. Namely, people with better executive control prior to language rehabilitation had a worse outcome. Most of the evidence, however, shows a key role of executive functions processes in predicting language recovery (Simic et al., 2019).

There are several studies, on the other hand, that have not investigated a single executive component but are aimed at establishing the relationship between the language system and different cognitive functions. One example is the study by Wall et al. (2017), who administered various neuropsychological tests to 36 PWA. The language disorder was assessed by the Boston Naming Test and the Comprehensive Aphasia Test (Swinburn et al., 2005). The latter investigates several language domains; for the purpose of the study, the subjects' verbal comprehension was measured. On the other hand, cognitive functions were estimated using a complex neuropsychological battery. The Star Cancellation (Wilson et al., 1987) consists of an A4 sheet of paper with stimuli and distractors; subjects are required to cancel only the stars. The task of the Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) is to identify a specific pattern of stimuli among different schemas. The Trail Making Test (Reitan & Wolfson, 1993) consists of two sections: in part A, individuals are asked to connect circles containing numbers from 1 to 25 in the shortest possible time; in part B, the task is to connect letters and numbers alternately (A-1-B-2, etc.). The Digit Span Test (Wechsler, 1997) measures verbal working memory in which participants are asked to repeat an increasing string of numbers. The Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001) is a test of verbal long-term memory. Subjects are asked to learn 12 words from a list and to repeat them immediately afterwards. After 20 minutes, they are asked again to repeat the same words. During the Rey Complex Figure (Osterrieth, 1944), participants are first asked to copy a complex figure; this figure is then removed, and they are asked to perform the task again, after 5 and 30 minutes from the first presentation, by revoking the figure from memory. The

Kettle Test (Hartman-Maeir et al., 2009) measures the individual's ability to perform everyday functional tasks. The Animal Fluency test (Rosen, 1980) tests the individual's ability to name as many animals as possible in one minute. The analyses conducted on these data revealed a positive correlation in the Comprehensive Aphasia Test and Boston Naming Test — naming and verbal comprehension — with all scores on the cognitive scales (all $p < 0.001$), except for the Star Cancellation and the Kettle Test.

Schumacher et al. (2019) also investigated the relationship between language impairment and executive functions. Thirty-eight PWA completed several neuropsychological tests: the Test of Attentional Performance, the Delis-Kaplan Executive Function System, the Tower of London, the Kramer test, the PM47, and the Brixton test. The Test of Attentional Performance (Zimmerman & Fimm, 1995) is a computerized procedure that measures accuracy and response times in various attentional tasks. From this battery, five tasks were chosen: alertness, GoNoGo, divided attention, and sustained attention (Schumacher et al., 2019). From the Delis-Kaplan Executive Function System battery (Delis et al., 2001), the Design Fluency and Trail Making tasks were extracted. In the Design test, participants are required to connect dots and lines to form a figure; the latter was illustrated in the previous study. The Tower of London (Shallice, 1982) requires the subject to carry out visuospatial planning tasks, rearranging the order of balls drilled on three beams to build up a new figure. The Kramer test (Balzer et al., 2011) requires the subject to divide eight cards into two groups according to specific criteria. Results showed that the scores of almost half of the participants were below average on at least five of the tests performed. As in previous studies, the work by Marinelli et al. (2017) also investigated the relationship between executive functions and aphasia. The cognitive functions of 189 subjects were examined by administering the Cognitive Test Battery for Global Aphasia (Van Mourik et al., 1992), an instrument explicitly designed for severe PWA. The five subscales of attention, executive functions, reasoning, memory, and visual-auditory recognition do not require verbal responses but rather a response through gestures. In the evaluation of the results, three subgroups were identified based on their educational level. Individuals with a higher degree of education performed better both in the cognitive and in the language tests, suggesting that educational attainment might be a positive prognostic factor in aphasic disorder outcomes (Marinelli et al., 2017).

In the next chapter, a brief overview of the most important tDCS aphasia treatment findings which, according to the traditional approach, have applied the electrodes on the classical areas of language will be reported. Subsequently, in line with the connectionist point of view, more recent studies will be described in which tDCS has been applied on cerebral regions which had never been considered before to support language, such as the motor cortex, the cerebellum, the spinal cord and the prefrontal cortex, which could serve as ancillary systems to promote language recovery.

CHAPTER III

TRANSCRANIAL DIRECT CURRENT STIMULATION AND APHASIA

3.1 Non-invasive brain stimulation (NIBS)

Over the past few decades, the introduction and development of non-invasive brain stimulation (NIBS) techniques have provided researchers and clinicians a valuable means to modulate the activity of cerebral areas in humans and, thereby, to contribute to the exploration of brain-behavior relationships. This has also led to the development of treatments for various neurological and psychiatric disorders. NIBS has been shown to not only alter neural activity during application but to also induce long-lasting alterations of cortical excitability and activity. Transcranial Electrical Stimulation (tES) and Transcranial Magnetic Stimulation (TMS) are two of the most well-known forms of NIBS that influence neural activity based on different electromagnetic principles (Yavari et al., 2018). tES is a generic term that designates several techniques based on the modality of the applied electricity, which can be direct currents (transcranial direct current stimulation, tDCS), alternating currents (transcranial alternating current stimulation, tACS), or random noise currents (transcranial random noise stimulation, tRNS). tDCS, which is the most widely used form of tES, delivers weak direct currents to the scalp through two or more electrodes. tACS involves the application of a balanced sinusoidal current across the scalp, and tRNS, a specific type of tACS, typically involves the use of a current which randomly fluctuates between a frequency range 0.1–640 Hz (Antal et al., 2008; Antal & Paulus, 2013; Deans et al., 2007; Helfrich et al., 2014; Nitsche & Paulus, 2000; Nitsche and Paulus, 2001). Acute effects of modern NIBS techniques distinguish tES from TMS, where the activation of neurons is pertinent. TMS induces high intensities of short-lasting electromagnetic currents in the cerebral cortex, which subsequently generate a supra-threshold activation of the neurons. In contrast, tES does not generate action potentials in neurons, but bi-directionally modulates their spontaneous firing activity via subthreshold alterations of resting membrane potentials (Barker et al., 1985;

Nitsche & Paulus, 2000; Nitsche et al., 2003a; Purpura & McMurtry, 1965; Wagner et al., 2007). With regard to the after-effects, although the presumed induction procedure differs between respective stimulation protocols, it has been suggested that, depending on the stimulation parameters, all are able to produce long-lasting facilitatory or inhibitory plastic changes in the neural system (Dayan et al., 2013; George & Aston-Jones, 2010; Nitsche & Paulus, 2001; Rossini & Rossi, 2007; Rothwell, 1993). Concurrent application of stimulation with behavioral tasks is more difficult with rTMS compared to tES, as suprathreshold activations may inevitably disrupt task-relevant activity whereas the subthreshold polarization induced by tDCS allows the online stimulation to enhance or reduce task-dependent neuronal activation. Whereas the spatial and temporal resolution of TMS is superior, tES tools are generally more cost-effective, easier to operate, and easily adaptable for double-blind, sham-controlled studies. Both techniques are valuable adjunctive tools in neuroscience research and have the potential to overcome an inherent limitation of neuroimaging techniques: the difficulty to infer causal involvement of brain areas or functional networks in specific motor, perceptual, or cognitive processes (Yavari et al., 2018). For the purpose of my thesis, in the following section, I will focus on tDCS as a technique reintroduced in the field of NIBS.

3.2 Transcranial direct current stimulation (tDCS)

tDCS was first investigated fifty-eight years ago in anesthetized rats revealing that neural activity and cortical excitability could be modified by the application of direct current on the sensorimotor cortex. These effects depend on stimulation polarity and persist for hours after the end of stimulation (Bindman et al., 1964). A few years later, it was established that a current flow sufficiently large to achieve physiological and functional effects could also be induced into the brain via transcranial application of such direct currents in both healthy subjects and patients suffering from psychiatric diseases (Dymond et al., 1975; Lolas, 1977; Rush & Driscoll, 1968). However, mainly due to the lack of relevant tools to assess its heterogeneous effects, this technique was nearly forgotten in the following years. About twenty years ago, tDCS was re-discovered as a tool to modulate human brain activity and its physiological effects started to be systematically explored (Lefaucheur et al., 2017; Nitsche & Paulus, 2000; Priori et al., 1998).

tDCS is a well-established neurostimulation technique that allows stimulation of the cerebral cortex in a safe and non-invasive way. Stimulation is conducted via two or more electrodes with opposite polarities (i.e., anodal and cathodal) placed on the scalp and connected with a battery-driven constant current stimulator with a maximum output in the milliampere (mA) range. A relatively weak electrical direct current (usually 1 ~ 2 mA) is applied via the electrodes, and a proportion of it enters the brain (Nitsche & Paulus, 2000; Nitsche et al., 2008). At the macroscopic level, anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases it (Stagg & Nitsche, 2011). Generally, in experimental studies the anodal and cathodal stimulations are compared with a placebo condition (the so called "sham" condition) in which the stimulator is turned off after 30 sec (Gandiga et al., 2006).

However, the impact and directionality of the effects of tDCS on cortical excitability are also influenced by stimulation intensity, as suggested by the study by Batsikadze et al. (2013) where both anodal and cathodal tDCS at 2 mA increased corticospinal excitability, whereas 1 mA cathodal tDCS decreased it. The effects on cortical excitability can last for up to 90 min after a single stimulation session of 13 ~ 20 min duration (Nitsche & Paulus, 2000), and can be further extended by repeated stimulation (i.e., cumulative effects) (Monte-Silva et al., 2013). The physiological aftereffects of prolonged (i.e., application for several minutes) anodal and cathodal tDCS are dependent on synaptic modulation. This assumption is supported by pharmacological studies in humans (Nitsche et al., 2012) and animal models (Fritsch et al., 2010; Kronberg et al., 2017). For example, enhanced long-term potentiation (LTP) in basal dendrites of rat hippocampal slices has been documented in response to anodal stimulation (Kronberg et al., 2017). Anodal stimulation increases intracortical facilitation (ICF), and its after-effects are prevented by NMDA receptor blockade, but enhanced by respective receptor agonists (Liebetanz et al., 2002; Nitsche et al., 2003b, 2005). NMDA receptor block can also prevent cathodal tDCS-generated after-effects (Nitsche et al., 2003b). Given the role of the glutamatergic receptor on ICF (Keller, 1993), it can, therefore, be assumed that glutamatergic neurons are crucial for the induction of plasticity by tDCS. Moreover, tDCS-induced glutamatergic plasticity might be prompted by tDCS-generated alterations of GABA activity. This is suggested by a magnetic resonance spectroscopy (MRS) study documenting a reduction of GABA content of the motor cortex (Stagg et al., 2009) following both anodal and cathodal tDCS (Vicario et al., 2019).

In the context of clinical research, several studies have shown that tDCS could induce specific changes in neuropsychologic, psychophysiologic, and motor activity as a function of targeted brain areas (Boggio et al., 2006; Brunoni et al., 2012; Fecteau et al., 2007; Fregni et al., 2005). Indeed, certain appealing characteristics of tDCS (such as the fact that it is noninvasive and has mostly well-tolerated, transient, and mild adverse effects) have sparked an increase in clinical studies particularly for motor deficits (Fregni et al., 2021), mood disorders (Brunoni et al., 2013), chronic pain (Knotkova et al., 2021) and neurological disorders such as Alzheimer's disease (da Silva et al., 2022), Parkinson's disease (Brak et al., 2021) and Aphasia (Marangolo, 2020).

However, despite a growing body of studies, the real clinical impact of tDCS needs to be further determined since the variety of the published studies, to date, has not yet made it possible to clearly define which parameters (i.e., number of treatments, type of dosage, target area, intensity, and duration of stimulation) are the most effective to obtain the greatest effectiveness of the technique.

In conclusion, tDCS is a valid tool for the following reasons:

1. Safety: the technique does not appear to have any major adverse effects, provided that the stimulation parameters comply with safety limits (Lefaucheur et al., 2017).
2. Practicality: tDCS is a practical, inexpensive, and easy-to-use tool compared to other techniques. It is also can be used as a home-based device (Alonzo & Charvet, 2016).
3. Simple way of inducing placebo effect: subjects cannot easily distinguish between real and sham conditions (Gandiga et al., 2006).
4. Efficacy in treating several clinical conditions: psychiatric and neurological disorders (Fregni et al., 2021).

In the next paragraphs, a brief overview of the most important tDCS aphasia treatment findings which, according to the traditional approach, have applied the electrodes on the classical areas of language will be reported.

Subsequently, in line with the connectionist point of view, more recent studies will be described in which tDCS has been applied on cerebral regions which had never been considered before to support language, such as the motor cortex, the cerebellum, and the spinal cord. In addition, a section will be devoted to tDCS stimulation over the prefrontal regions, including the dorsolateral prefrontal cortex, which have strong interconnections with the frontal areas and seem to support aphasia recovery. Indeed, given that the majority of the left-brain damaged patients present large cortical lesions, it is becoming increasingly urgent to explore other neural structures which could serve as ancillary systems to promote language recovery.

3.3 tDCS and the classical language areas: evidence on post-stroke aphasia

As reported in literature, a growing body of evidence has already suggested that tDCS provides an adjunctive treatment approach for language deficits in patients with chronic stroke-induced aphasia (Marangolo & Caltagirone, 2014; Marangolo, 2020). Indeed, there is substantial agreement on its role in rebalancing the activity of both hemispheres after a stroke. Particularly, it has been proposed that in patients with left hemispheric damage, the homotopic contralateral right hemispheric areas may be in a state of abnormally high activation and may exert an inhibitory effect over the left damaged hemisphere (Belin, 1996; Murase et al., 2004). Thus, language recovery may be enhanced either by increasing the output of the perilesional left hemisphere through excitatory stimulation (Baker et al., 2010; Campana et al., 2015; Fiori et al., 2011, 2013; Fridriksson et al., 2011, 2018b; 2018c; Lee et al., 2013; Marangolo et al., 2011, 2013a, 2013b, 2014a; Norise et al., 2017; Richardson et al., 2015; Santos et al., 2017; Shah-Basak et al., 2015; Spielmann et al., 2018; Vestito et al., 2014;Vila-Nova et al., 2019; Woodhead et al., 2018) or decreasing the inhibition from the intact right hemisphere over the left hemispheric areas by applying inhibitory current over the contralesional cortex (Fiori et al., 2019; Flöel et al., 2011; Kang et al., 2011; Norise et al., 2017; Shah-Basak et al., 2015; Silva et al., 2018; Vines et al., 2011). There were no reported side effects in any of the studies, even when tDCS was applied in a multiple session paradigm (Fregni et al., 2021; Lefaucheur et al., 2017). Together with these two approaches, more recently, dual stimulation has been proposed in which the left and right hemisphere are simultaneously targeted with anodal and cathodal stimulation, respectively, to enhance activity into the left perilesional cortex (Guillouët et al., 2020; Marangolo et al., 2013c, 2014b, 2016). Indeed, a modeling study by Galletta et al. (2015), which compared the most used electrode montages in tDCS aphasia studies, has suggested that unilateral stimulation over the left perilesional area exerts higher electric field magnitude over this region compared to the right unilateral inhibition. Moreover, this effect was even higher after dual stimulation. Thus, most of the tDCS aphasia studies have used these montages to exert the highest effects over the left perilesional region and, thus, to enhance the recovery of language.

The classical modular approach has been most often adopted; thus, positioning the active electrode either over the left Broca's area (Baker et al., 2010; Campana et al., 2015; Fiori et al., 2013; Guillouët et al., 2020; Lee et al., 2013; Marangolo et al., 2011, 2013a, 2013b, 2013c, 2014a, 2014b, 2016; Norise et al., 2017; Santos et al., 2017; Spielmann et al., 2018; Vestito et al., 2014; Vila-Nova et al., 2019; Woodhead et al., 2018), the left Wernicke's area (Fiori et al., 2011, 2013; Flöel et al., 2011; Fridriksson et al., 2011, 2018b, 2018c; Marangolo et al., 2013a, 2013b, 2014a; Spielmann et al., 2018) and, less often, over the right homologues (Cipollari et al., 2015; Fiori et al., 2019; Flöel et al., 2011; Kang et al., 2011; Norise et al., 2017; Shah-Basak et al., 2015; Silva et al., 2018; Vines et al., 2011). Indeed, most of the research has proven that anodal stimulation over these areas combined with language therapy increases different aspects of language. Not surprisingly, the Broca's area is a crucial part of the language network involved in different aspect of language processing (Gough et al., 2005; Hagoort, 2005; Marini & Urgesi, 2012) and it also plays an important role in the recovery of units with high communicative value, such as content units (Marangolo et al., 2013b, 2014a). More specifically, a significant improvement has been shown in noun naming after anodal tDCS over the left frontal gyrus (Baker et al., 2010; Campana et al., 2015; Lee et al., 2013; Marangolo et al., 2014b; Norise et al., 2017; Vestito et al., 2014)¸ the left temporal gyrus (Fiori et al., 2011, 2013; Fridriksson et al., 2011, 2018b, 2018c; Marangolo et al., 2013a), or the right homologues (Flöel et al., 2011; Kang et al., 2011; Norise et al., 2017; Silva et al., 2018). Some other studies have targeted the left inferior frontal gyrus in order to improve verb naming (Campana et al., 2015; De Aguiar et al., 2015; Fiori et al., 2013; Marangolo et al., 2013a, 2013b, 2014b), speech fluency (Campana et al., 2015;

Marangolo et al., 2013b, 2014a, 2014b), repetition (Marangolo et al., 2011, 2013c, 2016; Vila-Nova et al., 2019) and reading (Woodhead et al., 2018). A couple of reports (Cipollari et al., 2015; Vines et al., 2011) have also investigated whether melodic intonation therapy (MIT) combined with anodal stimulation over the right inferior frontal gyrus would increase articulatory difficulties in post-stroke aphasia. Both studies showed positive results with a greater improvement in syllables, words, and sentences repetition after the active condition (Cipollari et al., 2015; Vines et al., 2011).

With regard to the number of stimulation sessions, the studies were not homogeneous varying from one (Lee et al., 2013; Santos et al., 2017) to five (Baker et al., 2010; Fiori et al., 2011, 2013, 2019; Fridriksson et al., 2011; Guillouët et al., 2020; Kang et al., 2011; Marangolo et al., 2011, 2013a, 2013c; Silva et al., 2018; Vila-Nova et al., 2019; Woodhead et al., 2018) to fifteen sessions (Cipollari et al., 2015;Fridriksson et al., 2018b, 2018c; Marangolo et al., 2016). While for current intensity, there was a substantial agreement to use 1 mA (Baker et al., 2010; De Aguiar et al., 2015; Fiori et al., 2011, 2013, 2019; Flöel et al., 2011; Fridriksson et al., 2011, 2018b, 2018c; Marangolo et al., 2011, 2013a, 2013b, 2013c, 2014a; Richardson et al., 2015; Spielmann et al., 2018; Vila-Nova et al., 2019) to 2 mA (Campana et al., 2015; Cipollari et al., 2015; Fiori et al., 2019; Guillouët et al., 2020; Kang et al., 2011; Lee et al., 2013; Marangolo et al., 2014b, 2016; Norise et al., 2017; Santos et al., 2017; Shah-Basak et al., 2015; Silva et al., 2018; Woodhead et al., 2018). Unfortunately, almost half of the reported studies did not include follow-up sessions (Campana et al., 2015; De Aguiar et al., 2015; Guillouët et al., 2020; Kang et al., 2011; Lee et al., 2013; Marangolo et al., 2014a; Santos et al., 2017; Spielmann et al., 2018; Vines et al., 2011) and, in the remaining studies, tDCS effects were measured up to 1–4 weeks after the treatment (Baker et al., 2010; Cipollari et al., 2015; Fiori et al., 2011, 2013, 2019; Flöel et al., 2011; Fridriksson et al., 2011, 2018b, 2018c; Marangolo et al., 2011, 2013a, 2013b, 2013c, 2014b, 2016; Norise et al., 2017; Richardson et al., 2015; Shah-Basak et al., 2015; Silva et al., 2018; Vestito et al., 2014; Vila-Nova et al., 2019; Woodhead et al., 2018).

Anyway, beyond this variability, the literature agrees on some aspects which might assure the long-term maintenance of stimulation efficacy. Long term effects are more easily obtained stimulating the subjects for several consecutive days (Baker et al., 2010; Cipollari et al., 2015; Fiori et al., 2011, 2013, 2019; Fridriksson et al., 2011, 2018b, 2018c; Marangolo et al., 2011, 2013a, 2013b, 2013c, 2014b, 2016; Norise et al., 2017; Richardson et al., 2015; Shah-Basak et al., 2015; Silva et al., 2018; Vestito et al., 2014; Vila-Nova et al., 2019; Woodhead et al., 2018). Indeed, the hypothesis underlying multiple session paradigms is that short-lasting effects from a single session will accumulate with repeated sessions and eventually lead to a permanent improvement in the treated function and/or on untrained materials (for a review, see Marangolo, 2020). It has also been suggested that higher current intensity (i.e., 2 mA) brings greater benefits than lower (i.e., 1 mA) (Fiori et al., 2019). Fiori et al. (2019) highlighted that the systematic determination of stimulation intensity appears to be crucial for obtaining relevant effects. The authors found a significant improvement in verb naming only after cathodal high definition (HD)-tDCS at 2 mA compared to 1 mA.

One important point on which there is a total agreement is that tDCS must be delivered with concomitant language treatment (Fregni et al., 2021; Marangolo, 2020). Indeed, the rationale of the treatment is to potentiate the training (Marangolo, 2020).

In summary, although the results of these studies look very promising, it is worth noting that most of the studies have used a naming treatment approach (i.e., computerized matching, picture naming; Fiori et al., 2011, 2013; Flöel et al., 2011; Fridriksson et al., 2018b; Kang et al., 2011; Lee et al., 2013; Marangolo et al., 2013a; Norise et al., 2017; Santos et al., 2017; Shah-Basak et al., 2015; Vestito et al., 2014) which has not always been considered effective in the literature (Brady et al., 2016).

However, this approach has been combined with tDCS because it offers a highly constrained replicable treatment method, possibly aimed at promoting repetition and intensity of the treatment, which are both aspects known to promote neuroplasticity (Kleim & Jones, 2008). Only very few studies have considered combining tDCS with evidence-based treatment (Cipollari et al., 2015; De Aguiar et al., 2015; Marangolo et al., 2013c, 2014a, 2014b; Vines et al., 2011). Indeed, it is possible that pairing noninvasive brain stimulation with appropriate cognitive tasks and behavioral therapies may increase the "behavioral resolution" of the stimulation procedures. A final missed point was the lack of outcome measures for quantifying the improvement in functional communication. Indeed, one of the major challenges in aphasia rehabilitation is to find the persistence of gains in language and generalization to functional communication outcomes after the intervention (Brady et al., 2016).

In conclusion, although several aspects need to be clarified, there are a series of advantages that make tDCS suitable to be combined with aphasia treatment. tDCS is cost-effective, very well tolerated with low adverse effects, easy-to-use, thus, it can be administered easily in a variety of settings, as during language therapy (Bikson et al., 2016; Lefaucheur et al., 2017). Moreover, the low spatial and temporal resolution which does not allow for specifically targeting a particular language area (Ardolino et al., 2005; Boros et al., 2008; Kwon et al., 2008; Lang et al., 2015; Marshall et al., 2004) might result in a further advantage. Indeed, the diffusion of current inside a damaged system (i.e., the left hemisphere), if it exerts its influence also far away from the targeted area, it may not be entirely negative since it might simultaneously affect several undamaged areas resulting in greatest language recovery (Marangolo, 2020).

3.4 tDCS and the motor cortex: evidence on post-stroke aphasia

In line with the assumption outlined in Chapter 2 that the motor system can support language recovery due its anatomically and functionally link with perisylvian eloquent areas, new approaches to the use of tDCS for aphasia treatment have relied to the hypothesis of modulating the motor regions.

In a pilot study Santos and colleagues (2013) examined whether motor cortex modulation improved language recovery in patients with aphasia. For this purpose, nineteen chronic aphasics underwent ten transcranial direct current stimulation sessions lasting 20 minutes each on consecutive days, using a current of 2 mA. The anode was positioned over the supraorbital area and the cathode over the contralateral motor cortex. They chose to apply tDCS on this area to revert increased transcallosal inhibition of the affected motor cortex in stroke. In all patients, language measures (i.e., oral language comprehension, copying, dictation, reading, writing, naming and verbal fluency) were collected before (T0) and at the end (T10) of treatment. The findings showed that that cathodal tDCS of the unaffected primary motor cortex was associated with significant improvements in simple phrase comprehension, naming, and verbal fluency in relation to names of animals (Santos et al., 2013).

In Meinzer et al.'s work (2016) it was explored whether anodal tDCS delivered over the left motor cortex with concomitant language training improved the naming abilities and functional communication in post-stroke aphasia, also addressing the long-term maintenance of tDCS effects. In a randomized, parallel group, sham-controlled, double-blind clinical trial, 26 aphasics received a highly intensive naming therapy over 2 weeks (8 days, 2 × 1.5 h/day). Concurrently, anodal or sham stimulation was administered to the left primary motor cortex twice daily at the beginning of each training session. The primary outcome was naming ability for specifically trained items. Secondary outcomes comprised transfer to untrained items and generalization to everyday communication ability. All outcome measures were evaluated before and immediately after the end of the intervention and during a 6-month follow-up period. Naming ability for trained items was significantly improved immediately after the end of the intervention in both the anodal and sham-transcranial direct current stimulation groups, with a trend for larger gains in the anodal-transcranial direct current stimulation group. Treatment effects for trained items were significantly better maintained in the anodal-transcranial direct current stimulation group 6 months later. In addition, transfer to untrained items was significantly larger in the anodal-transcranial direct current stimulation group after the training and during the 6-month follow-up assessment. Interestingly, transfer effects were only maintained in the anodal-transcranial direct current stimulation group. Functional communication was significantly more improved in the anodal-transcranial direct current stimulation group at both time points compared to patients treated with sham-transcranial direct current stimulation (Meinzer et al., 2016).

To corroborate this benefit from anodal-tDCS over the motor cortex, in another study (Stahl et al., 2019), 130 chronic aphasics received real or placebo stimulation associated to intensive speech-language therapy consisting of computerized naming treatment and face to-face communicative-pragmatic therapy, after an extensive baseline screening. These tasks included a variety of situations of everyday life that required verbal and non-verbal skills in social interaction. The treatment was administered in two daily sessions over a period of three consecutive weeks (2 h of daily naming therapy; 30 min of daily communicative-pragmatic therapy). Results indicated that intensive SLT combined with A-tDCS on the primary motor cortex enhanced naming and communication skills in chronic post-stroke aphasia, with medium to large effect sizes (Stahl et al., 2019).

Darkow et al. (2017) applied anodal tDCS during fMRI in 16 patients with chronic aphasia and mild naming impairments to investigate how neuromodulation interacts with the residual language network. Anodal tDCS was applied over the left primary motor cortex, as in Meinzer et al.' study (2016). To measure "pure" stimulation effects independent of performance and language treatment, the authors selectively included items that could be reliably named by the patients without therapy. Relative to sham tDCS, anodal tDCS significantly decreased activity in domain-general brain regions that were previously associated with high-level cognitive control. An independent component analysis further revealed increased activity in a larger language-related network and increased connectivity between these regions. In comparison with unstimulated healthy controls, tDCS resulted in a normalization of network activity and connectivity in PWA. The overall reduction in task-related activity was taken to reflect enhanced neural efficiency and less effortful processing (Darkow et al., 2017).

To test whether tDCS stimulation of the motor cortex was able to influence and modulate some aspects of specific lexico-semantic information (i.e., object vs. action words), Branscheidt and colleagues (2018) conducted an experiment in which 16 post-stroke aphasics were asked to perform a lexical decision task judging whether the presented stimuli were words or pseudowords. In all subjects, anodal tDCS delivered over the left motor cortex (20 min, 2 mA; reference electrode over the right subraorbital area) improved accuracy in lexical decision, especially for words with action-related content and pseudowords with an "action-like" ending but not for words with object-related content and pseudowords with "object-like" characteristics. Given the functional role of the motor cortex in processing word meanings related to actions and motor activity (Pulvermüller, 2005), the authors assumed that the stimulation on this site has strengthen content-specific word-to-semantic concept associations only for words, such as action verbs, associated to motor schemata (Branscheidt et al., 2018).

Recently, a study of PWA with severe apraxia of speech (Wang et al., 2019) found that, combined with speech therapy, anodal tDCS administered on the left primary motor cortex (A-tDCS-M1 group) significantly promoted participants' performance in tasks such as auditory word-picture matching and picture naming, and this positive effect was more evident than in the Broca's and sham stimulation group (Wang et al., 2019). In the same study, results for approximate entropy revealed that not only the left motor cortex but also the dorsolateral prefrontal cortex and Broca's area in the ipsilateral hemisphere were significantly activated in the A-tDCS-M1 group, suggesting that stimulation over the left motor cortex could result in an extensive effect on the activation of other speech-related areas in the articulatory network, improving language production (Wang et al., 2019).

In conclusion, these studies show that tDCS over the motor cortex combined with language treatments improves the retrieval of language stimuli with sensorimotor features, such as action verbs and articulatory abilities, providing a novel 'backdoor' approach in aphasia rehabilitation.

3.5 tDCS and the cerebellum: evidence on post-stroke aphasia

Given that the cerebellum is involved in motor coordination, and it is functionally and anatomically linked to major language areas in the left hemisphere, several researchers wondered whether it might be a promising alternative stimulation target site for language recovery.

In a pioneering work, Sebastian et al. (2017) applied anodal tDCS over the right cerebellum in a double-blind, sham-controlled, within-subject cross-over case design studying a mute chronic, stroke patient with bilateral lesions in the middle cerebral artery territory. The stimulation protocol was applied over 2 intervention phases (anodal vs sham) of 15 sessions, 3–5 per week, separated by 2 months, concurrently with a behavioral spelling treatment. The findings showed that both anodal and sham resulted in improved spelling to dictation for trained and untrained words immediately after and 2 months post-treatment, but the improvement was greater with anodal tDCS than with sham especially for untrained items. Further, generalization to written picture naming was noted only with tDCS. Finally, the resting state functional connectivity data indicated that improvement in spelling was accompanied by an increase in cerebro-cerebellar network connectivity (Sebastian et al., 2017).

Similarly, Marangolo and colleagues (2018) aimed to verify whether the cerebellum, as part of the motor system, contributed to verb retrieval. In particular, the authors wanted to investigate if cerebellar stimulation would be efficacious for any language task or only if the task would require cognitive efforts and, thus, the activation of some other cognitive components (i.e., working memory) which supports language processing. Indeed, several studies have already suggested that the role of the cerebellum in language processing depends on task demands (Ackermann et al., 2007; Pope & Miall, 2014; Stoodley et al., 2010; Stoodley et al., 2012). Ackermann et al. (2007) have argued that non-linguistic aspects of task performance, such as the amount of effort or the degree of automaticity, might account for cerebellar involvement during verb generation. Similarly, Stoodley and Schmahmann (2009) have claimed that the cerebellum takes part not in the language function *per sé* but only when the task is cognitively demanding and, thus, engages other cognitive components, such as working memory and/or executive functions (Stoodley & Schmahmann, 2009). Indeed, apart from motor control and higher order aspects of speech production, a variety of studies have pointed to a contribution of the cerebellum in executive and memory tasks (Ackermann et al., 2007). Because the paradigm of verb generation involves the production and selection of different verbal responses (Thompson-Schill et al., 1998), pre-articulatory rehearsal processes are engaged as well, which rely on working memory processes (Ackermann et al., 2007, Helmuth et al., 1997).

Following these hypotheses, Marangolo and collaborators (2018) investigated the effect of cerebellar DCS coupled with a verb training in 12 PWA by contrasting two different language tasks with different demands in terms of cognitive effort: a verb naming and a verb generation task. Indeed, with respect to verb naming in which the production of the correct answer is facilitated by the presented picture, verb generation requires the patient to creatively link a noun to a verb choosing among competing response alternatives (Thompson-Schill et al., 1998), thus, relies on different cognitive strategies (Ackermann et al., 2007; Justus et al., 2005).

Interestingly, although verb generation is a task more cognitively demanding than verb naming and persons with aphasia generally experience greatest difficulty with verb generation (Martin & Cheng, 2006; Thompson-Schill et al., 1998), in Marangolo et al.'s study (2018), PWA benefited only for this task after right cerebellar cathodal stimulation. Because these results point to potential therapeutic benefits of cerebellar stimulation only for complex language tasks, the authors believe that these findings have important implications for aphasia. Indeed, they address the possibility that the cerebellum might support cognitive functions which sustain language recovery (Marangolo et al., 2018).

In a recent follow-up investigation, Sebastian et al. (2020) performed a randomized, double-blind, sham-controlled, within-subject cross-over study design, where individuals with chronic aphasia received 15 treatment sessions (3–5 sessions per week, washout period of 2 months) of anodal cerebellar tDCS (N=12) or cathodal cerebellar tDCS (N=12) plus computerized aphasia therapy as well as sham plus computerized aphasia therapy. The authors found that tDCS was more effective than sham in the immediate post-treatment phase for participants who received “tDCS first”; a significant effect of tDCS for untrained naming was also observed immediately and 2 months post-treatment. Greater gains in naming (relative to sham) were noted for participants receiving cathodal stimulation for both trained and untrained items (Sebastian et al., 2020).

To date, only an open-label pilot study by DeMarco and colleagues (2021) demonstrated that anodal cerebellar tDCS does not enhance language processing. In this study, 24 patients with chronic post-stroke aphasia were recruited: 10 individuals received active stimulation and 14 individuals sham stimulation. The stimulation protocol (5 consecutive days of 1 hour for both conditions) was associated with a multimodal speech therapy targeted anomia. Before treatment, once at 24 hours post treatment, and at the 3-month follow-up, all participants underwent five behavioral tests to assess aphasia quotient, speech production at the sentence level, lexical retrieval and category and letter fluency. Cloze sentence completion, verb generation, verb naming and motor production were only administered to the stimulation group. Cerebellar tDCS did not significantly enhance language processing measured either immediately following treatment or at the 3-month follow-up. The effect sizes of tDCS over sham treatment were generally nil or small, except for the mean length of utterance on the picture description task and for the response time on the verb generation task (DeMarco et al., 2021).

Despite this controversial outcome, the above-mentioned studies corroborate the concept that cerebellar stimulation might be an optimal target site for aphasia rehabilitation, especially for heterogeneous patients whose left hemisphere lesions vary in size and location.

3.6 tDCS and the spinal cord: evidence on post-stroke aphasia

Following the hypothesis of an involvement of the motor system in processing some aspects of speech (i.e., action verbs), Marangolo et al. (2017) investigated whether the spinal cord might also take part in verb retrieval. Indeed, several studies have shown that the spinal cord possesses capacities of activity-dependent plasticity for the acquisition and maintenance of behavioural pattern on motor function/ skills both in normal condition and after spinal cord injury (see Wolpaw & Tennissen, 2001 for review).

Moreover, given the well-known strong reciprocal connections between the cortex and the spinal cord (Di Lazzaro et al., 2012, 2013; Roche et al., 2009, 2011), the authors assumed that the stimulation of the spinal cord would influence activity into the sensorimotor cortex, through its ascending spinal pathways, which, in turn, would facilitate words with sensorimotor properties, such as action verbs. Indeed, it has been shown that transcutaneous spinal direct current stimulation (tsDCS) delivered over the thoracic vertebrae modulates spinal cord activity along the lemniscal pathways increasing or reducing cortical excitability possibly by inducing depolarization or hyperpolarization of the neural membrane resting potential (Bocci et al., 2015a, 2015b).

Thus, Marangolo et al. (2017) explored the combined effect of tsDCS and language treatment for the recovery of verbs and nouns in 14 chronic aphasics. During each treatment, each subject received tsDCS (20 min, 2 mA) over the thoracic vertebrae (10th vertebra) in three different conditions: (1) anodal, (2) cathodal and (3) sham, while performing a verb and noun naming tasks. In all conditions, the reference electrode was placed over the right shoulder. Each experimental condition was run in five consecutive daily sessions over 3 weeks with 6 days of intersession interval. Results showed that anodal tsDCS differently affected the amount of improvement in noun and verb naming. Indeed, while nouns and verbs significantly improved in all patients in each condition at the end of training due to the language treatment, anodal tsDCS boosted recovery only for verbs. There were no significant differences for the recovery of nouns in the three experimental conditions. This specificity argues against an effect simply due to enhanced cognitive arousal which should have influenced both verb and noun naming. Given that one of the main functions of the spinal cord is to translate sensory information into motor output and that tsDCS exerts its influence also into the brain (Bocci et al., 2015a, 2015b, 2015c; Nitsche et al., 2005), the authors argued that tsDCS contributed to the recovery of verbs since action verbs are made of motor properties (i.e., to bite). Conversely, nouns not related to specific action (i.e., cloud) did not activated the motor pathways and, therefore, did not benefit from this facilitation (Marino et al., 2012, 2014). Very recently, the same authors (Marangolo et al., 2020) replicated the above study also measuring, through resting state functional magnetic imaging (rs-fMRI), possible functional connectivity changes due to spinal stimulation. As in the previous study, after anodal stimulation, PWA showed a significant greater improvement in verb retrieval with respect to the sham condition. Interestingly, this improvement was significantly correlated with functional connectivity changes into a cerebellar-cortical network which involved the left cerebellum, the right parietal lobe and the premotor cortex, all regions related to action semantics and verb processing (Marangolo et al., 2020).

Although this finding seems surprising and it requires further investigation, it suggests that spinal stimulation exerts its influence at the cortical level, thus, acting as a “bridge” for conveying tsDCS induced changes into brain networks involved in verb production.

3.7 tDCS and the prefrontal cortex: evidence on post-stroke aphasia

A new approach in aphasic neurorehabilitation is to move from a language-centric understanding of aphasia toward one focusing on non-linguistic factors that can support and possibly reshape neural networks engaged in language recovery (Cahana-Amitay & Albert, 2015). This alternative approach involves targeting stimulation to areas of the brain that are farther away from the damaged regions but interconnected to the linguistic areas. The few studies that have considered this perspective in aphasia have primarily focused on stimulating the dorsolateral prefrontal cortex (DLPFC) (Pestalozzi et al., 2018; Riley et al., 2022; Saidmanesh et al., 2012). It is well known that DLPFC is engaged in higher level cognition and, in particular, in executive functions control (i.e., inhibition, set-shifting and updating components) (Miller & Cohen, 2001). Although the DLPFC has never been considered as specifically related to language tasks, its role for implementing functional connectivity between the language network and other cognitive domains has been widely recognized (for a review see Hertrich et al., 2021).

Based on this assumption, in Saidmanesh et al.'s work (2012) it was investigated whether anodal tDCS (2 mA, 20 min) over the left dorsolateral prefrontal cortex (DLPFC) and cathodal tDCS over the right DLPFC versus sham stimulation improves working memory and aphasia quotient in individuals with post-stroke aphasia. Twenty patients with chronic non-fluent aphasia received both real and sham tDCS for ten days. Before and after the interventions, the Persian Aphasia and the 2-Back Test were administered. The Persian AQ scores improved significantly in the active stimulation group compared to sham, as did working memory by 2-Back test. The latter improvement implied that there had been an effect on DLPFC. Although increase in working memory leading to improvement in speech performance might be one way to speculate the significant increase in AQ, in the work, it is not clearly discussed how dual stimulation over DLPFC might have played a role in speech recovery.

Interestingly, Pestalozzi and colleagues (2018) have explored whether strengthening executive control through anodal tDCS over the left DLPFC facilitated lexical access in chronic poststroke aphasia. In a randomized-controlled and double blind within-subject design, 14 participants with chronic poststroke aphasia underwent language assessment (baseline) and two tDCS sessions (1mA; 20 min): anodal and sham, separated by one week interval. Performances in picture naming, verbal fluency, and word repetition were evaluated immediately after stimulation. The authors found that anodal stimulation of the intact left DLPFC modulated performance of PWA in a verbal fluency task, supporting the idea that increasing prefrontal excitability could have exerted beneficial effects on language functioning in aphasia. Moreover, despite no overall effects on picture naming and repetition, prefrontal stimulation had a facilitative effect on naming high-frequency words. Therefore, the present study indicated that strengthening executive control functions after stroke could complement speech and language–focused therapy (Pestalozzi et al., 2018).

Based on evidence that non-perilesional tDCS stimulation targets have the potential to improve response to aphasia treatment, in an open-label study Riley and co-workers (2022) wanted to verify whether anodal tDCS over DLPFC improved sustained attention, facilitating language learning in persons with aphasia. Twelve participants with mild/moderate aphasia received ten 30-min training sessions (20 minutes of simultaneous tDCS and artificial grammar training and 10 minutes of only artificial grammar training).

During the artificial grammar task, participants were presented with strings of forms that followed specific rules of an artificial grammar and asked to recall them in a matching task using laminated cards while the examiner provided auditory feedback on response accuracy. Sustained attention was measured pre- and post-training using a Continuous Performance Task (CPT) and artificial grammar learning was measured post-training using a 2-choice grammaticality judgment task and an artificial grammar rules test. The findings showed an improvement in CPT accuracy and in two artificial grammar learning measures. Despite the small sample size and the lack of a control treatment condition, this research emphasizes how anodal tDCS over DLPFC can enhance cognitive and linguistic performance in post-stroke aphasia (Riley et al., 2022).

Taken together, these studies support the idea that increasing prefrontal excitability through tDCS might have positive effects on language recovery after stroke-induced aphasia. Indeed, future studies are needed to better understand the effects of DLPFC stimulation on different linguistic aspects.

In the following chapter, I will present the research carried out during my three Ph.D. years which pursued the hypothesis to further investigate the effectiveness of tDCS for language recovery. In particular, starting from the traditional assumption of stimulating the classical language areas, I will first report a study on tDCS application for the recovery of writing abilities. Then, to further explore the role of the spinal cord in the processing of sensorimotor language components, a study on the effectiveness of spinal cord stimulation for apraxia of speech disorders will be described. Finally, to further understand the relationships between the executive control domain and the ability to rely on functional communication in severe aphasia, a tDCS study will be reported which, applying tDCS over the dorsolateral prefrontal cortex, measures the language and communication improvement by using executive tasks.

CHAPTER IV

EXPERIMENTAL SECTION

This chapter describes all the research conducted during my three years of Ph.D. which led to the publication of three scientific articles reported in the next paragraphs. In all studies, the use of tDCS for the recovery of language in post-stroke chronic aphasia was investigated. In the first experiment, following the traditional approach of language representation, tDCS was applied over the left temporo-parietal cortex to investigate its role for the recovery of writing disorders. In the second experiment, the use of transpinal stimulation was compared with tDCS applied over the frontal region to verify which of the two techniques is the most effective for the recovery of articulatory difficulties. In the third experiment, following the connectionist approach, an executive function training combined with tDCS over the right dorsolateral frontal cortex was investigated to evaluate its impact on functional communication in severe aphasia.

4.1 EXPERIMENT 1

DUAL-tDCS Treatment over the Temporo-Parietal Cortex Enhances Writing Skills: First Evidence from Chronic Post-Stroke Aphasia[1]

Abstract

The learning of writing skills involves the re-engagement of previously established independent procedures. Indeed, the writing deficit an adult may acquire after left hemispheric brain injury is caused by either an impairment to the lexical route, which processes words as a whole, to the sublexical procedure based on phoneme-to-grapheme conversion rules, or to both procedures. To date, several approaches have been proposed for writing disorders, among which, interventions aimed at restoring the sub-lexical procedure were successful in cases of severe agraphia. In a randomized double-blind crossover design, fourteen chronic Italian post-stroke aphasics underwent dual transcranial direct current stimulation (tDCS) (20 min, 2 mA) with anodal and cathodal current simultaneously placed over the left and right temporo-parietal cortex, respectively. Two different conditions were considered: (1) real, and (2) sham, while performing a writing task. Each experimental condition was performed for ten workdays over two weeks. After real stimulation, a greater amelioration in writing with respect to the sham was found. Relevantly, these effects generalized to different language tasks not directly treated. This evidence suggests, for the first time, that dual tDCS associated with training is efficacious for severe agraphia. Our results confirm the critical role of the temporo-parietal cortex in writing skills.

4.1.1 Introduction

Aphasia is an acquired language impairment following left-hemisphere brain injury (Ali et al., 2015). The aphasic symptoms vary in terms of severity and degree of involvement across the different language modalities, such as oral expression, comprehension, reading, and writing. Despite the fact that clinicians and therapists are generally more attentive to spoken than written language disorders, persons with aphasia (PWA) also show severe difficulties in writing (Sinanović et al., 2011; Thiel et al., 2015), which interferes with everyday activities (e.g., to take notes; to make a shopping list). Indeed, to date, due to

[1] Pisano, F., Caltagirone, C., Incoccia, C., & Marangolo, P. (2021). DUAL-tDCS Treatment over the Temporo-Parietal Cortex Enhances Writing Skills: First Evidence from Chronic Post-Stroke Aphasia. *Life (Basel, Switzerland)*, *11*(4), 343. https://doi.org/10.3390/life11040343

the overuse of internet devices (i.e., computers, tablets, mobile phones, emails), written language has become more important than previously considered.

One of the major models proposed for writing is the dual-route model (DRM). In its most simplified version, the model assumes two independent procedures which operate in parallel: a lexical route that processes words as a whole, and a sublexical one based on phoneme-to-grapheme conversion procedures (Beeson et al., 2002; Ellis, 2000; Kiran, 2005). A dual-route model accounts for how a literate person can write both regular, and irregular words and legal nonwords. As within the lexical route for word naming, the lexical route for writing includes two stores encompassing the phonological and orthographic lexical representation of words and a semantic store that contains their semantic representation (Coslett et al., 2000). This route allows a person to write any type of familiar words (regular vs. irregular) but cannot be used when spelling unfamiliar words or nonwords; thus, it is the only method available for writing irregular words (Beeson et al., 2002; Ellis, 2000; Kiran, 2005). On the contrary, sublexical procedures rely on phoneme-to-grapheme conversion rules which translate a string of sounds (i.e., phonemes) into its corresponding graphemes. This procedure is used to write regular words and nonlexical phonemic strings (nonwords) (Angelelli et al., 2018; Beeson et al., 2002; Ellis, 2000; Kiran, 2005).

The major evidence for a dual-route procedure for writing derives from the observation of PWA affected by writing disorders (Baxter & Warrington, 1985; Beauvois & Dérouesené, 1981; Harris & Coltheart, 1986; Patterson, 1986; Shallice, 1981). Indeed, the writing deficits an adult subject may acquire after left hemispheric brain injury might be caused by either an impairment to the lexical route, to the sublexical one, or to both procedures. The most frequent syndrome due to a damage to the lexical pathway is surface dysgraphia (Beauvois & Dérouesené, 1981; Goodman & Caramazza, 1986). Errors in spelling irregular words are the most frequent symptom. Thus, this syndrome is more easily detected in languages with irregular spelling such as English. In "transparent languages" (i.e., Italian, Spanish), this difficulty translates into "dysorthography" (Angelelli et al., 2018; Ardila et al., 1996; Bigozzi et al., 2016; Luzzi et al., 2003). Indeed, in those languages, the sub-lexical route allows a person to correctly transcribe the phonological strings through the phoneme-to-grapheme correspondence based on either sound–letter conversion or syllabic conversion so that the lexical route is largely superfluous (Angelelli et al., 2018; Bigozzi et al., 2016; Laiacona et al., 2009). The alternate pattern of impairment, due to damage to the phoneme-to-grapheme conversion procedure, leads to phonological dysgraphia. In this case, if the word is common and stored in the orthographic lexicon, the word may still be spelled appropriately, while, if the word is unknown, writing errors would occur (Roeltgen et al., 1983; Shallice, 1981). Thus, patients with selective damage to the phonological pathway may still be able to write both regular and irregular familiar words, but they cannot write unfamiliar words or stimuli that are not real words (nonwords) which rely on the sub-lexical route (Roeltgen et al., 1983; Shallice, 1981). In the most severe cases, both the lexical and the sublexical routes are damaged, resulting in central agraphia—the complete loss of the ability to communicate through writing (Bub & Kertesz, 1982).

To date, several rehabilitative approaches have been proposed for writing disorders which aim either at restoring the compromised written subcomponents or at promoting compensatory strategies (Beeson, 2004; Hillis & Heidler, 2005; Johnson et al., 2019; Thiel et al., 2015). Treatments targeting sub-lexical processes in writing require the patient to segment the words and/or nonwords into syllables and phonemes, to write graphemes for each dictated phoneme, and to associate a specific grapheme with the words starting with that grapheme (Beeson et al., 2000; Cardell & Chenery, 1999; Kiran, 2005; Luzzatti et al., 2000; Thiel et al., 2015). In the case of Italian, specific training aimed at restoring the sub-lexical route was also successful in cases of severe agraphia since, due to the transparency of the language, this procedure also offers a rapid generalization of the acquired learning to untrained items (Carlomagno & Luzzatti, 1997). Indeed, generalization to untreated items is expected as, through this procedure, the patient learns the correspondence between sounds and graphemes regardless of their position within the word. Since in the Italian language the conversion procedures take place at the syllabic level (Bigozzi et al., 2016; Caravolas, 2004; Marinelli et al., 2015; Notarnicola et al., 2012), syllabic segments were used to stimulate the sublexical processes. Accordingly, from a development point of view, in the early phases of writing acquisition, Italian children segment the phonological input string and translate into the corresponding orthographic sequence. Later on, after a rapid development of the sub-lexical route, they gradually acquire the orthographic lexical representation of the whole word, relying on the lexical route (Bigozzi et al., 2016; Caravolas, 2004; Marinelli et al., 2015; Notarnicola et al., 2012).

To date, new treatment approaches have emphasized the role of non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), in enhancing language improvement in PWA (for a review, see Marangolo, 2020). Through tDCS, a weak electrical current (1–2 mA) is administered via two surface electrodes applied to the scalp. It is generally assumed that anodal stimulation increases the excitability over the targeted area, while cathodal stimulation diminishes it by affecting the resting membrane potential of the cell (Stagg & Nitsche, 2011). Depending on the duration, polarity and intensity of stimulation, these effects may last for minutes to hours compared with a placebo condition (known as a "sham" condition), in which the stimulator is turned off after 30 s (Lefaucheur et al., 2017; Nitsche & Paulus, 2011). More recently, a new approach, "Dual-tDCS", has been suggested, in which the left and the right hemisphere are simultaneously stimulated with opposite current. In the case of aphasic disorders, generally, anodal stimulation has been delivered over the left injured language areas with cathodal stimulation over the right homologous ones (De Aguiar et al., 2015; Lee et al., 2013; Marangolo et al., 2013c, 2016). Indeed, although several studies have shown that the chronically reorganized language system can sometimes engage homotopic language areas in the right hemisphere (Crinion & Price, 2005; Leff et al., 2002; Robson et al., 2014), particularly in the case of an extended lesion to the left hemisphere (Leff et al., 2002; Robson et al., 2014; Turkeltaub et al., 2011), an abnormal interhemispheric imbalance due to an increase in the excitability of the undamaged right hemisphere which exerts interhemispheric inhibition (IHI) over the lesioned one has also been often described after unilateral left-hemispheric stroke. Thus, in order to restore this maladaptive condition, dual-tDCS has also been proposed (see for a review Marangolo, 2020; Picano et al., 2021). To our knowledge, to date, only a single case with post-stroke aphasia has been reported in which the use of dual tDCS resulted in successful improvement of written language (De Tommaso et al., 2017). In this study, the concurrent application of dual-tDCS over the left and right temporo-parietal regions for twelve sessions (three consecutive days for four weeks) combined with sublexical procedure training (i.e., reading and writing lists of syllables) resulted in greater effects of real stimulation compared to sham. Indeed, after dual-tDCS, the patient improved in nonword and word writing, with a generalization effect also in reading (De Tommaso et al., 2017). Indeed, recent meta-analyses of neuroimaging studies have reported a considerable overlapping between the cortical regions involved in writing and reading (DeMarco et al., 2017; Planton et al., 2013; Purcell et al., 2011). In particular, these studies have corroborated the role of several perysilvian cortical areas for gaining access to sublexical procedures, among which is the temporo-parietal cortex (Beeson et al., 2003; Clark & Wagner, 2003; DeMarco et al., 2017; Purcell et al., 2011; Rapcsak & Beeson, 2015; Tsapkini & Rapp, 2010). Accordingly, most tDCS studies have targeted the left temporo-parietal cortex through real stimulation in order to improve word reading efficiency (Turkeltaub et al., 2012) and nonword reading speed (Cancer & Antonietti, 2018; Costanzo et al., 2016, 2019). Interestingly, with reference to the present study, the left temporo-parietal region showed greater activation during nonword with respect to real word writing, suggesting a specific involvement of this region in sublexical processing (DeMarco et al., 2017; Ludersdorfer et al., 2015).

Thus, in line with all the previous literature, the aim of the present work was to investigate the effect of dual-tDCS over the left and right temporo-parietal cortex combined with a writing treatment in a group of post-stroke chronic aphasia patients with central agraphia. Since all were Italian subjects, we used syllabic segments in order to restore the sublexical route (Bigozzi et al., 2016; Caravolas, 2004; Marinelli et al., 2015; Notarnicola et al., 2012).

4.1.2 Materials and Methods

Participants

Fourteen chronic post-stroke non-fluent aphasics (7 females and 7 males) with a single left hemisphere stroke were recruited in the study (see Table 4.1.1). Inclusion criteria were native Italian proficiency, a single left hemispheric stroke at least 6 months prior to the investigation, pre-morbid right handedness (based on the "Edinburgh Handedness Questionnaire"; Oldfield, 1971) and no acute or chronic neurological symptoms needing medication. Subjects over 75 years of age and those with seizures, implanted electronic devices (e.g., pacemaker) and previous brain damage were excluded. In order to avoid confounding therapy effects, none of the participants had received language treatment for at least 6 months before the time of inclusion in the study.

Table 4.1.1 Sociodemographic and clinical data of the fourteen non-fluent aphasic patients (Ciurli et al., 1996).

P	Sex	Age	Ed. Level	Time post onset	Stroke type	Lesion side (LH)	Oral NN	Oral VN	Written NN	Written VN	WR	NWR	W Read	NW Read	W D	N W D	TT
1	M	57	13	3 y	I	FTI	7.5	10	0	0	35	22.5	15	5	0	0	4
2	M	59	13	3y	I	T	0	0	0	0	25	30	17.5	15	0	0	2.5
3	M	53	17	1y	I	FTI	0	0	0	0	22.5	30	12.5	15	0	0	6
4	F	65	8	3y	I	FTI	15	15	0	0	42.5	20	20	10	0	0	10
5	M	55	13	4y	I	T	15	10	0	0	20	15	15	5	0	0	10
6	M	64	13	1y	I	FTP	0	0	0	0	0	0	0	0	0	0	2
7	M	62	17	1y	I	FTI	7.5	0	0	0	40	32.5	12.5	2,5	0	0	10
8	M	63	17	4y	I	FTI	0	0	0	0	0	0	0	0	0	0	2
9	F	55	13	3y	I	FTP	15	15	0	0	80	35	32.5	10	0	0	8
10	F	57	8	1y	I	T	0	0	0	0	0	0	0	0	0	0	10
11	F	55	13	1y	H	FTP	15	15	0	0	85	70	15	15	0	0	10
12	F	65	13	2y	I	FTP	10	15	0	0	15	10	15	15	0	0	10
13	F	58	8	4y	I	FTP	10	10	0	0	20	20	12,5	5	0	0	7.5
14	F	65	13	3y	I	FTP	15	12.5	0	0	10	15	15	5	0	0	4

Legend: P = Participants; M= male; F= female; Ed. Level = Educational Level; y=year/years; I = Ischemic; H = Hemorrhagic; LH = Left hemisphere; FTI = fronto-temporo-insular; T = temporal; FTP = fronto-temporo-parietal; Oral NN = Noun Naming; Oral VN = Verb Naming; Written NN = Noun Naming; Written VN = Verb Naming; WR = Word Repetition; NWR = Nonword Repetition; W Read = Word Reading; NW Read = Nonword Reading; WD = Word under Dictation; NWD = Nonword under Dictation; TT = Token Test (cut-off score 29/36).

Ethics Statement

The data analyzed in the current study were collected in accordance with the Helsinki Declaration and the Institutional Review Board of the IRCCS Fondazione Santa Lucia, Rome, Italy. Prior to participation, all patients signed informed consent forms. In particular, they acknowledged that: "The most common reported adverse effects of tDCS in the literature (Lefaucheur et al., 2017) include skin tingling, itching, mild burning sensations, and discomfort, most of which are temporary and well tolerated. The physical adverse effects are restricted to the site of stimulation. The therapist is thoroughly informed as to the technique and adverse effects and the procedure will be fully supervised by a neurologist”. They also knew that: “If you take part in this study, the insurance will cover any possible damage resulting from the application of tDCS”.

Clinical Data

All patients were affected by severe non-fluent aphasia. Subjects were not able to spontaneously speak, but they did not present with articulatory difficulties. To investigate their language performance in depth, each participant underwent a standardized language test (Esame del Linguaggio II; Ciurli et al., 1996). The test included different language tasks: oral and written noun and verb-naming (n = 20 for noun naming, i.e., penna (pen); n = 10 for verb naming, i.e., mangiare (to eat), dormire (to sleep)), words and sentences repetition, reading and writing under dictation (words, n = 20, i.e., tavolo (table), sentences, n = 10, i.e., il marinaio sale sulla nave (the sailor gets on the ship)), nonword syllable repetition, reading and writing under dictation (n = 20, i.e., bo, fime, tarino), and oral and written word (i.e., pipa (pipe)) and sentence (i.e., apra il libro (open the book)) comprehension. Since the test has been constructed in order to investigate language abilities in severe aphasia, all were high and medium frequency words. The stimuli were divided according to the grammatical class (nouns, verbs), frequency (high ≥ 30/million, medium ≥ 20/million) and length (short = 4/6 phonemes, long ≥ 6 phonemes).

All subjects were able to produce few words in noun and verb naming, and to repeat and to read some words and nonwords (see Table 4.1.1). They presented with a very severe impairment in writing. They were not able to write any single words and/or syllables (nonwords), showing severe damage both to the lexical and sublexical procedures (Ellis & Young, 2000). All subjects were able to auditorily comprehend simple words and commands of the language test (Esame del Linguaggio II; Ciurli et al.,1996), while they were not able to accomplish more complex auditory comprehension tasks (Token test cut-off 29/36, De Renzi & Faglioni, 1978).

Materials

Two lists of sixty stimuli were constructed. Each list contained twenty syllables (e.g., BU, CE, FO), twenty disyllabic (CVCV consonant–vowel, e.g., BUCE) and twenty trisyllabic nonwords (CVCVCV consonant–vowel, e.g., BUCEFO). According to the International Phonetic Alphabet (International Phonetic Association, Smith, 1999), syllables encompass different places (e.g., plosive, nasal, fricative) and manners of articulation (e.g., bilabial, dental, velar).

Procedure

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) was applied using a battery driven Eldith (neuroConn GmbH) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 cm × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the ipsilesional and the cathode over the contralesional temporo-parietal cortex (CP5 and CP4 of the extended International 10–20 system for EEG electrode placement). For sham stimulation, the same electrode positions were used. The current was ramped up to 2 mA and slowly diminished over 30 s to guarantee the typical initial tingling sensation (Gandiga et al., 2006). In both conditions (real vs. sham), patients were administered simultaneous language treatment (see below), which was performed in ten daily one-hour treatment sessions (Monday–Friday, weekend off, Monday–Friday). There was a 14-day intersession interval between the real and the sham condition. The order of conditions was randomized across subjects. Both the clinician and the patient were blinded with respect to the administration of tDCS, which was applied by a third person who was not involved in the study. At the end of each condition, subjects were asked if they were aware of which condition (real or sham) they were in. None of the subjects was able to determine differences in sensation and intensity between the two conditions.

Language Treatment

All patients underwent the standardized language test at the beginning (baseline; T0), at the end (T10) of each treatment condition, and one week after the end of the treatment (follow-up; F/U).

Since each patient showed the presence of severe agraphia which equally affected the lexical and sublexical route (Beeson et al., 2002; Ellis & Young, 2000; Kiran, 2005) and our patients were all native Italian speakers, based on previous evidence (Beeson et al., 2010; Cardell & Chenery, 1999; Kiran, 2005), the intervention was aimed at restoring the sublexical route via syllable repetition, reading and writing.

Before the treatment, all 120 stimuli (syllables, disyllabic and trisyllabic nonwords) were auditorily randomly presented to each patient. The participant had to read and write each stimulus within 30 s. As all participants failed to correctly write all the presented stimuli, the whole lists were subdivided into two lists of sixty stimuli. Each list was randomly assigned to each participant and to one of the two experimental conditions (real vs. sham). For each condition, the order of presentation of stimuli was randomized across the training sessions. The therapy method was similar for all patients. For each condition (real vs. sham), during each session, the whole list of stimuli was presented. The clinician presented one stimulus at a time and for each stimulus, the treatment relied on three different steps which would progressively facilitate the patient in correctly writing it.

Step 1: The clinician auditorily presented the whole stimulus and asked the patient to write it. If the patient correctly wrote the stimulus, the clinician would proceed with the other stimulus, but if he or she made mistakes the clinician would move on to the next step.

Step 2: The clinician auditorily presented the stimulus again and asked the patient to write it. If the patient correctly wrote the stimulus, the clinician would ask the participant to read it, but if he or she made mistakes the clinician would move on to the next step.

Step 3: The clinician wrote the stimulus and asked the patient to read it. After a few seconds, the clinician covered the stimulus and asked the patient to write it again. If the patient could not solve the task, the clinician proceeded with another stimulus.

The response was registered as correct only if the patient wrote the stimulus in the first step. The clinician manually recorded the response type on a separate sheet.

Data Analysis

The patients' performance was evaluated by considering the mean percentage of response accuracy for syllables and disyllabic and trisyllabic nonwords for each condition (real vs. sham). Data were analyzed using SPSS 20.0 software (IBM SPSS Statistics, version 20, Armonk, NY, USA). Three repeated measures ANOVAs were performed separately for syllables and disyllabic and trisyllabic nonwords. For each analysis, two "within" factors were considered: CONDITION (real vs. sham) and TIME (baseline (T0) vs. end of treatment (T10) vs. follow-up (FU)). The post hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of $p \leq 0.05$ were considered statistically significant. Before and after each treatment condition, the patients' responses to the different re-administration of the standardized language test (Language Examination II; Ciurli et al.,1996) were also analyzed using χ^2-test.

4.1.3 Results

Accuracy Data

Syllables

The analysis showed a significant effect of CONDITION (real vs. sham, F (1,13) = 83,27, $p < 0.001$) and TIME (baseline (T0) vs. end of treatment (T10) vs. follow-up (F/U), F (2,26) = 353,78, $p < 0.001$). The interaction TIME × CONDITION was also significant (F (2,26) = 88,65, $p < 0.001$). Bonferroni's post hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (real 5% vs. sham 5% $p = 1$), the mean percentage of accuracy was significantly greater in the real than in the sham condition at T10 (real 70% vs. sham 40%, $p < 0.001$) and persisted at F/U (real 70% vs. sham 40% $p < 0.001$). Significant differences also emerged between T0 and T10 for the sham condition (35%, $p < 0.001$) (see Figure 4.1.1).

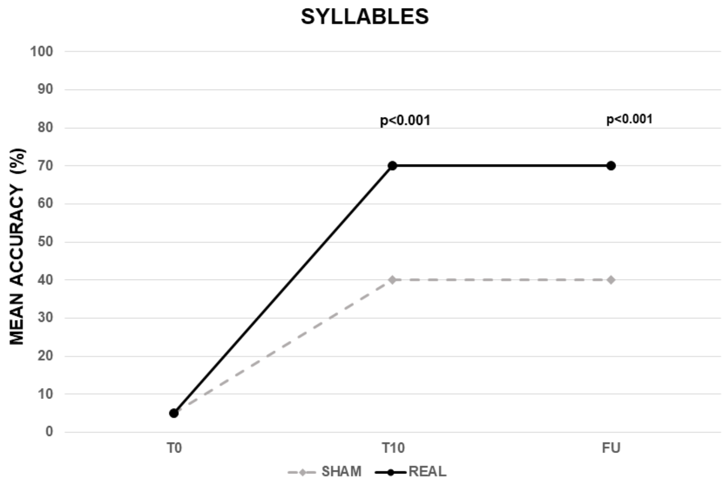

Figure 4.1.1 Mean percentage of response accuracy for syllables at baseline (T0), at the end of treatment (T10), and at follow-up (F/U) for the real and sham condition, respectively.

We ran further analysis by adding the order of conditions (real vs. sham) as a fixed factor. The analysis revealed that the results were not significantly affected by the order of condition (F (1,12) = 1.16, $p = 0.30$). Moreover, a mixed analysis of variance (ANOVA) with ORDER of CONDITIONS as the between-subjects factor (first treatment vs. second treatment) and CONDITION (real vs. sham) and TIME (baseline (T0) vs. last day (T10) vs. follow up (FU)) as two within-subjects factors confirmed that the ORDER of CONDITIONS was not significant (F(1,12) = 1.40, $p = 0.26$) as well as the interaction of ORDER of CONDITIONS × CONDITION (F (1,12) = 0.00 $p = 1$), ORDER OF CONDITIONS × TIME (F (2,24) = 0.02, $p = 0.98$) and ORDER of CONDITIONS × CONDITION × TIME (F (2,24) = 1.64, $p = 0.21$). As in the previous analysis, independently of the order of conditions, the interaction of CONDITION × TIME was significant (F (2,24) = 55.30, $p < 0.001$).

Disyllabic Nonwords

The analysis showed a significant effect of CONDITION (real vs. sham, F (1,13) = 104,99, $p < 0.001$) and TIME (baseline (T0) vs. end of treatment (T10) vs. follow-up (F/U), F (2,26) = 223.08, $p < 0.001$). The interaction TIME × CONDITION was also significant (F (2,26) = 117.19, $p < 0.001$). Bonferroni's post hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (real 5% vs. sham 5%, $p = 1$), the mean percentage of accuracy was significantly greater in the real than in the sham condition at T10 (real 80% vs. sham 25%, $p < 0.001$) and persisted at F/U (real 80% vs. sham 20% $p < 0.001$). Significant differences also emerged between T0 and T10 for the sham condition (20%, $p < 0.001$) (see Figure 4.1.2).

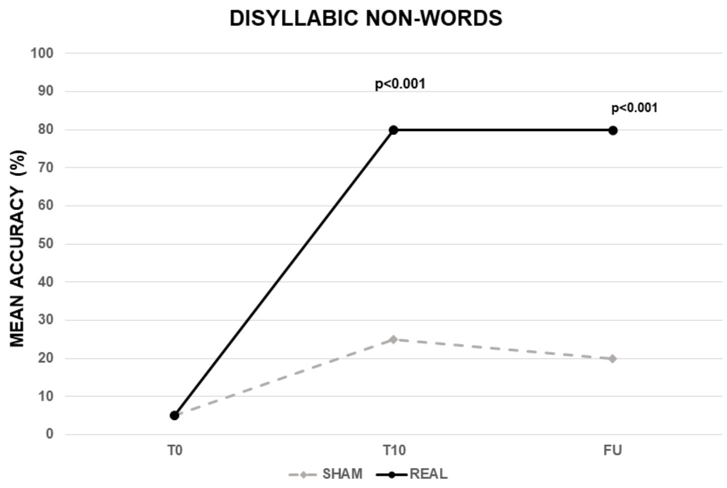

Figure 4.1.2 Mean percentage of response accuracy for disyllabic nonwords at baseline (T0), at the end of treatment (T10), and at follow-up (F/U) for the real and sham condition, respectively.

We ran further analysis by adding the order of conditions (real vs. sham) as a fixed factor. The analysis revealed that the results were not significantly affected by the order of condition ($F(1,12) = 1.77$, $p = 0.21$). Moreover, a mixed analysis of variance (ANOVA) with ORDER of CONDITIONS as the between-subjects factor (first treatment vs. second treatment) and CONDITION (real vs. sham) and TIME (baseline (T0) vs. last day (T10) vs. follow up (FU)) as two within-subjects factors confirmed that the ORDER of CONDITIONS was not significant ($F(1,12) = 3.7$, $p = 0.09$) as well as the interaction of ORDER of CONDITIONS × CONDITION ($F(1,12) = 0.06$, $p = 0.81$), ORDER OF CONDITIONS × TIME ($F(2,24) = 0.49$, $p = 0.62$) and ORDER of CONDITIONS × CONDITION × TIME ($F(2,24) = 0.02$, $p = 0.98$). As in the previous analysis, independently of the order of conditions, the interaction of CONDITION × TIME was significant (F (2,24) = 108.32, $p < 0.001$).

Trisyllabic Nonwords

The analysis showed a significant effect of CONDITION (real vs. sham, F (1,13) = 408.82, $p < 0.001$) and TIME (baseline (T0) vs. end of treatment (T10) vs. follow-up (F/U), F (2,26) = 477.66, $p < 0.001$). The interaction TIME × CONDITION was also significant (F (2,26) = 386.56, $p < 0.001$). Bonferroni's post hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (real 0% vs. sham 0%, $p = 1$), the mean percentage of accuracy was significantly greater in the real than in the sham condition at T10 (real 50% vs. sham 5%, $p \leq 0.001$) and persisted at F/U (real 50% vs. sham 5% $p < 0.001$). No significant differences emerged between T0 and T10 for the sham condition (0%, $p = 1$) (see Figure 4.1.3).

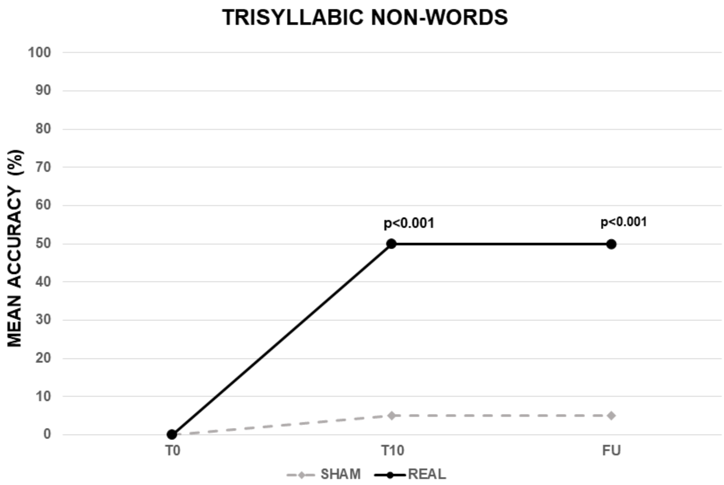

Figure 4.1.3 Mean percentage of response accuracy for trisyllabic nonwords at baseline (T0), at the end of treatment (T10), and at follow-up (F/U) for the real and sham condition, respectively.

We ran further analysis by adding the order of conditions (real vs. sham) as a fixed factor. The analysis revealed that the results were not significantly affected by the order of condition (F (1,12) = 1.000, $p = 0.34$). Moreover, a mixed analysis of variance (ANOVA) with ORDER of CONDITIONS as the between-subjects factor (first treatment vs. second treatment) and CONDITION (real vs. sham) and TIME (baseline (T0) vs. last day (T10) vs. follow up (FU)) as two within-subjects factors confirmed that the ORDER of CONDITIONS was not significant ($F(1,12) = 0.09$, $p = 0.77$) as well as the interaction of ORDER of CONDITIONS × CONDITION ($F(1,12) = 0.44$, $p = 0.52$), ORDER OF CONDITIONS × TIME ($F(2,24) = 0.61$, $p = 0.55$) and ORDER of CONDITIONS × CONDITION × TIME ($F(2,24) = 0.43$, $p = 0.66$). As in the previous analysis, independently of the order of conditions, the interaction of CONDITION × TIME was significant ($F(2,24) = 369.57$, $p < 0.001$).

Finally, "generalization effects" in the language test indicated that, in most of the patients, there was a significant difference in the percentage of correct responses before and after the treatment in different language tasks, which was greater after the real than in the sham condition (see Table 4.1.2).

Table 4.1.2 Percentage of Correct Responses in the Different Language Tasks (Esame del Linguaggio II, Ciurli et al., 1996) at Baseline (T0) and at the End of Treatment (T10) for the real and sham condition, respectively (Cut-off Score100%).

p	C	Oral NN		Oral VN		Written NN		Written VN		W R		NW R		W Read		NW Read		W Dict		NW Dict	
		T0	T10	T0	T10	T0	T10	T0	T10	T0	T10	T0	T10	T0	T10	T0	T10	T0	T10	T0	T10
Real First																					
1	R	7.5	80^	10	60^	0	55^	0	40^	35	92.5^	22.5	90^	15	67.5^	5	50^	0	72.5^	0	55^
	S	80	85	60	70	55	55	40	45	92.5	90	90	95	67.5	70	50	45	72.5	75	55	55
3	R	0	67.5^	0	60^	0	37.5^	0	35^	22.5	85^	30	80^	12.5	42.5^	15	60^	0	50^	0	52.5^
	S	67.5	80*	60	80**	37.5	35	35	40	85	92.5	80	95**	42.5	45	60	60	50	55	52.5	62.5
5	R	15	70^	10	80^	0	42.5^	0	32.5^	20	82.5^	15	80^	15	60^	5	62.5^	0	57.5^	0	67.5^
	S	70	77.5	80	85	42.5	42.5	32.5	35	82.5	97.5^	80	80	60	60	62.5	62.5	57.5	57.5	67.5	52.5
7	R	7.5	55^	0	60^	0	30^	0	27.5^	40	72.5^	32.5	87.5^	12.5	62.5^	2.5	47.5^	0	40^	0	45^
	S	55	75**	60	70	30	35	27.5	27.5	72.5	72.5	87.5	87.5	62.5	57.5	47.5	47.5	40	40	45	45
9	R	15	45^	15	65^	0	40^	0	15^	80	100^	35	82.5^	32.5	80^	10	50^	0	50^	0	12.5^
	S	45	54	65	70	40	55*	15	15	100	92.5	82.5	92.5*	80	80	50	50	50	42.5	12.5	17
11	R	15	60^	15	80^	0	55.5^	0	17.5^	85	95*	30	92.5^	15	60^	15	77.5^	0	65^	0	20^
	S	60	60	80	80	55.5	60	17.5	20	95	97.5	92.5	95	60	60	77.5	82	65	65	20	27.5
13	R	10	67.5^	10	75^	0	42.5^	0	30^	20	65^	20	70^	12.5	65^	5	45^	0	55^	0	47.5^
	S	67.5	65	75	80	42.5	50	30	30	65	72.5	70	70	65	65	45	50	55	57.5	47.5	47
Sham First																					
2	S	0	20^	0	5	0	10**	0	5	25	35	30	35	17.5	12.5	15	15	0	20^	0	5
	R	20	45^	5	10	10	40^	5	20**	35	85^	35	90^	12.5	57.5^	15	57.5^	20	50^	5	42.5^
4	S	15	27.5*	15	30*	0	5	0	10**	42.5	47.5	20	20	20	30	10	10	0	25^	0	25^
	R	27.5	55^	30	62.5^	5	50^	10	35^	47.5	62.5*	20	62.5^	30	75^	10	62.5^	25	55^	25	67.5^
6	S	0	2.5	0	0	0	0	0	0	0	17.5^	0	20^	0	0	0	5	0	0	0	5
	R	2.5	15**	0	0	0	10**	0	0	17.5	47.5^	20	65^	0	10**	5	15*	0	0	5	25^
8	S	0	0	0	0	0	0	0	0	0	5	0	5	0	0	0	0	0	0	0	0
	R	0	20^	0	0	0	15^	0	0	5	17.5**	5	25^	0	12.5^	0	15^	0	0	0	20^
10	S	0	0	0	0	0	5	0	0	0	20^	0	20^	0	15^	0	2.5	0	0	0	0
	R	0	45^	0	35^	5	35^	0	10**	20	65^	20	62.5^	15	42.5^	2.5	25^	0	40^	0	35^
12	S	10	15	15	20	0	10**	0	0	15	20	10	22.5*	15	30*	15	20	0	25^	0	10**
	R	15	60^	20	65^	10	55^	0	15^	20	72.5^	22.5	75^	30	75^	20	65^	25	70^	10	50^
14	S	15	32.5**	12.5	20	0	5	0	0	10	17.5	15	15	15	27.5*	5	10	0	15^	0	5
	R	32.5	80^	20	80^	5	45.5^	0	20^	17.5	72.5^	15	65^	27.5	75^	10	35^	15	65^	5	57.5^

Legend: P= Participants; C= Conditions; Oral NN= Noun Naming; Oral VN= Verb Naming; Written NN= Noun Naming; Written VN=Verb Naming; WR= Word Repetition; NWR= Nonword Repetition; W/NW

Read= Word/Nonword Reading; W/NW Dict= Word/Nonword under Dictation; S= Sham; R= Real stimulation; *= $p < 0.05$; **=$p < 0.01$; ^=$p < 0.001$.

4.1.4 Discussion

The aim of the present study was to explore whether dual-tDCS combined with a language treatment would improve writing skills in fourteen chronic patients with severe agraphia. Since all were Italian patients, we employed as a treatment nonword writing in order to rely on the sublexical procedure (Bigozzi et al., 2016; Caravolas, 2004; Marinelli et al., 2015; Notarnicola et al., 2012). We used dual-tDCS based on the hypothesis that simultaneously up- and down-regulating activity, respectively, in the left and right temporo-parietal cortex would enhance the recovery process in the left hemisphere (Galletta et al.,2015; Lee et al., 2013; Marangolo et al., 2013c, 2016). Indeed, the comparison between different electrode montages, which have been used in tDCS post-stroke aphasia studies, has shown that bilateral stimulation over the left and right inferior frontal gyrus (IFG) determines a clear incoming current into the left hemisphere more focally distributed over the left perilesional region and a component of outgoing current from the right hemisphere with respect to unilateral montage with the anode placed over the left IFG (Galletta et al.,2015; Lee et al., 2013; Marangolo et al., 2013c, 2016). Accordingly, our findings showed that, after real stimulation, there was a greater improvement in syllables and disyllabic and trisyllabic nonword writing with respect to the sham condition which persisted after one week from the end of the treatment. This last result is consistent with the previous tDCS literature in healthy subjects and brain-damaged individuals showing longer-term changes in motor abilities, learning and language recovery (Dockery et al., 2009; Kadosh et al., 2010; Marangolo et al., 2011, 2013c; Meinzer et al., 2016; Reis et al., 2009). Indeed, unlike single tDCS session effects, which are mediated by transient neural modulations (Stagg & Nitsche, 2011), repeated stimulation sessions combined with training are thought to act via mechanisms similar to long-term potentiation, which is critical for neuroplasticity and memory consolidation (Fritsch et al., 2010; Reis et al., 2009, 2015). Significant differences were also present in the sham condition, but only for syllabic and disyllabic nonwords. Thus, the language training alone was successful, but only for the simplest stimuli. Interestingly, patients had a better writing performance with disyllabic nonwords with respect to one syllable. Although we do not have a final interpretation of this result, we believe that it could be determined by the partial sparing of nonwords repetition which was already present at the beginning of the treatment in most of the subjects (see Table 4.1.1). Indeed, subjects might have made use of spared phonological rehearsal processes which have facilitated the retention of longer nonwords and, thus, their conversion into the corresponding graphemes.

Moreover, most of the patients showed significant changes in different oral and written language tasks of the language test, administered before and after the treatment, particularly in oral and written noun and verb naming, nonword and word writing to dictation and word/nonword reading. Thus, as already suggested by previous studies, relying on the sublexical procedure also resulted in generalization effects of the acquired learning on untrained items (Beeson et al., 2000, 2010; Cardell & Chenery, 1999; Carlomagno & Luzzatti, 1997; Kiran, 2005; Luzzatti et al., 2000; Thiel et al., 2015). Indeed, recent meta-analyses of neuroimaging studies have shown that the cortical areas involved in written language overlap with those implicated in reading (Planton et al., 2013; Purcell et al., 2011). Thus, in agreement with those studies, our results showed that dual temporo-parietal tDCS also exerted its influence on reading. Accordingly, high frequency repetitive transcranial magnetic stimulation (rTMS) over the left inferior parietal lobule (IPL) improves nonword reading accuracy (Costanzo et al., 2012). A similar improvement was also found in dyslexic patients (Costanzo et al., 2013) after stimulation of the left IPL and in adults with typical reading after anodal stimulation over the left posterior temporal cortex compared to sham (Turkeltaub et al., 2012). Several tDCS studies have also suggested that the left temporo-parietal region refers to a large network implicated in phonological processing (Costanzo et al., 2016, 2019) and in the acquisition of new vocabulary (Fiori et al., 2011, 2017; Flöel et al., 2008; Meinzer et al.,2014; Perceval et al., 2017; Savill et al., 2015). Indeed, Price (2012) has pointed out that the left temporo-parietal cortex is involved in several language processes, including phonological, orthographic and semantic processing and grapheme-to-phoneme conversion. In particular, according to several neuroimaging studies, the temporo-parietal cortex is activated during phonological encoding and memory performance for new words (Breitenstein et al., 2005; Clark & Wagner, 2003; Paulesu et al., 2009). In line with this evidence, Savill and collaborators (2015) have shown that tDCS over the temporo-parietal cortex facilitated word learning by enhancing the acquisition of phonological forms during a serial word recall task. In addition, Maloney's work (2009) has indicated that nonword letter strings can be easily represented in the orthographic input and phonological output lexicon after a small number of repetitions. Indeed, the authors have shown the development of a new orthographic and phonological lexical route through the conversion from sublexical to lexical procedures for nonwords.

Thus, given the role played by the left temporo-parietal cortex in several language tasks, we should have expected a generalization effect to other language tasks, which was the case.

Before concluding, a final point is worth noting, which we believe is highly relevant from a clinical perspective. Indeed, since all of our patients were in the chronic phase and they had very severe agraphia, the presence of an improvement, after dual-tDCS, for the most difficult items (i.e., trisyllabic nonwords) and generalization effects in the language tasks was not necessarily taken for granted. Previous results on chronic post-stroke aphasia led to similar results (De Aguiar et al., 2015; Marangolo et al., 2013c, 2016), suggesting that the combination of tDCS with language training also boosts the recovery process in cases of severe aphasia. Indeed, tDCS induces neuroplasticity in humans, thus, it has the potential to foster physiological plasticity in neurological diseases such as post-stroke chronic aphasia (Hamilton et al., 2011; Hartwigsen, 2016; Kuo et al., 2014). Given that, in the chronic phase, interhemispheric connections between the left and the right hemisphere might be detrimental for language recovery, we might hypothesize that, in our work, dual tDCS has temporarily reversed the interhemispheric imbalance, thus improving language skills in our patients (Kiran, 2012; Sehm et al., 2012).

4.1.5 Conclusion

Although our results are encouraging for identifying tDCS protocols for language improvement in chronic post-stroke aphasia, we are aware that they have some limitations due to the small sample size considered and the absence of pre-treatment mapping of spared language regions using functional MRI. Indeed, we know that the choice of our stimulation sites might have been not entirely appropriate due to variable lesion sizes and locations among our patients as well as interindividual differences in functional language network reorganization. Thus, fMRI would have helped us to better identify the stimulation sites.

However, apart from these limitations, we believe that research concerning tDCS in aphasia is crucial to promote our understanding of the neural mechanisms by which tDCS improves language functions in the chronic stage.

4.2 EXPERIMENT 2

Spinal or cortical direct current stimulation: Which is the best? Evidence from apraxia of speech in post-stroke aphasia[2]

Abstract

To date, new advances in technology have already shown the effectiveness of non-invasive brain stimulation and, in particular, of transcranial direct current stimulation (tDCS), in enhancing language recovery in post-stroke aphasia. More recently, it has been suggested that the stimulation over the spinal cord improves the production of words associated to sensorimotor schemata, such as action verbs. Here, for the first time, we present evidence that transpinal direct current stimulation (tsDCS) combined with a language training is efficacious for the recovery from speech apraxia, a motor speech disorder which can co-occur with aphasia. In a randomized-double blind experiment, ten aphasics underwent five days of tsDCS with concomitant treatment for their articulatory deficits in two different conditions: anodal and sham. In all patients, language measures were collected before (T0), at the end (T5), and one week after the end of treatment (F/U). Results showed that only after anodal tsDCS patients exhibited a better accuracy in repeating the treated items. Moreover, these effects persisted at F/U and generalized to other oral language tasks (i.e., picture description, noun and verb naming, word repetition, and reading). A further analysis, which compared the tsDCS results with those collected in a matched group of patients who underwent the same language treatment but combined with tDCS, revealed no differences between the two groups.

Given the persistency and severity of articulatory deficits in aphasia and the ease of use of tsDCS, we believe that spinal stimulation might result a new innovative approach for language rehabilitation.

4.2.1 Introduction

Speech is one of the most complex and fully exercised motor skills in humans. All normally developing individuals acquire it from birth and exercise speech motor behavior day by day, over their whole lifetime (Levelt et al., 1999; McNeil et al., 1997; Spencer &

[2] Pisano, F., Caltagirone, C., Incoccia, C., & Marangolo, P. (2021). Spinal or cortical direct current stimulation: Which is the best? Evidence from apraxia of speech in post-stroke aphasia. *Behavioural brain research*, *399*, 113019. https://doi.org/10.1016/j.bbr.2020.113019

Rogers, 2005). According to Levelt's theory (1999), in any language, the frequent use of the same articulatory gestures participating in the construction of words transforms the correspondent motor pattern into a stable, overlearned movement program represented onto the motor-cortical hard-disk which stores the human's phonetic lexicon (Kearney & Guenther, 2019, Levelt et al., 1999).

Focal brain damage to the dominant (typically left) hemisphere can cause an alteration in this orchestration of movements, known as "apraxia of speech" (AOS) (Dronkers et al., 2004; Hillis et al., 2004; Maas et al., 2008; Marangolo et al., 2013c, 2016). AOS is an acquired motor speech disorder characterized by an impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sounds (Knollman-Poter, 2008; Ogar et al., 2005; Wertz et al., 1984). Darley first described AOS as "a disorder of motor speech programming manifested primarily by errors in articulation" (Darley et al., 1975). It varies from a complete inability to articulate any given syllable and/or word to distortions of consonants and vowels that may be perceived as sound substitutions in the absence of reduced strength or tone of muscles and articulators controlling phonation (Duffy, 2005; McNeil et al., 2000). Over the last decades, a variety of treatment approaches has been developed to remediate the AOS disorder with no one approach proved to be effective for all patients (Knock et al., 2000; Rosenbek et al., 1973; Wambaugh, 2002). For patients with moderate to severe AOS, therapy is mostly focused on relearning oral postures of individual speech sounds through nonwords (i.e., syllables) and word repetition. Indeed, repetition is a multistage process dependent upon the left-dominant dorsal pathway which maps sound-based codes to articulatory codes which involve pre-articulatory planning in Broca's area and subsequent planning of articulatory gestures prior to motor execution in the premotor and motor cortices (Flinker et al., 2015; Hickok & Poeppel, 2004). Thus, nonword and word repetition results specially adapted to the needs of patients with AOS disorders (Bailey et al., 2017; Baker et al., 2001; Coady & Evans, 2008; Dell et al., 1999; Rvachew & Brosseau-Lapré, 2012; Shriberg et al., 2009). Accordingly, studies in patients with AOS have suggested that together with damage to the Broca's area (Hillis et al., 2004; Mohr et al., 1978; Moser et al., 2009), impairment to other brain structures, such as the left anterior insula (Dronkers et al., 2004; Moser et al., 2009) and the premotor and motor regions (Basilakos et al., 2015; Graff-Radford et al., 2014; Itabashi et al., 2016; Jonas, 1981; Josephs et al., 2006, 2012) leads to AOS. A recent voxel-based lesion mapping study by Basilakos and colleagues (2015) revealed that the pattern of brain damage associated with AOS is most strongly associated with damage to the left cortical motor regions, with additional involvement of the left somatosensory areas (Terband et al., 2009, 2014). Thus, taken together, all of these results point to a crucial role of the sensorimotor network in speech articulation (Hickok et al., 2014).

In more recent years, new advances in technology have shown that transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique, results efficacious in the recovery of different cognitive abilities (Lefaucheur et al., 2017; Schlaug et al., 2008, 2011) among which language in aphasic individuals (Fridriksson et al., 2018b; Marangolo, 2020). During tDCS weak polarizing direct currents are delivered to the cortex via two electrodes placed on the scalp. The nature of the effects depends on the polarity of the current. Generally, the anode increases cortical excitability when applied over the region of interest with the cathode above the contralateral orbit or above the shoulder (as the reference electrode), whereas the cathode decreases it, limiting the resting membrane potential. These effects may last for minutes to hours depending on the polarity, duration, and intensity of stimulation, and they are generally compared with a placebo condition (the so-called "sham" condition) in which the stimulator is turned-off after 30 s (Nitsche & Paulus, 2011). With regard to AOS disorder, previous tDCS studies have shown that bihemispheric tDCS, with simultaneous excitatory stimulation over the left inferior frontal gyrus and inhibition over the right homologous, combined with a repetition language training improves the patients' performance not only in terms of better accuracy in articulating the treated stimuli but also for untreated items on different language tasks (picture description, noun, and verb naming, word repetition, word reading) (Marangolo et al., 2013c, 2016). Moreover, according to the hypothesis of sensorimotor involvement (Basilakos et al., 2015; Graff-Radford et al., 2014; Hickok et al., 2014; Itabashi et al., 2016; Josephs et al., 2006, 2012; Kearney & Guenther, 2019), in the Marangolo et al. study (2016), anodal stimulation exerted stronger functional connectivity changes into the left premotor and motor areas and in the left cerebellum compared to sham (2016).

Given that speech articulation requires the involvement of motor planning (Basilakos et al., 2015; Itabashi et al., 2016; Levelt et al., 1999), in the present study, we wondered whether other auxiliary systems functionally connected to the brain, which process sensorimotor information, might facilitate the recovery of AOS. Indeed, it has already been shown that spinal cord stimulation induces neurophysiological modifications at the cortical level through the activation of tonic afferent pathways to the cortex (Bocci et al., 2015a, 2015b; Marangolo et al., 2017). In particular, transpinal direct current stimulation (tsDCS) applied over the thoracic vertebrae (T9-T11 level, 2 mA, 20 min) induced supraspinal effects by modulating intracortical excitability in the motor cortex. Anodal tsDCS decreased motor-evoked potentials (MEPs), while cathodal tsDCS elicited opposite effects (Bocci et al., 2015a; Cogiamanian et al., 2008; Truini et al., 2011). Accordingly, recent modeling studies have proved that, despite some inter-individual differences, the electric field induced by thoracic tsDCS is longitudinally directed along the vertebral column, especially when the return electrode is placed over the right arm (Fiocchi et al., 2016; Parazzini et al., 2014). Yet, the electric field induced by thoracic tsDCS is maximum at the thoracic level and it increases somatosensory activity from the spinal cord to the brain (Fiocchi et al., 2016; Parazzini et al., 2014). More recently, by using resting state functional imaging (rs-fMRI), Schweizer and co-workers (2017) investigated whether tsDCS-induced reported changes in neurophysiological measures (Bocci et al., 2015a, 2015b; Cogiamanian et al., 2008; Truini et al., 2011) might also be reflected in spontaneous brain activity. In their study, resting state functional connectivity was measured in twenty healthy subjects by using blood oxygenation level-dependent, functional magnetic resonance imaging before and after anodal, cathodal, and sham tsDCS (20 min, 2.5 mA) with the active electrode centered over the thoracic vertebrae (T9-T11). As compared with sham, anodal tsDCS resulted in connectivity changes into the somatosensory cortex (S1) and the ipsilateral posterior insula for both left and right hemispheres. Additional changes were present in the thalamus and in the anterior cingulate cortex. Thus, these results provide further evidence for supraspinal effects induced by tsDCS suggesting that spinal stimulation might be considered a new noninvasive intervention for targeting cortical networks (Schweizer et al., 2017).

Given that speech articulation requires the activation of motor plans (Levelt et al., 1999; McNeil et al., 1997; Spencer & Rogers, 2005) and that tsDCS induces changes in cortical areas (Bocci et al., 2015a, 2015b; Schweizer et al., 2017; Truni et al.,2011) involved in speech articulation (Basilakos et al., 2015; Dronkers et al., 2004; Moser et al., 2009), we might hypothesize that spinal stimulation, by influencing activity into the sensorimotor networks, would result efficacious for AOS recovery.

In line with this hypothesis, very recently, in a group of fourteen PWA, Marangolo et al. (2017) have shown that anodal tsDCS delivered over the thoracic vertebrae combined with a picture naming task led to a greater increase of words related to sensorimotor schemata, such as action verbs (i.e., *to run*), compared to nouns not typically related to specific action (i.e., *the cloud*). More importantly, in a more recent rs-fMRI study (Marangolo et al., 2020), the authors found that the amount of verb improvement found after anodal tsDCS significantly correlated with supraspinal functional changes into a cerebello-cortical network which specifically influenced regions, such as the left premotor cortex and the left cerebellum known to be involved in motor processing (Mariën et al., 2019; Priftis et al., 2020).

Thus, given all of the above evidence, in the present study we wanted to investigate if tsDCS combined with a repetition training would facilitate AOS in post-stroke aphasic individuals.

4.2.2. Materials and methods

Participants

Ten patients with chronic aphasia (6 females and 4 males) who had suffered a single left hemisphere stroke were included in the study. All participants were native Italian speakers with right premorbid manual dominance (based on the "Edinburgh Handedness Questionnaire", Oldfield, 1971), they were all affected by a single left hemispheric stroke occurred at least 6 months prior to experimentation. Subjects over 75 years of age with seizures, previous brain injuries, possible spinal cord comorbidity and any type of implanted electronic device (e.g., pacemaker) were excluded. None of the participants has received structured language therapy for at least 6 months before the time of inclusion in the study in order to prevent confounding therapy effects.

Ethics statement

The data analysed in the current study were conformed with the Helsinki Declaration. Our named Institutional Review Board (IRCCS Fondazione Santa Lucia, Rome-Italy) specifically approved this study with the understanding and written consent of each subject.

Clinical data

In all patients, magnetic resonance imaging showed an ischemic lesion involving the left hemisphere. All patients presented non-fluent speech with severe AOS. Subjects were not able to produce any words in spontaneous speech. Their language production was limited to a few syllables with severe articulatory groping and distortions of phonemes in naming, repetition and reading tasks of twenty simple syllables (e.g., PA, MA, FU) and words [e.g., pipa [pipe]), casa [home] of a standardized test for the evaluation of articulation (Fanzago, 1983). To thoroughly investigate the language performance, each participant was also administered a standardized language test (Esame del Linguaggio II, Ciurli et al., 1996). Articulatory errors and distortions of phonemes were present in naming, repetition and reading aloud. Noun and verb written naming and word writing under dictation were also severely impaired. Auditory comprehension abilities were adequate for simple words and commands in the language test (Esame del Linguaggio II, Ciurli et al., 1996), while patients experienced significant difficulties in more complex auditory comprehension tasks (Token test cut-off 29/36, De Renzi & Faglioni, 1978). To evaluate nonverbal oral motor skills, the Buccofacial Apraxia Test was also administered (De Renzi et al., 1966). None of the patients showed buccofacial apraxia (see Table 4.2.1).

Table 4.2.1 For each language task, the percentage of correct responses are reported (Esame del Linguaggio II, cut-off 100%, Ciurli et al.,1996).

P	Sex	Age	Ed. Level	Time post onset	PD	NN	VN	WR	NWR	W Read	NW Read	WNN	WVN	WD	NWD	TT
1	F	65	8	7y 2mo	0	5	5	2,5	0	2,5	10	15	5	2,5	0	12
2	F	75	8	2y	0	5	5	5	5	5	0	0	0	5	0	14
3	F	73	18	12y	0	0	0	5	5	0	0	0	0	0	0	10
4	F	64	13	6y 6mo	0	2,5	0	2,5	0	5	15	0	0	5	5	12
5	F	68	18	1y 2mo	0	0	2,5	0	0	5	5	0	0	0	0	18
6	M	56	13	2y 6mo	0	0	0	0	0	0	0	0	0	0	0	14
7	F	70	5	4y	0	7,5	10	10	7,5	0	0	0	0	5	0	15
8	M	51	13	8mo	0	0	0	5	5	5	5	5	0	5	5	12
9	M	58	8	8mo	0	0	0	0	0	10	15	0	0	5	0	14
10	M	61	13	1 y 7mo	0	0	0	0	0	0	0	0	0	0	0	14

Legend: P= Participants; M= male; F= female; Ed. Lev. = Educational Level; PD = Picture Description; NN = Noun Naming; VN = Verb Naming; WR = Word Repetition; NWR = Non Word Repetition; W Read = Word Reading; NW Read = Non word Reading; WNN = Written Noun Naming; WVN = Written Verb Naming; WD = Word under Dictation; NWD = Non Word under Dictation; TT = Token Test (cut-off score 29/36).

Materials

Two lists of 90 stimuli each were prepared. Each list included 28 CV syllables (eg. MA, NA, RI), 15 CCV syllables (e.g., STA, TRA, PLE), 25 CVCV and CVCCV bysillabic words (e.g. pipa (pipe), luna (moon), nonno (grandfather), panna (cream)), 12 CVCVCV trisyllabic words (e.g. tavolo (table), limone (lemon)) and 10 sentences made of the syllables and words presented in the list (e.g. il nonno fuma la pipa (the grandfather smokes the pipe)). According to the International Phonetic Alphabet (Smith, 1999), syllables included different places (e.g., plosive, nasal, fricative) and manners of articulation (e.g., bilabial, dental, velar).

Procedure

Transcutaneous spinal direct current stimulation

tsDCS was applied using a battery driven Eldith (NeuroConn GmbH, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the 10th thoracic vertebra (spanned from the ninth to the 11th thoracic vertebrae) while the reference electrode was positioned over the right shoulder on the deltoid muscle. For sham stimulation, the same electrodes position was used. The current was ramped up to 2 mA and slowly decreased over 30 s to ensure the typical initial tingling sensation (Gandiga et al., 2006). Since in previous works it was shown that only anodal tsDCS exerted a significant improvement on verb recovery (Marangolo et al., 2017, 2020), only two experimental conditions were used: anodal tsDCS and sham. All patients underwent the two conditions in a randomized double-blind procedure. Both the experimenter and the patient were blinded with respect to the stimulation condition and the stimulator was turned on/off by another person. At the end of each condition, none of the participants noticed differences in the intensity of sensation between the two conditions, not being aware of what condition they were performing (O'Connell et al., 2012). In both conditions, patients underwent concurrent speech therapy for their articulatory disorders. The language treatment was performed in five daily sessions (Monday to Friday). There was 14-day intersession interval between the real and the sham condition. The assignment of each list of stimuli (N = 90) to each stimulation condition (anodal vs. sham) was randomized across conditions and the order of stimuli presentation was randomized between treatment sessions.

Language treatment

For each condition, patients were administered all the standardized language tests at the beginning (baseline; T0), at the end (T5) and 1 week after the end of treatment (follow-up; F/U). Once the electrodes were placed, subjects performed the language treatment for their articulatory disorders. Different from our previous published studies (Marangolo et al., 2017, 2020), whose aim was to enhance verb production, here, we wanted to restore the patient's ability to translate speech plans into its correspondent motor programs in order to improve speech articulation. Thus, we chose a very simple repetition task which requires to translate the incoming sensory information (i.e., the auditory target) into its outgoing motor production (Duffy, 2005; Knock et al., 2000; McNeil et al., 2000; Rosenbek et al., 1973; Wambaugh, 2002).

The therapy method was similar for all patients (for the same method see also Marangolo et al., 2011, 2013c). For each condition, the entire list of stimuli was presented in each daily session. The therapist and the patient were seated face to face so that the patient could watch the articulatory movement of the therapist as she spoke. The therapist presented one stimulus at a time and the treatment involved four consecutive steps, which were designed to progressively induce the patient to reproduce correctly the stimulus.

Step 1: The clinician auditorily presented the whole stimulus and asked the patient to repeat it. If the patient correctly repeated the stimulus, the clinician would present another stimulus, if she/he made errors the clinician would move on the next step. Step 2: The clinician auditorily presented the stimulus with a pause between each syllable, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same.

Step 3: As in Step 2, the clinician auditorily presented the stimulus again with a pause between each syllable, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same.

Step 4: The clinician auditorily presented one syllable at a time, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same.

Step 5: As in step 4, the clinician auditorily presented one syllable at a time again, prolonged the vowel sound, exaggerated the articulatory gestures and asked the patient to do the same. Each participant’s response was transcribed and recorded on audiotape.

In order to assure the double-blind procedure, all responses, without any identification label, were analyzed by an independent external examiner, who was totally unaware of the aim of the treatment and/or of the experimental condition (anodal vs. sham) to which the patient has been subjected. Responses were scored as correct only if all sounds in the syllables, words or sentences were correctly articulated.

Data analysis

The patients' performance was evaluated by taking into account the mean percentage of response accuracy for syllables, words and sentences. Data were analysed using SPSS 17.0 software. Three repeated measures ANOVAs were performed separately for syllables, words and sentences. For each analysis, two "within" factors were considered: TIME (baseline (T0) vs. end of treatment (T5) vs. follow up (FU) and CONDITION (anodal vs. sham). The post-hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of $p \leq 0.05$ were considered statistically significant.

Inter-rater and intra-rater reliability were established using a two-way mixed, consistency single measures by the intraclass correlation coefficient (ICC). For the intra-rater reliability, ICC was > 0.90 for syllables, words and sentences treatments, indicating excellent reliability.

Inter-rater reliability (IRR) was established by the primary rater and another examiner who rated patients by independently listening to speech recordings. ICC was computed for ratings on syllables, words and sentences treatments. The ICC was > 0.80 for the three treatments, indicating good reliability between the two raters.

Before and after each treatment condition, the patients' responses to the different re-administration of the standardized language tests (Esame del Linguaggio II, Ciurli et al., 1996) were also analyzed using χ^2-test.

4.2.3. Results

Accuracy data

Syllables

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), $F(2,18) = 11{,}31$, $P = .001$] and CONDITION (anodal vs. Sham, $F(1,9) = 25{,}14$, $P = .001$). The interaction TIME x CONDITION was also significant ($F(2,18) = 6{,}86$, $P = .01$). Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal 33 % vs. sham 33 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal 56 % vs. sham 37 %, P = .01) and persisted at F/U (anodal 51 % vs. sham 30 % P = .00). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (4%, P = 1) (see Figure 4.2.1).

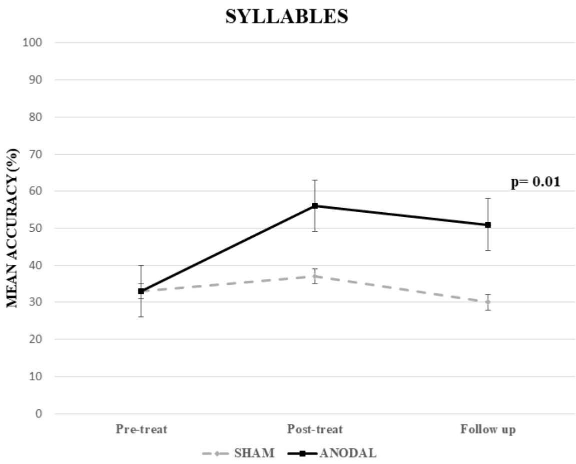

Figure 4.2.1 Mean percentage of response accuracy for syllables at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

Words

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,18) = 13,17, P = .000) and CONDITION (anodal vs. sham; F (1,9) = 23,69, P = .001). The interaction TIME x CONDITION was also significant (F (2,18) = 8,79, P = .002). Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal: 35 % vs. sham 38 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition, at T5 (anodal 65 % vs. sham 41 %, P = .002) and persisted at F/U (anodal 54 % vs. sham 30 %, P = .003). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (3%, P = 1) (see Figure 4.2.2).

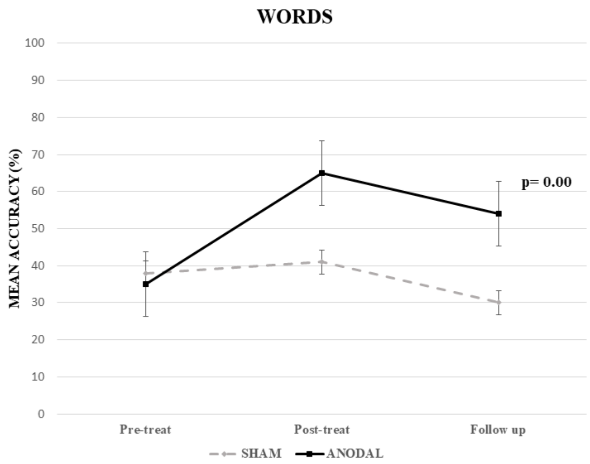

Figure 4.2.2 Mean percentage of response accuracy for words at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

Sentences

The analysis showed a significant effect of TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,18) = 14,33, P = .000) and CONDITION (anodal vs. sham, F (1,9) = 26,57, P = .001). The interaction TIME x CONDITION was also significant F (2,18) = 5,19, P = .02). Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal: 10 % vs. sham 10 %, P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition, at T5 (anodal 50 % vs. sham at 20 %, P = .01) and persisted at F/U (anodal 40 % vs. sham 20 %, P = .03). No significant differences emerged in the mean percentage accuracy between T0 and T5 for the sham condition (10 %, P = 1) (see Figure 4.2.3).

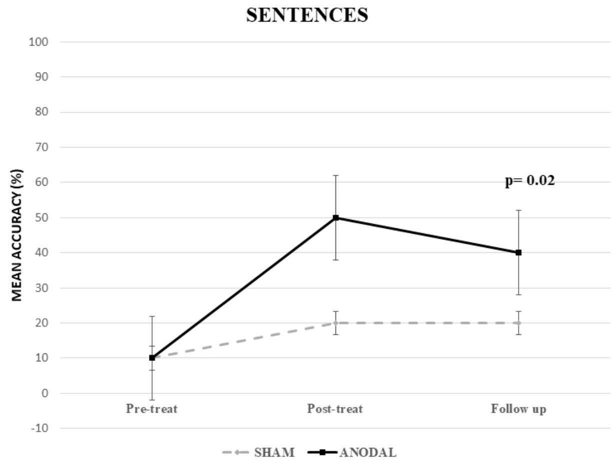

Figure 4.2.3 Mean percentage of response accuracy for sentences at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition, respectively.

Finally, results on the "transfer of treatments effects" in the language examination indicated that, in most of the patients, there was a significant difference in the percentage of correct responses before and after the treatment in different oral language tasks, which was more pronounced after the anodal than after the sham condition (see Table 4.2.2).

Table 4.2.2. Mean Percentage of Correct Responses in the Different Language Tasks (Esame del Linguaggio II, Ciurli et al., 1996) at Baseline (T0) and at the End of Treatment (T5) for the anodal and sham condition, respectively (Cut-off Score100%).

P	C	PICTDESC		VERB N		NOUN N		W Repet		NW Repet		WRIT N		WRIT W		W READ		NW READ		W DICT		NW DICT	
		T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5	T0	T5
REAL FIRST																							
1	R	0	20^	5	50^	5	50^	2,5	65^	0	42,5^	15	20	5	5	2,5	56,5^	10	15	2,5	10	0	0
	S	20	20	50	25	50	30	65	42,5	42,5	37,5	20	25	5	7,5	56,5	42,5	15	22,5	10	15	0	0
3	R	0	0	0	10^	0	25^	5	52,5^	5	42,5^	0	2,5	0	0	0	0	0	0	0	0	0	0
	S	0	0	10	5	25	0	52,5	42,5	42,5	32,5	2,5	2,5	0	0	0	0	0	0	0	2,5	0	0
5	R	0	0	2,5	25^	0	32^	0	52^	0	22,5^	0	5	0	0	5	10	5	5	0	10	0	0
	S	0	0	25	20	32,5	40	52,5	52,5	22,5	25	5	5	0	5	50	47,5	5	0	10	20	0	0
7	R	0	0	10	20	7,5	17,5*	10	57,5^	7,5	22,5**	0	0	0	0	0	10^	0	5	5	10	0	5
	S	0	0	20	0	17	17	57,5	42,5	22,5	30	0	0	0	0	10	15	5	0	10	15	5	0
9	R	0	0	0	0	0	2,5	0	15^	0	35^	0	5	0	0	10	15	15	20	5	5	0	5
	S	0	0	0	0	2,5	7,5	15	10	35	30	5	5	0	0	15	12,5	20	17,5	5	5	0	0
SHAM FIRST																							
2	S	0	0	5	10	5	10	5	12,5	5	10	0	2,5	0	2,5	5	15*	0	10^	5	10	0	10
	R	0	20^	30	50**	10	37^	12,5	47**	10	22,5	2,5	5	2,5	5	15	45^	10	27**	10	10	10	20
4	S	0	0	0	0	2,5	0	0	55^	2,5	10	0	0	0	0	5	10	15	20	5	10	5	10
	R	0	0	10	35^	0	15^	55	77,5^	10	62,5^	0	0	0	0	10	82^	20	25	20	25	10	17,5
6	S	0	0	0	0	0	0	0	20^	0	5	0	0	0	0	0	5	0	5	0	0	0	0
	R	0	0	0	0	0	0	20	92,5^	10	67,5^	0	0	0	0	10	10	5	7,5	0	0	0	0
8	S	0	0	0	0	0	0	5	10	5	10	5	2,5	0	0	5	10	5	5	5	10	5	10
	R	0	0	0	0	0	32,5^	22,5	50^	32,5	45	2,5	0	0	0	10	10	5	5	10	17,5	10	10
10	S	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	2,5	0	0	0	0	0	0
	R	0	0	0	0	0	0	0	5	5	20**	0	0	0	0	2,5	0	0	5	0	0	0	0

Legend: P= Participants; C= Conditions; PICTDESC= Picture Description; VERB N= Verb Naming; NOUN N= Noun Naming; W Repet= Word Repetition; NW Repet= Nonword Repetition; WRIT N= Written Noun Naming; WRIT V= Written Verb Naming; W/NW READ= Word/Nonword Reading; W/NW DICT= Word/Nonword under Dictation; S= Sham; R= Real stimulation; *= $p < 0.05$; **=$p < 0.01$; ^=$p < 0.001$.

Comments

In summary, the above results clearly suggest that tsDCS is effective for improving articulatory deficits and, more importantly, it exerts its influence not only on treated items but also on untreated ones of the language examination test. Interestingly, these data very much resemble those of our previous published results performed on two different groups of patients which underwent the same language treatment but combined with bihemispheric tDCS (Marangolo et al., 2013c, 2016). Since these patients were all nonfluent aphasics with severe AOS disorders (Marangolo et al., 2013c, 2016) and shared the same clinical characteristic of our tsDCS group, in the next experiment, we wanted to investigate if the two techniques would result equally efficacious for improving apraxia of speech. Thus, we compared the tsDCS results with the results collected in two subgroups of patients from our previous published studies (N = 5 from each study) (Marangolo et al., 2013c, 2016) who were called back again in order to perform a new study.

4.2.4 tDCS vs. tsDCS comparison

Participants

The experiment included ten participants whose clinical characteristics were the same as the tsDCS group. Patients were part of two subgroups (N = 5 for each subgroup) from our previously published tDCS studies (Marangolo et al., 2013c, 2016) but they were called back again in order to perform a new experiment. Details of the ten patients have been reported previously (for details see Marangolo et al., 2013c, 2016). All patients had nonfluent speech. Subjects were not able to produce any words in spontaneous speech. Their language production was limited to a few syllables due to their apraxia of speech disorder.

Procedure

The materials, the experimental procedure and the language treatment were the same as in the tsDCS experiment.

Bihemispheric transcranial direct current stimulation

Transcranial direct current stimulation was applied using a battery driven Eldith (NeuroConn GmbH, Germany) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Real stimulation consisted of 20 min of 2 mA direct current with the anode placed over the ipsilesional and the cathode over the contralesional IFG (F5 and F7 of the extended International 10–20 system for EEG electrode placement). For sham stimulation, the same electrode positions were used. In both conditions, patients underwent concurrent speech therapy for their apraxia of speech disorder.

Results

Data analysis

Data were analyzed with SPSS 17.0 software. The outcome for each group was the mean percentage of correct responses. A three-way mixed analysis of variance (ANOVA) with one between-subjects factor [GROUP (spinal vs. bihemispheric)] and two within-subjects factors [CONDITIONS (anodal vs. sham) and TIME (baseline (T0) vs. last day (T5) vs. follow up (FU)] was performed. The post-hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of p = < 0.05 were considered statistically significant.

Syllables

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. sham, F (1,18) = 52,70, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 52,95, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 10,72, P = .000), but the interaction GROUP*TIME* CONDITION was not significant (F (2,36) = 0.12, P = 0.89). In particular, for both groups, Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 33 % vs. sham spinal 33 %, P = 1; anodal cortical: 37 % vs. sham cortical: 31 % P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 56 % vs. sham spinal 37 %, P = .006; anodal cortical 72 % vs. sham cortical 46 %, P = .002) and persisted at F/U (anodal spinal 51 % vs. sham spinal 30 %, P = .005; anodal cortical 67 % vs. sham cortical 44 % P = .006).

Words

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. sham, F (1,18) = 36,39, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 49,88, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 14,86, P = .000) but the interaction GROUP*TIME* CONDITION was not significant (F (2,36) = 1.73, P = 0.19). In particular, for both groups, Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 35 % vs. sham spinal 38 %, P = 1; anodal cortical: 36 % vs. sham cortical: 29 % P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 65 % vs. sham spinal 41 %, P = .002; anodal cortical 66 % vs. sham cortical 42 %, P = .000) and persisted at F/U (anodal spinal 54 % vs. sham spinal 30 %, P = .003; anodal cortical 60 % vs. sham cortical 43 % P = .001).

Sentences

The three-way mixed ANOVA showed a significant effect of CONDITION (anodal vs. Sham, F (1,18) = 41,06, P = .000) and TIME [Baseline (T0) vs. End of treatment (T5) vs. Follow-up (F/U), F (2,36) = 45,40, P = .000]. The interaction CONDITION x TIME was also significant (F (2,36) = 15,43, P = .000), but the interaction GROUP*TIME* CONDITION was not significant (F (2,36) = 0,02 P = 0.98). In particular, for both groups, Bonferroni's post-hoc test revealed that, while no significant differences emerged in the mean percentage of correct syllables between the two conditions at T0 (anodal spinal: 10 % vs. sham spinal 10 %, P = 1; anodal cortical: 3% vs. sham cortical: 1% P = 1), the mean percentage of accuracy was significantly greater in the anodal than in the sham condition at T5 (anodal spinal 50 % vs. sham spinal 20 %, P = .008; anodal cortical 44 % vs. sham cortical 15 %, P = .000) and persisted at F/U (anodal spinal 40 % vs. sham spinal 20 %, P = .03; anodal cortical 35 % vs. sham cortical 11 % P = 0.000) (see Figure 4.2.4).

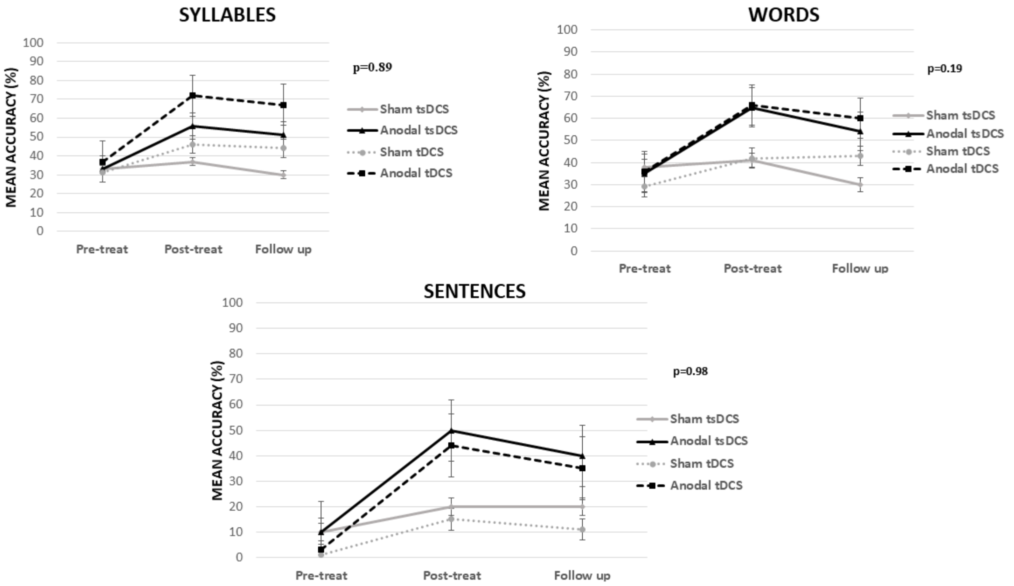

Figure 4.2.4 Mean percentage of response accuracy for syllables, words, and sentences at baseline (T0), at the end of treatment (T5) and at follow-up (F/U) for the anodal and sham condition in the tDCS and tsDCS group, respectively.

4.2.5 Discussion

The aim of this study was to investigate whether tsDCS would improve speech articulation in a group of ten chronic aphasic patients with concurrent AOS. At the end of treatment, results showed that only after anodal tsDCS articulatory errors significantly decreased for the treated stimuli (syllables, words and sentences). Moreover, this improvement also persisted at one week after the treatment (F/U) and generalized to the language test. Indeed, most of the patients showed significant changes in different oral language tasks (noun and verb naming, word and non-word repetition, word and non-word reading) administered before and after the treatment. No significant changes were found before and after the treatment in writing (see Table 4.2.2). This specificity argues against an effect simply due to enhanced cognitive arousal which should have influenced both oral and written tasks.

Thus, after anodal tsDCS, most patients showed a progressive reduction of phonological distortions in different oral tasks, the reduction being due to improvement in AOS. Interestingly, as also noted in our previous tDCS works (Marangolo et al., 2013c, 2016), only anodal stimulation produced significant changes. Indeed, the language treatment alone did not produce significant improvement in the sham condition. This result could be ascribed primarily to the severity and chronicity of the articulatory deficit present in all patients, which is in itself particularly resistant to change (Au et al., 2016; Knock et al., 2000; McNeil et al., 2000; Wambaugh, 2002). Indeed, since the treatment of AOS requires to plan intensive language training with repetitiveness of the exercises, it could be hypothesized that in the sham condition five days of language training were insufficient to improve performance. However, interestingly, the same amount of treatment associated with anodal tsDCS over the same period exerted beneficial effects. Thus, similarly to previous results (Marangolo et al., 2013c, 2016), combining stimulation with language training boosted language recovery overcoming the difficulties caused by the severity of the deficit. These findings are, thus, very promising as five days of tsDCS produced beneficial effects that were not achieved in the absence of stimulation.

To date, a growing body of evidence has already suggested that the neurostimulation provided by tDCS might enhance the effects of traditional language treatments for people with aphasia (Fridriksson et al., 2018b; Marangolo, 2020). With regard to AOS, previous tDCS studies have already been proven effective in improving speech articulation in post-stroke chronic aphasia (Marangolo et al., 2013c, 2016). In particular, bihemispheric tDCS with simultaneous excitatory stimulation to the left Broca's area and inhibitory current over the right homologous improved articulatory performance in a group of aphasic individuals (Marangolo et al., 2013c, 2016). Interestingly, these effects significantly correlated with functional connectivity changes which were most pronounced in the left perilesional cortex (Marangolo et al., 2016). In particular, since the behavioural treatment was focused on the motor aspects of speech production, significant changes were found in regions related to planning, maintenance, and execution of speech, such as the left premotor cortex, the left supplementary motor area and the cerebellum (Marangolo et al., 2016). Thus, the results of this study revealed the activation of different sensorimotor structures involved in speech articulation confirming that articulatory processing is related to motor activity (Darley et al., 1975; Levelt et al., 1999; McNeil et al., 1997; Spencer & Rogers, 2005).

As stated in the Introduction, to date, a growing body of evidence has suggested that spinal stimulation exerts supraspinal changes by specifically influencing cortical regions, such as the sensorimotor cortices (Bocci et al., 2015a, 2015b; Truini et al., 2011). Modelling studies have further supported this issue confirming that the current delivered over the spinal thoracic vertebrae, by increasing somatosensory activity from the spinal cord to the brain, induces neurophysiological changes over the cortex (Fiocchi et al., 2016; Parazzini et al., 2014). Accordingly, in a very recent rs-fMRI study, Schweizer and co-workers (2017) have shown that anodal tsDCS resulted in connectivity changes into the somatosensory cortices. Similarly, Marangolo and collaborators (2020) have reported a significant correlation between the amount of verb improvement found after anodal tsDCS and supraspinal functional changes into the motor network.

Thus, given that speech articulation involves the activation of motor plans (Basilakos et al., 2015; Graff-Radford et al., 2014; Itabashi et al., 2016; Jonas, 1981; Josephs et al., 2006, 2012; Moser et al., 2009) and that tsDCS induces changes into the motor cortex (Bocci et al., 2015a, 2015b; Marangolo et al.,2020), we might expect that in our study tsDCS would have influenced activity into the sensorimotor networks resulting efficacious for AOS recovery, which was the case.

Therefore, it could be hypothesized that either directly delivering the current over the frontal cortex through bihemispheric tDCS (Marangolo et al., 2013c, 2016) or influencing the sensorimotor network in a bottom-up manner through spinal cord stimulation (Bocci et al., 2015a, 2015b; Marangolo et al.,2020) would result equally effective for the recovery of AOS. Indeed, a direct comparison of the results obtained in the tsDCS group with those collected in the bihemisperic tDCS group, revealed no differences between the two techniques. Thus, spinal stimulation resulted efficacious as cortical stimulation.

Even if the exact underlying tsDCS mechanisms over the corticospinal system, in our study, remain largely speculative, in line with previous suggestions (Lang et al., 2004; Monti et al., 2008), the hypothesis might be advanced that anodal tsDCS has decreased the excitability of cortical inhibitory interneurons in the motor cortex, thus improving the efficacy of their correspondent areas. Indeed, while anodal tDCS is generally facilitatory to the cortex (Di Lazzaro et al., 2012, 2013; Nitsche et al., 2005), it has been suggested that anodal tsDCS exerts inhibition due to a hyperpolarization of the axons running along the spinal columns (Cogiamanian et al., 2008, 2011). An effect of tsDCS on neurotransmitters cannot also be ruled out. For instance, neurotransmitters such as GABA and glutamate undergo substantial changes after cortical tDCS over the motor cortex (Stagg et al., 2009, 2011). Although this effect might be task specific, one further hypothesis might be that, in our study, the inhibitory current delivered through anodal tsDCS has decreased both GABA and glutamate levels into the sensorimotor cortices leading to an improvement of their function (Kim et al., 2014; Stagg et al., 2009, 2011). According to previous hypothesis (Bocci et al., 2015c), we cannot also rule out the possibility that anodal tsDCS has induced an interhemispheric delay in motor connectivity, thus, enhancing the functionality of the left sensorimotor cortices through inhibition of its right homologs (Bocci et al.,2015c). Indeed, the model of interhemispheric interaction (similar to models of motor recovery after stroke) suggests that, after a left hemisphere damage to the language areas, the homotopic right hemisphere regions could result abnormally activated and, thus, might exert an inhibitory effect over the residual left language area (Belin et al., 1996; Murase et al., 2004). In this way, improvement could be possible either by stimulating the left-damaged hemisphere (Baker et al., 2010; Fiori et al., 2011, 2013) or inhibiting the right contralesional areas (Kang et al., 2011; Naeser et al., 2005; Yung et al.,2011). Thus, the hypothesis could also be advanced that tsDCS has inhibited the motor regions of the right hemisphere increasing activity of the left correspondent areas which in turn facilitated speech articulation.

In summary, since the two techniques, in our study, yield the same results, we might suggest that, due to the ease with which tsDCS can be applied over the spinal cord, tsDCS might represent a valid new tool for the recovery of language in aphasia, at least for those aspects related to motor processing, such as action verbs and speech articulation. Indeed, current theories postulate that the language function, among which articulatory planning, is subserved by a large network of regions widely distributed across the brain (Dick et al., 2014; Klingbeil et al., 2019; Ripamonti et al., 2018). It has also been recently suggested that a wide circuitry of distributed left motor cortical areas can be modulated by tsDCS (Marangolo et al., 2020). Thus, differently from previous tDCS paradigms (Marangolo, 2020), we might hypothesize that tsDCS could result easier to use than tDCS for those language units which carry motor information, because an appropriate positioning of the anode over the spinal cord would remove the need to establish in advance which part of the sensorimotor system should be specifically targeted with DCS. Given that PWA, very frequently, report difficulties in verb production and/or articulatory deficits which dramatically impact the ability to produce informative speech and its intelligibility, if our results will be further confirmed in the future, we believe that tsDCS might be considered as a suitable method for the recovery of these deficits.

4.2.6 Conclusion

We are aware that our study has some limitations, the major ones are represented by the small samples of participants included and the lack of longitudinal follow-ups. Indeed, despite previous works that have been already published, due to the above reported limitations, there is still conflicting evidence for the efficacy of tDCS in post-stroke aphasia. However, considering all of these limitations, we believe that our study provides preliminary suggestions that spinal stimulation might be considered a new approach for language recovery.

4.3 EXPERIMENT 3

Does Executive Function Training Impact on Functional Communication? A Randomized Controlled tDCS Study on Post-Stroke Aphasia[3]

Abstract

New approaches in aphasia rehabilitation have recently pointed out the crucial role of executive functions (EFs) in language recovery, especially for people with severe aphasia (PWSA). Indeed, EFs include high-order cognitive abilities such as planning and problem-solving which enable humans to adapt themselves to novel situations and are essential for everyday functional communication. In a randomized double-blind crossover design, twenty chronic Italian PWSA underwent ten workdays of transcranial direct current stimulation (tDCS) (20 min, 2 mA) over the right dorsolateral prefrontal cortex (DLPFC). Two different conditions were considered: (1) anodal, and (2) sham, while performing four cognitive tasks (alertness, selective attention, visuo-spatial working memory, and planning) all related to executive functions processing. After anodal tDCS, a greater improvement in selective attention, visuospatial working memory, and planning abilities was found compared to the sham condition; this improvement persisted one month after the intervention. Moreover, a significant improvement was also observed in functional communication, measured through the Communication Activities of Daily Living Scale, in noun and verb naming, in auditory and written language comprehension tasks and in executive functions abilities. This evidence emphasizes, for the first time, that tDCS over the right DLPFC combined with executive trainings enhances functional communication in severe aphasia.

4.3.1 Introduction

The traditional model of language organization, often referred to as the ‘‘Broca–Wernicke–Lichtheim–Geschwind model” (Geranmayeh et al., 2014; Poeppel & Hickok, 2004), focuses almost exclusively on the involvement of the inferior frontal and posterior temporal regions for expressive and receptive language functions, respectively, and the connection between these sites (arcuate fasciculus) as a key pathway for language

[3] Pisano, F., Manfredini, A., Castellano, A., Caltagirone, C., & Marangolo, P. (2022). Does Executive Function Training Impact on Communication? A Randomized Controlled tDCS Study on Post-Stroke Aphasia. *Brain sciences*, *12*(9), 1265. https://doi.org/10.3390/brainsci12091265

comprehension and production interaction. However, in recent years, behavioral and neuroimaging results have shown that the network subserving the language function is much larger distributed across the brain than previously considered (Duncan & Small, 2017; Tremblay & Dick, 2016; Ulm et al., 2018). Indeed, most contemporary models propose a much more complex architecture encompassing regions which might also include bilateral cortical networks as well as subcortical circuits (Crosson, 2013; Hebb & Ojemann, 2013; Hickok & Poeppel, 2008; Marien et al., 2014; Price, 2010). In line with this view, a growing body of evidence has led to the concept of "neuronal multifunctionality", in which these complex neuronal circuits subserve both linguistic and non-linguistic information, creating dynamic cognition-language interactions in the brain (Blumstein & Amso, 2013; Cahana-Amitay & Albert, 2015). Based on this perspective, new approaches in aphasia rehabilitation have emphasized that non-linguistic functions may also subserve language recovery. Accordingly, several works have already shown that multiple cognitive domains, including attention (Erickson et al., 1996; Hula & McNeil, 2008; Lesniak et al., 2008; Murray, 2012; Peach et al., 1994), memory (Helm-Estabrooks, 2002; Lapointe & Erickson,1991) and executive functions, may be utilized to improve communication and language performance in aphasia (Fridriksson et al., 2006; Keil & Kaszniak, 2002; Ramsberger, 2005; Schumacher et al.,2019). Since in persons with severe aphasia (PWSA) language does not always adequately meet the communicative needs (e.g., social interaction and information transfer) of the individual (Darrigrand et al., 2011), to communicate successfully it is necessary to enhance skills and strategies that allow PWSA to bypass their limitations in everyday activities. The impact of inadequate strategic competence in everyday life in PWSA clearly points out to the importance of training executive functions for successful functional communication in aphasia (Olsson et al., 2019, 2020). Indeed, executive functions (EFs) include high-order cognitive abilities such as cognitive flexibility, planning and problem solving which enable humans to achieve goals, to adapt themselves to novel everyday life situations, and to manage social interactions (Miyake & Friedman, 2012; Miyake et al., 2000; Toplak et al., 2012). To date, several definitions, and theoretical models for EFs processing have been proposed which were specifically designed to achieve different research purposes (Suchy et al., 2017). With regard to the relationship between executive functions and functional communication, clinically oriented models are the most suitable choice.

Indeed, clinical models, which originate from clinical neuropsychology, tend to be comprehensive, including multiple sub-components of EF which correspond to the deficits observed in brain-damaged populations. Examples of such models include those by Lezak, et al. (2012), Stuss (2011), and Suchy (2015). Particularly, Suchy and colleagues (2017) have proposed a model which describes the relationship between executive functions and functional communication. The model comprises five components: 1) planning and problem-solving skills based on working memory and mental flexibility; 2) initiation and continuation of the behaviors necessary to implement a given action; 3) response selection, i.e. the ability to choose an appropriate action among several competitors, based on the processes of inhibition and updating; 4) multitasking, i.e. monitoring and coordinating multiple goals in a prospective view; 5) social cognition, i.e. understanding socially relevant verbal communication and paralinguistic messages. Thus, the authors consider the importance of executive functions to accomplish several communication skills (Suchy et al., 2017). As an example, while holding a conversation, the speaker should contemporarily store the interlocutor's information, plan the responses to be given, and sometimes inhibit inappropriate ones, all tasks implemented by EF processing.

Consistent with this hypothesis, several lines of evidence have already emphasized how executive functions could provide support to conversational skills when spared but they might also interfere with functional communication when impaired (Ramsberger, 2005). Indeed, different reports to date have clearly shown that PWA may also present with executive deficits, which negatively affect language treatment outcomes (Gilmore et al., 2019; Schumacher et al.,2019; Simic et al., 2019) and communication skills (Fridriksson et al., 2006; Olsson et al., 2019, 2020). Very recently, Olsson and colleagues (2019) have specifically investigated the relationship between executive function, language abilities and functional communication in a large sample of forty-seven PWSA. Participants were first divided into two groups with respect to their ability to rely or not on verbal output (spoken or written). The nonverbal group presented with a more severe aphasia than the verbal group. In order to evaluate executive functions processing, the authors administered four subtests from the "Cognitive Linguistic Quick Test (CLQT)" (Helm-Estabrooks, 2001). Language abilities were examined through the "Comprehensive Aphasia Test" (CAT) (Swinburn et al., 2005), while the "Scenario test" (van der Meulen et al., 2010) and the "Communicative Effectiveness Index" (Lomas et al., 1989) were included to measure functional communication. The results showed that most of the PWA (79%), presented with executive functions deficits which partially correlated with the participants verbal and communication abilities. As a group, the nonverbal participants had more severe impairments of executive functions which partially correlated with functional communication when controlling for linguistic ability. In the verbal subgroup, no relations were found between executive functions, language, and functional communication.

In recent years, new technological advances have shown the effectiveness of transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technology, in the recovery of several cognitive abilities, including language recovery (Lefaucheur et al., 2017; Marangolo, 2020). Through tDCS a weak current at low intensity (1-2mA) is delivered on the scalp by means of two electrodes: the anode and the cathode (Nitsche & Paulus, 2011). Depending on the polarity of the current, there is a general agreement that anodal stimulation causes a depolarization of the neural membrane resulting in excitability of the target area, whereas cathodal stimulation might induce hyperpolarization with an inhibition of the activity of the stimulated region (Sudbrack-Oliveira et al., 2021). Typically, these two conditions (anodal, cathodal) are compared with a sham condition (placebo condition) in which the stimulator is switched off after 30 seconds without the subject's awareness (Fregni et al., 2020; Lefaucheur et al., 2017).

It is well known that the dorsolateral prefrontal cortex (DLPFC) is involved in higher-level cognition and, in particular, in domain general executive functional control such as in selective attention, inhibition, switching, planning, and working memory (WM) tasks (Badre & Wagner, 2004; Brunoni & Vanderhasselt, 2014; Fassbender et al., 2006; Hart et al., 2013; for a review see Hertrich et al., 2021). Despite this consensus, to date, the research regarding the role of the left or right DLPFC involvement for the different cognitive functions (Badre & Wagner, 2004; Brunoni & Vanderhasselt, 2014; Fassbender et al., 2006; Hart et al., 2013) has led to inconsistent conclusions in the tDCS literature (Medina & Cason, 2017). With regard to selective attention, which requires not only the selection of an adequate and relevant response but also the inhibition of inappropriate reactions, a couple of works have indicated an increase in response inhibition capacity after anodal tDCS over the left DLPFC (Loftus et al., 2015), while others have emphasized the effectiveness of either anodal (Friehs & Frings, 2018; Hsu et al., 2011) or cathodal tDCS over the right DLPFC (Weidacker et al., 2016) in selective attention performance. Very recently Chen et al. (2021) have investigated the effects of tDCS over the DLPFC on response inhibition in ninety-two healthy subjects. Three groups of participants were recruited: 1) the anodal tDCS over the right DLPFC group, 2) the cathodal tDCS over the right DLPFC group and 3) the sham group. Before and after stimulation, all participants underwent a computerized behavioral response inhibition task. Although an improvement in the inhibition component was observed in the anodal and cathodal tDCS group compared to the sham group, only after anodal stimulation the participants were more attentive to discrimination and decision-making processes. In the context of WM, while some studies have successfully targeted the left DLPFC (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016; Zaehle et al., 2011), others have addressed the role of its right homologous (Trumbo et al., 2016; Wu et al., 2014). Jeon and Han (2014) investigated whether tDCS over the DLPFC improve different cognitive abilities among which visuospatial working memory. To verify this, thirty-two healthy adults were divided into three groups: 1) the anodal tDCS right DLPFC group; 2) the anodal tDCS left DLPFC group and 3) the sham group. Interestingly, only after anodal tDCS over the right DLPFC, an enhancement in the ability to resolve a computerized visuo-spatial working memory task was found. Similar findings were shown by Giglia et al. (2014) and Trumbo et al. (2016). Particularly, Trumbo et al. (2016) have confirmed that stimulation over the right but not the left DLPFC improves spatial n-back task performance, indicating that the right DLPFC is involved in spatial WM location-monitoring.

It is worth noting that planning is a higher-level cognitive function (Cristofari et al., 2019) in which several cognitive sub-processes come into play, such as decision-making, reflective judgement, monitoring. Not surprisingly, people who have difficulty in planning in real-life contexts may manifest a failure to shift between mental sets and have poor judgment regarding adequacy and completeness of a plan (Cristofari et al., 2019). According to the literature, the right DLPFC has a key role in cognitive control and set shifting involved in judgment, decision-making performance, and error awareness (Fleming et al., 2012; Toplak et al., 2011). In line with these assumptions, Harty and colleagues (2014) have investigated the effects of both anodal and cathodal stimulation over the right and left DLPFC in a group of 106 healthy older adults, who presented a low error awareness. For the first time, an association between anodal tDCS over the right DLPFC and an increase in error awareness was found, measured through the Error Awareness Task (EAT) (Hester et al., 2005). In a sample of fifty-five healthy subjects, Heinze and colleagues (2014) investigated the effects of bilateral tDCS over the DLPFC combined with an eye-tracking while performing a planning task by using the Tower of London test. Results showed a reduction in initial thinking time following left cathodal/right anodal DLPFC stimulation in parallel with a shorter duration of the last gaze before task's solution. Based on these findings, the authors concluded that anodal stimulation over the right DLPFC is associated with a reduction in the time spent in evaluation processes during planning tasks. With regard to decision making and judgement processes, very recently Edgcumbe et al. (2021) have shown an amelioration of the cognitive reflection performance after anodal tDCS over the right DLPFC with respect to left DLPFC stimulation and sham condition in forty-four participants.

Although the DLPFC has never been considered as specifically related to language tasks, its role for implementing functional connectivity between the language network and other cognitive domains has been widely recognized (for a review, see Hertrich et al., 2021). Thus, several studies have stimulated the left DLPFC to improve error detection in sentences (Nozari et al., 2014) or to reduce interference in picture naming tasks (Wirth et al., 2010). Very recently, Pestalozzi and collaborators (2018) have investigated whether strengthening executive control through anodal tDCS over the left DLPFC would facilitate lexical retrieval processing in a group of fourteen PWA. Results showed an increase in verbal fluency and in naming speed of high frequency words during anodal condition with respect to sham.

As far as we know, to date, none of the reported studies have investigated whether tDCS over the DLPFC combined with executive functions trainings improves the recovery of functional communication in PWSA.

It is widely known that pragmatic language skills such as the ability to use language properly in a social context (Lindell, 2006), encompass linguistic (i.e., appropriate initiation, turn-taking, topic maintenance) and extralinguistic functions (gestures, facial expression, body movement) (Holler & Levinson, 2019), relying on different cognitive systems and higher order abilities, such as executive functions processing (Barkley, 2001; Camia et al., 2022; Martin & McDonald, 2003; Rad, 2014). For instance, in production and comprehension of narratives, the actors have to hold in mind and update the information, to suppress one's self-perception and flexibly respond to the interlocutor. These pragmatic abilities require the involvement of the right hemisphere, which helps to keep track of the topic or theme of a speech, to draw high-level inferences and to integrate the meaning into a broader discourse or social context (Stemmer, 2005).

Since the most recent tDCS literature has clearly suggested the involvement of the right DLPFC in different executive functions processes and in pragmatic language skills, in the present study we investigated whether anodal tDCS over the right DLPFC combined with different cognitive trainings involving executive functions processing would enhance the ability to communicate in everyday life in twenty PWSA.

4.3.2 Materials and Methods

Study Design

A randomized double-blinded cross-over design was conducted from January 2020 to June 2022 at the Behavioral Neurological Laboratory of the IRCCS Santa Lucia in Rome, Italy. Thirty chronic persons with post-stroke aphasia were examined through a detailed neuropsychological assessment. Ten were excluded for the following reasons: failure to meet the inclusion criteria, difficulty in transporting means and personal reasons. Thus, a final sample size of twenty patients was recruited.

G*Power 3.1 (Faul et al., 2009) was used to calculate the sample size with $\alpha = 0.05$, a power = 90%, two measurements (anodal vs sham), and effect size $f = 0.4$. The analysis indicated that a total sample size of $N \geq 19$ was necessary to detect a significant effect in our study.

All twenty patients received both interventions (AB → anodal-sham and BA → sham-anodal). The order of conditions was randomized across subjects. Half of the participants ($n = 10$) started with condition A (anodal tDCS) followed by condition B (sham tDCS), while the other half began ($n = 10$) with condition B (sham tDCS) followed by condition A (anodal tDCS). The allocation sequences were generated by a technician of the laboratory. To avoid carryover effects, a washout period of four weeks was established between condition A and B (and vice versa). As this was a double-blinded study, both the examiner and the patient were blinded regarding the stimulation condition and the stimulator was turned on/off by a third person, who assigned participants to the AB or BA intervention.

Participants

Twenty left-brain-damaged participants (ten men and ten women, mean age: 61.04; SD 7.02) with severe chronic aphasia were included in the study. Inclusion criteria were native Italian proficiency, a single left ischemic stroke at least 6 months prior to the investigation, pre-morbid right handedness (based on the "Edinburgh Handedness Questionnaire"; Oldfield, 1971) and no acute or chronic neurological symptoms needing medication. Subjects over 75 years of age and those with seizures, implanted electronic devices (e.g., pacemaker) and previous brain damage were excluded. None of the participants has received structured language therapy for at least 6 months before the time of inclusion in the study in order to prevent confounding therapy effects (see Table 4.3.1).

Table 4.3.1 Sociodemographic and clinical data of the twenty non-fluent aphasic patients (Esame del Linguaggio II (Ciurli et al., 1996), cut-off 100%; Token test (TT) (De Renzi & Vignolo, 1962), cut-off score 29/36). In each test, the percentages of correct responses are reported except for the Token Test whose score cannot be converted in percentage.

P	Sex	Age	Ed. Level	Time Post-Onset	Stroke Type	Lesion Side LH	Oral NN	Oral VN	Writ NN	Writ VN	WR	NWR	W Read	NW Read	WD	NW D	TT
1	M	50	8	4 y	I	FTP	5	5	0	0	20	15	12.5	5	0	0	5
2	M	58	13	3 y	I	FTP	0	5	0	0	10	0	10	0	0	0	5
3	M	60	8	1 y	I	FT	0	0	0	0	17.5	10	10	5	0	0	4
4	F	72	8	1 y	I	FTI	0	0	0	0	0	0	10	0	0	0	5
5	M	66	13	1 y	I	FT	0	0	0	0	20	12.5	15	5	0	0	4
6	M	67	17	2 y	I	FT	0	0	0	0	0	0	0	0	0	0	5
7	F	58	13	2 y	H	FTI	5	5	0	0	20	10	10	0	0	0	5
8	F	72	8	1 y	I	FTP	0	0	0	0	0	0	0	0	0	0	7
9	M	59	13	2 y	I	FTI	0	5	0	0	17.5	10	10	0	0	0	5
10	M	59	17	6 mo	I	FTI	5	0	0	0	0	0	0	0	0	0	4
11	F	72	8	2 y	I	FTP	0	0	0	0	15	5	12.5	5	0	0	7.5
12	M	54	17	6 mo	I	FTP	5	0	0	0	15	5	15	0	0	0	4
13	F	58	13	3 y	I	FTP	5	0	0	0	15	5	10	0	0	0	5
14	F	65	17	1 y	I	FT	5	0	0	0	10	0	10	0	0	0	4
15	M	69	8	2 y	I	FTP	5	5	0	0	0	0	0	0	0	0	4
16	M	55	13	3y	I	FT	0	0	0	0	0	0	0	0	0	0	6
17	F	52	17	6mo	I	FTP	0	5	0	0	0	0	0	0	0	0	5
18	F	61	8	1 y	I	FTI	5	0	0	0	0	0	0	0	0	0	5
19	F	53	13	2 y	I	FTP	0	0	0	0	0	0	0	0	0	0	4
20	F	68	13	4 y	I	FTP	0	5	0	0	0	0	0	0	0	0	5

Legend: P = Participants; M= male; F= female; Ed. Level = Educational Level; y=year/years; mo=months; I = Ischemic; H = Hemorrhagic; LH = Left hemisphere; FTP = fronto-temporo-parietal; FT=frontotemporal; FTI = fronto-temporo-insular; Oral NN = Noun Naming; Oral VN = Verb Naming; Writ NN = Written Noun Naming; Writt VN = Written Verb Naming; WR = Word Repetition; NWR = Nonword Repetition; W Read = Word Reading; NW Read = Nonword Reading; WD = Word under Dictation; NWD = Nonword under Dictation; TT= Token Test.

Ethics Statement

The data analyzed in the current study were collected in accordance with the Declaration of Helsinki and the institutional review board of the IRCCS Fondazione Santa Lucia, Rome, Italy. Before participation, all patients signed informed consent forms.

Clinical Data

All patients were diagnosed with severe non-fluent aphasia. Subjects were not able to spontaneously speak, as their verbal output was totally absent. The aphasic disorders were assessed using standardized language testing (Esame del Linguaggio II (EDL), Ciurli et al.,1996) and the Token Test (De Renzi & Vignolo, 1962). The EDL test included different tasks among which oral and written noun and verb-naming (n = 20 for noun naming, i.e., *topo* (mouse); n = 10 for verb naming, i.e., *leggere* (to read)), words repetition, reading and writing under dictation (words, n = 20, i.e., *tavolo* (table)), nonwords repetition, reading and writing under dictation (n = 20, i.e., *bo*, *fime*, *tarino*). Although some residual repetition and reading abilities were still present, all subjects were severely affected in the naming tasks and in the auditory comprehension test (Token test; cut-off 29/36) (see Table 4.1). Oral (n=60, i.e., *la moto ha superato la macchina* (the motorbike passed the car) and written comprehension (n=45, i.e., *le bambine sono applaudite dal bambino* (the girls are applauded by the boy) were also assessed through two subtests of the BADA test (Batteria per l'analisi dei deficit afasici, Miceli et al., 1994). In both tests, the aphasic performance was very compromised (see Table 4.2). To assess functional communication, we used the Italian version of CADL-2 (Pigliautile et al., 2019), an ecological evaluation tool which consists of 50 items in the form of role-playing activities revolving around fictitious environments (e.g., going to the doctor's office, grocery shopping, making a phone call, looking for directions, driving a car), depicted by questions and pictures (Pigliautile et al., 2019). All PWA obtained low CADL-2 percentage scores, indicating a poor level of functional communication (0-23 low percentage scores, 24-77 average percentage score, 78-100 high percentage score). To investigate executive functions processing, all participants were also administered the attention Visual Search test (Spinnler & Tognoni, 1987; cut-off score 30), the spatial short-term memory Corsi test (Monaco et al., 2012; cut-off score 3,08), the non-verbal Smirni subtest which measures the ability to recognize previously presented faces and buildings (Smirni et al., 2010; cut-off percentage score >10) and, for planning abilities, the Tower of London test (TOL, Krikorian et al., 1994; cut-off percentage score 80). In the Visual Search task, all patients performed close to the cut-off score, while in the Corsi test their performance was not impaired. In the Smirni test and in the TOL test, all patients were below the cut-off percentage score (see Table 4.3.2).

Table 4.3.2 Clinical data of the twenty non-fluent aphasic patients in Auditory and Written sentence comprehension of the BADA test (Batteria per l'Analisi dei Deficit Afasici, Miceli et al., 1994), in the CADL-2 test (Communication Activities of the Daily Living, Pigliautile et al., 2019; 0–23 low percentage scores, 24–77 average percentage score, 78–100 high percentage score), in the Visual Search (Spinnler & Tognoni, 1987; cut-off score 30), in the Corsi Span Backward (Monaco et al., 2013; cut-off score 3,08), in the Smirni test (Smirni et al., 2010; cut-off percentage score > 10) and in the TOL test (Tower of London, Krikorian et al., 1994; cut-off percentage score 80). The percentages of correct responses are reported for all tests except for Auditory and Written sentence comprehension of the BADA test, the Corsi test and the Visual Search whose score cannot be converted in percentage.

P	Auditory Sentence Compreh	Written Sentence Compreh	CADL-2	Visual Search	Corsi backward	Smirni	TOL
1	5	5	20	31	4	5	75
2	4	2	23	31	5	10	72
3	4	3	21	32	5	10	78
4	3	2	16	34	4	5	70
5	2	4	17	33	4	5	78
6	3	4	15	32	4	5	72
7	5	5	23	32	4	10	71
8	2	2	20	34	4	5	76
9	4	4	19	33	5	10	76
10	3	3	22	32	4	10	73
11	4	2	18	31	4	5	70
12	5	4	19	31	4	10	71
13	5	3	20	34	5	10	70
14	4	2	17	32	5	5	71
15	3	4	18	31	4	5	76
16	2	4	21	34	4	5	74
17	3	5	19	31	4	5	72
18	3	5	20	33	4	5	73
19	5	3	21	34	4	10	70
20	4	4	22	31	5	10	78

Legend: P= Participants; Compreh= Comprehension; CADL-2= Communication Activities of the Daily Living; TOL=Tower of London

Materials

Cogniplus software (Schuhfried, https://www.schuhfried.com/cogniplus/ (accessed on 15 January 2020), Mödling, Austria, Europe), a cognitive battery for training different cognitive abilities embedded in lifelike scenarios, was used. Four cognitive tasks were selected: alertness, selective attention, visuo-spatial working memory, and planning.

In the alertness training, the patient drove a motorcycle at varying speed along a winding road. The aim was to carefully observe the stretch of the road in front of him/her and to press the keyboard as quickly as possible when an obstacle appeared on the road (i.e., a level crossing closes, a tree falls unexpectedly in the driver's path), in order to brake promptly before it.

In the selective attention task, the patient was an explorer on a boat along a river surrounded by a forest. During the journey, several animals appeared, including hippos, giraffes, elephants. The patient was asked to press the keyboard only when he/she saw the hippos.

In the spatial working memory task, the patient watched colorful butterflies in a natural environment. The butterflies flew over a meadow or sandy area. From time to time, one butterfly landed, and another started its flight and so on. Depending on the level of difficulty, the patient was asked to remember the position of the last butterfly, the second-to-last butterfly, the third-to-last butterfly and so on.

In the planning training, the patient saw a map of the city with nine buildings (e.g., post office, café, insurance office, cultural center). On the right side of the map, a box appeared in which pending and completed errands were listed. The patient was asked to accomplish several tasks in each building, formulating an appropriate strategy to decide in which order running the errands. The task difficulty varied according to the number of errands to be completed and the time spent.

Procedure

Transcranial Direct Current Stimulation (tDCS)

tDCS was applied using a battery driven Eldith (neuroConn GmbH) Programmable Direct Current Stimulator with a pair of surface-soaked sponge electrodes (5 × 7 cm). Anodal stimulation consisted of 20 min of 2 mA direct current with the anode placed over the right DLPFC (F4 of the extended International 10–20 system for EEG electrode placement) and the cathode (the reference electrode) above the contralateral frontopolar cortex (Fp1). For sham stimulation, the same electrode position was used. The current was ramped up to 2 mA and slowly decreased over 30 s to ensure the typical initial tingling sensation (Gandiga et al., 2006). The order of conditions was randomized across subjects. Half of the participants started with the anodal condition and the remaining half with the sham condition. There were four weeks of intersession interval between the two experimental conditions. Thus, after four weeks, the order of condition was inverted. For each experimental condition (anodal vs. sham), the rehabilitative program consisted of 10 one-hour sessions over two weeks (Monday-Friday, weekends off, Monday-Friday). Although tDCS stimulation was delivered from the beginning of the cognitive training up to 20 min, the cognitive training lasted 1 h per day. At the end of each treatment condition (anodal vs. sham) and after four weeks (follow-up), the neuropsychological battery was readministered to all patients. During the training, none of the participants noticed differences in the intensity of sensation between the two stimulation conditions (anodal vs. sham), not being aware of what condition they were performing (O'Connell et al., 2012).

Cognitive treatments

The cognitive treatment was administered through the Cogniplus software (Schuhfried). During each one-hour session, all participants underwent four types of training: alertness, selective attention, visuo-spatial memory, and planning presented in randomized order.

Data Analysis

Before, after the treatment and at follow-up (FU), the patients' performance was evaluated by comparing the mean score obtained in the alertness, selective attention, visuo-spatial working memory, and planning training. Data were analyzed using STATISTICA10 software. The Shapiro–Wilk test was applied which revealed a normal distribution of the data. Four repeated measures ANOVAs were performed separately for the four types of training. For each analysis, two "within" factors were considered: CONDITION (anodal vs. sham) and TIME (baseline (T0) versus end of treatment (T10) versus follow up (FU)). The post-hoc Bonferroni test was conducted on the significant effects observed in the ANOVA. The values of $p \leq 0.05$ were considered statistically significant. Before and after each treatment condition, the patients' responses to the different re-administration of the standardized language tests (EDL and BADA), CADL-2 test, Visual Search test, Smirni subtest and TOL test were also analyzed using $\chi 2$-test.

4.3.3 Results

Accuracy Data

Alertness

The analysis showed no significant effect of CONDITION (anodal versus Sham, F (1,19) = 1.51, $p = 0.23$, partial $\eta 2 = 0.07$ and observed power =0.21), but a significant effect of

TIME [Baseline (T0) versus End of treatment (T10) versus Follow-up (F/U), F (2,38) = 360.40, *p*≤0.001, partial η2 = 0.95, and observed power =1.000]. The interaction CONDITION×TIME was not significant (F (2,38) = 1.76, *p* = 0.19, partial η2 = 0.08 and observed power =0.35).

Selective Attention

The analysis showed a significant effect of CONDITION (anodal versus Sham, F (1,19) = 222.13, p ≤ 0.001, partial η2 = 0.92 and observed power =1.000) and of TIME (Baseline (T0) versus End of treatment (T10) versus Follow-up (F/U), F (2,38) = 427.84, *p*≤0.001, partial η2 = 0.96 and observed power =1.000). The interaction CONDITION x TIME was also significant (F (2,38) = 199.19, *p*≤0.001, partial η2 = 0.91 and observed power =1.000). Bonferroni's *post-hoc* test revealed that, while no significant differences emerged in the mean score between the two conditions at T0 (anodal 2 versus sham 2, *p* = 1), the mean score was significantly greater in the anodal than in the sham condition at T10 (anodal 8 versus sham 4, *p*≤0.001) and persisted at F/U (anodal 8 versus sham 4, *p*≤0.001). Significant differences also emerged between T0 and T10 for the sham condition (2, *p*≤0.001) (see Figure 4.3.1).

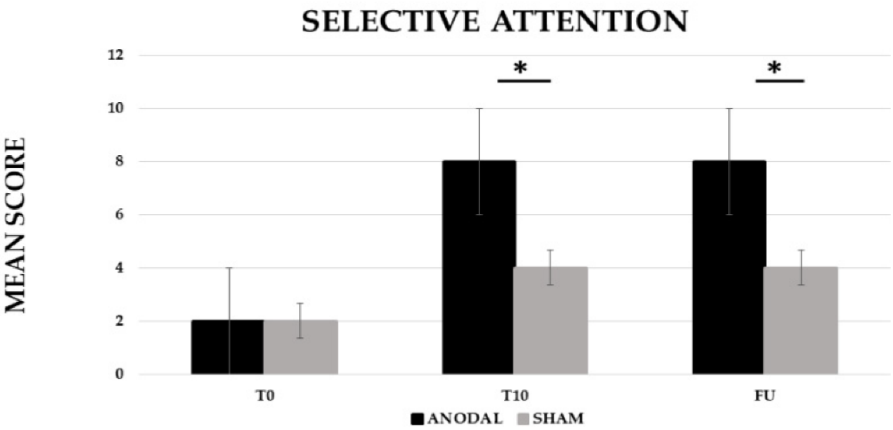

Figure 4.3.1 Mean score in the selective attention training at baseline (T0), at the end of treatment (T10) and at follow-up (F/U, 1 month after the end of treatment) for the anodal and sham condition, respectively. Sig. ANOVA: * $p \leq 0.001$.

Visuo-spatial working memory

The analysis showed a significant effect of CONDITION (anodal versus Sham, $F(1,19) = 20.29$, $p \leq 0.001$, partial $\eta 2 = 0.52$ and observed power =0.99) and TIME (Baseline (T0) versus End of treatment (T10) versus Follow-up (F/U), $F(2,38) = 169.29$, $p \leq 0.001$, partial $\eta 2 = 0.90$ and observed power =1.000). The interaction CONDITION x TIME was also significant ($F(2,38) = 18.99$, $p \leq 0.001$, partial $\eta 2 = 0.50$ and observed power =0.99). Bonferroni's *post-hoc* test revealed that, while no significant differences emerged in the mean score between the two conditions at T0 (anodal 2 versus sham 2, $p = 1$), the mean score was significantly greater in the anodal than in the sham condition at T10 (anodal 10 versus sham 7, $p \leq 0.001$) and persisted at F/U (anodal 9 versus sham 7, $p \leq 0.001$). Significant differences also emerged between T0 and T10 for the sham condition (5, $p \leq 0.001$) (see Figure 4.3.2).

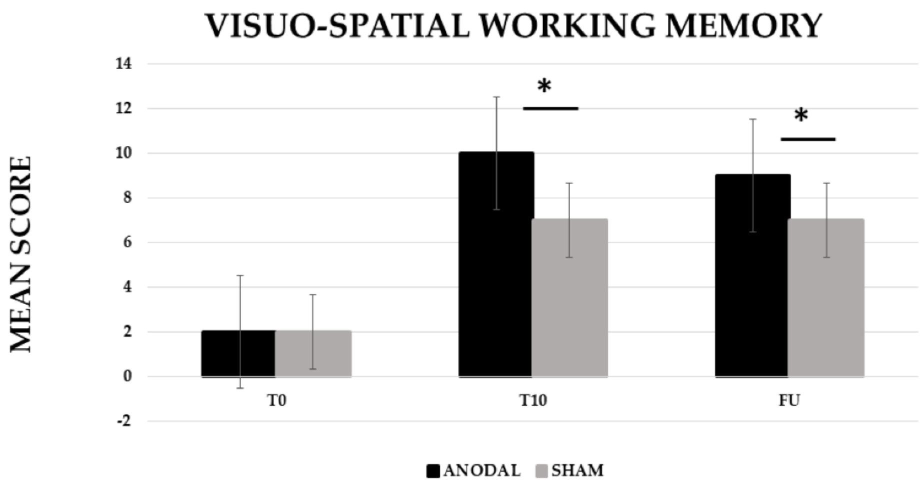

Figure 4.3.2 Mean score in the visuo-spatial working memory training at baseline (T0), at the end of treatment (T10) and at follow-up (F/U, 1 month after the end of treatment) for the anodal and sham condition, respectively. Sig. ANOVA: * $p \leq 0.001$.

Planning

The analysis showed a significant effect of CONDITION (anodal versus Sham, $F(1,19) = 201.06$, $p \leq 0.001$, partial $\eta 2 = 0.91$ and observed power =1.000) and TIME (Baseline (T0) versus End of treatment (T10) versus Follow-up (F/U), $F(2,38) = 438.24$, $p \leq 0.001$, partial η2 = 0.96 and observed power =1.000). The interaction CONDITION x TIME was also significant (F (2,38) = 237.05, $p \leq 0.001$, partial η2 = 0.93 and observed power =1.000). Bonferroni's *post-hoc* test revealed that, while no significant differences emerged in the mean score between the two conditions at T0 (anodal 3 versus sham 4, $p = 1$), the mean score was significantly greater in the anodal than in the sham condition at T10 (anodal 16 versus sham 10, $p \leq 0.001$) and persisted at F/U (anodal 16 versus sham 9, $p \leq 0.001$). Significant differences also emerged between T0 and T10 for the sham condition (6, $p \leq 0.001$) (see Fig. 4.3.3).

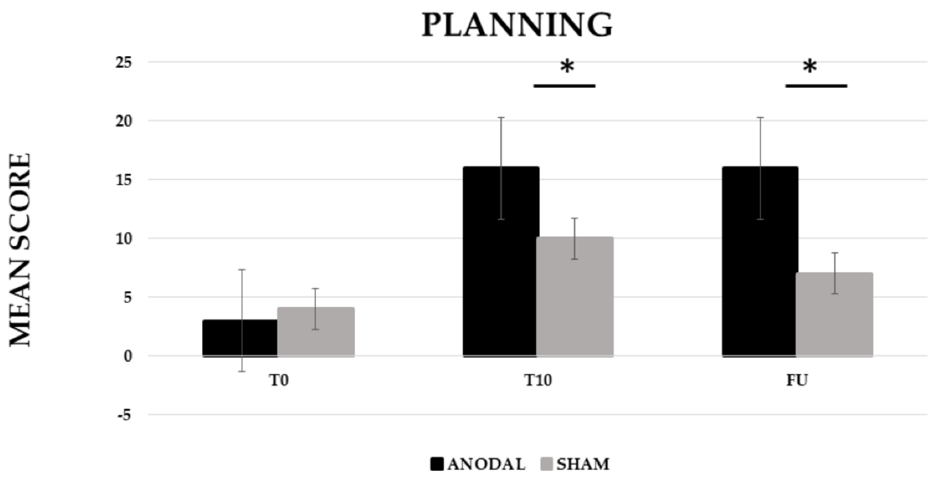

Figure 4.3.3 Mean score in the planning training at baseline (T0), at the end of treatment (T10) and at follow-up (F/U, 1 month after the end of treatment) for the anodal and sham condition, respectively. Sig. ANOVA: * $p \leq 0.001$.

Interestingly, the *χ2*-test also revealed that, when the training was combined with anodal stimulation, all patients significantly improved not only in the CADL-2 test but also in oral noun and verb naming and in oral and written comprehension of sentences (see Table 4.3.3).

Table 4.3.3 Correct Responses in the Different Language Tasks (Esame del Linguaggio II(EDL), Ciurli et al., 1996); Battery for the Analysis of Aphasic Disorders test (BADA, Miceli et al., 1994) and in the Communication Activities of the Daily Living test (CADL-2, Pigliautile et al., 2019), at Baseline (T0), at the End of Treatment (T10), and at Follow up (FU) for the real and sham condition, respectively.

P	C	ORAL NN			ORAL VN			AUDITORY SENT COMP			WRITTEN SENT COMP			CADL-2		
		T0	T10	FU	T0	T10	FU	T0	T10	FU	T0	T10	FU	T0	T10	FU
REAL FIRST																
1	R	5	30^	30	5	30^	30	5	17**	17	5	16*	14	20	48^	42
	S	30	32,5	25	30	35	30	17	19	16	16	18	14	48	50	40
3	R	0	17,5^	15	0	12,5^	15	4	15*	13	3	13*	13	21	50^	50
	S	17,5	17,5	15	12,5	15	12,5	15	17	14	13	16	14	50	54	52
5	R	0	15^	15	0	10**	10	2	14*	13	4	13*	11	17	36**	38
	S	15	15	10	10	10	10	14	14	12	13	14	13	36	40	38
7	R	5	20**	20	5	40^	42,5	5	15*	15	5	12	11	23	55^	50
	S	20	25	20	40	45	40	15	16	15	12	11	9	55	59	48
9	R	0	12,5^	15	5	30^	25	4	20^	20	4	18**	18	19	36**	40
	S	12,5	15	15	30	30	20	20	19	19	18	19	18	36	40	40
11	R	0	10**	10	0	20^	20	4	12	13	2	11*	12	18	40^	40
	S	10	15	15	20	25	25	12	13	13	11	11	11	40	46	44
13	R	5	15*	15	0	10**	10	5	13	11	3	14**	15	20	51^	51
	S	15	20	17,5	10	10	7,5	13	13	9	14	16	16	51	55	50
15	R	5	20**	20	5	30^	32,5	3	15**	15	4	16**	16	18	39**	36
	S	20	22,5	20	30	30	30	15	18	18	16	19	16	39	43	40
17	R	0	20^	17,5	5	25^	25	3	10	11	5	13	12	19	44^	48
	S	20	30	25	25	30	30	10	13	13	13	13	11	44	46	46
19	R	0	17,5^	15	0	20^	17,5	5	14*	14	3	13*	14	21	48^	48
	S	17,5	25	20	20	20	15	14	13	13	13	15	14	48	47	47
SHAM FIRST																
2	S	0	0	0	5	10	10	4	7	7	2	4	5	23	27	23
	R	0	15^	12,5	10	35^	30	7	18*	15	4	14*	14	27	46**	40
4	S	0	5	5	0	0	0	3	8	8	2	7	6	16	20	20
	R	5	25^	22,5	0	20^	15	8	18*	18	7	19*	17	20	44^	44
6	S	0	0	0	0	0	0	3	7	6	4	5	5	15	18	20
	R	0	10**	10	0	0	0	7	17*	14	5	14*	13	18	42^	44
8	S	0	0	0	0	0	0	2	4	4	2	4	4	20	25	25
	R	0	12,5	15	0	15^	15	4	15*	15	4	19^	18	25	53^	50
10	S	5	10	10	0	5	5	3	8	8	3	5	4	22	25	22
	R	10	30^	30	5	25^	22,5	8	23**	21	5	14*	13	25	55^	50
12	S	5	7,5	5	0	0	0	5	10	10	4	7	7	19	23	23

	R	7,5	20*	20	0	20^	20	10	20	21	7	18*	19	23	47^	47
14	S	5	10	10	0	0	0	4	6	5	2	4	4	17	22	20
	R	10	25**	20	0	20^	17,5	6	16*	15	4	15**	16	22	46^	42
16	S	0	5	5	0	10**	10	2	4	4	4	6	5	21	26	24
	R	5	22,5^	20	10	35^	30	4	14*	14	6	16*	14	26	53^	48
18	S	5	10	10	0	0	0	3	5	6	5	9	9	20	22	20
	R	10	25**	25	0	15^	15	5	17**	19	9	18	19	22	41**	41
20	S	0	0	0	5	10	10	4	7	7	4	8	7	22	24	24
	R	0	10**	7,5	10	30^	25	7	19*	19	8	20*	19	24	53^	53

Legend: P= Participants; C = Condition; ORAL NN = Noun Naming; ORAL VN = Verb Naming; AUDITORY SENT COMP = Auditory Sentence comprehension; WRITTEN SENT COMP = Written Sentence Comprehension; CADL-2= Communication Activities of the Daily Living; R = Real stimulation; S = Sham stimulation; *= p < 0.05; **=p<0.01; ^= p <0.001.

Moreover, after anodal stimulation, eleven out of twenty patients further improved their performance in the visual search test, while nine and fifteen patients passed the cut-off scores in the Smirni and TOL tests, respectively. These changes persisted at F/U. No changes were observed in the Corsi test whose score was already above the cut-off in all patients (see Table 4.3.4).

Table 4.3.4 Correct Responses in the Different Cognitive Tasks (Visual Search, Spinnler & Tognoni,1987; Smirni test, (Smirni et al.,2010); Tower of London (TOL), Krikorian et al.,1994) at Baseline (T0), at the End of Treatment (T10) and at Follow up (FU) for the real and sham condition, respectively.

P	C	VISUAL SEARCH			SMIRNI			TOL		
		T0	T10	FU	T0	T10	FU	T0	T10	FU
REAL FIRST										
1	R	31	40	40	5	5	5	75	90**	85
	S	40	40	41	5	5	5	90	90	80
3	R	32	41	39	10	50^	50	78	92**	90
	S	41	40	38	50	50	50	92	92	90
5	R	33	34	33	5	5	5	78	91*	94
	S	34	34	33	5	5	5	94	94	92
7	R	32	33	34	10	25*	25	71	79	75
	S	33	35	34	25	25	25	79	73	73
9	R	33	45*	46	10	25*	25	76	79	76
	S	45	46	48	25	25	25	79	76	76
11	R	31	40	41	5	5	5	70	88**	89
	S	40	39	40	5	5	5	88	88	90
13	R	34	43	45	10	50^	50	70	92^	95
	S	43	45	44	50	50	50	92	95	95
15	R	31	42	41	5	5	5	76	88*	85
	S	42	41	40	5	5	5	88	86	83

17	R	31	32	32	5	5	5	72	74	72
	S	32	32	31	5	5	5	74	73	72
19	R	34	35	34	10	25*	25	70	85*	84
	S	35	34	33	25	25	25	85	88	84
SHAM FIRST										
2	S	31	31	32	10	10	10	72	72	80
	R	31	31	31	10	25*	25	72	88*	89
4	S	34	35	38	5	5	5	70	75	73
	R	35	44	33	5	5	5	75	88*	89
6	S	32	33	33	5	5	5	72	72	71
	R	33	41	43	5	5	5	72	69	70
8	S	34	34	33	5	5	5	76	76	80
	R	34	34	34	5	5	5	76	89*	91
10	S	32	33	34	10	10	10	73	78	85
	R	33	34	35	10	50^	50	78	100^	95
12	S	31	32	31	10	10	10	71	4	75
	R	32	32	32	10	50^	50	74	85*	80
14	S	32	34	37	5	5	10	71	75	80
	R	34	44	45	5	10	10	75	87**	87
16	S	34	38	35	5	5	5	74	76	75
	R	38	40	38	5	5	5	76	75	75
18	S	33	36	40	5	5	10	73	71	77
	R	36	47	48	5	10	10	71	86*	88
20	S	31	34	38	10	10	10	78	78	83
	R	34	45	46	10	25*	25	78	93**	95

Legend: P= Participants; C = Condition; TOL= Tower of London; R = Real stimulation; S = Sham stimulation; *= $p < 0.05$; **=$p<0.01$; ^= $p <0.001$.

4.3.4 Discussion

In the present study, we investigated whether different types of executive function training combined with tDCS would enhance functional communication in twenty persons with chronic severe aphasia. After the training, an improvement in selective attention, spatial working memory and planning abilities was found in both stimulation conditions (anodal vs. sham) but it was greater in the anodal condition compared to sham. More importantly, this improvement persisted one month after the intervention. Thus, the executive training alone exerted its own effectiveness, but the recovery process was further improved after anodal tDCS. No differences were found between the two conditions in the alertness task. This last result argues against an explanation simply due to enhanced cognitive arousal which should have also influenced the alertness task.

Interestingly, after anodal stimulation, a significant improvement was also observed in functional communication, in noun and verb naming, in auditory and written language comprehension tasks and in different executive functions tests.

As stated in the Introduction, in persons with chronic severe aphasia, language skills might be dramatically impaired even years after the onset of the disease. This situation often impacts also on the person's ability to rely on functional communication. That is, the ability to effectively communicate his/her own needs in social contexts making use of compensatory strategies which allow to bypass the person's verbal limitations (Bambini et al., 2017; Lasker et al., 2007; Light & McNaughton, 2014). Indeed, all individuals can express their communicative intentions not only through language, but also through extralinguistic means such as hand gestures, body movements or facial expressions which are intentionally expressed to convey a message. The impact of inadequate strategic competence prevents severe aphasic people to maintain successful social relations and to pursue life goals (Agostoni et al., 2021). Consequently, in addition to the assessment of formal aspects of language (phonological, lexical, and grammatical domains), in persons with severe aphasia, the adjunct of a functional communication scale is particularly relevant to test their communicative abilities.

In the present study, together with standardized language tests, we administered the Communication Activities of Daily Living scale (CADL 2) (Pigliautile et al., 2019) which, among the different communication abilities assessment tools, is considered a valid ecological battery for functional communication assessment (Rad, 2014). The CADL 2 assesses a person's communication abilities in activities of daily life by asking him/her to simulate communication acts in hypothetical natural environments (e.g., going to the doctor, making a phone call, asking for directions). It has been widely employed in the assessment of everyday language abilities in persons with aphasia (Marshall et al., 2015; Rofes et al., 2015) and in the evaluation of intensive language rehabilitation programs (Persad, 2013). Interestingly, our results clearly showed that, while, before the training, all patients obtained very low percentage scores in the CADL-2, after two weeks of treatment, all of them reached an average percentage score but only when the training was combined with anodal tDCS. Thus, although the training was effective, the greater improvement obtained in the anodal condition was reflected in a positive change in the

CADL-2 only in this condition. Similar results, although not for all patients, were obtained in the tests of attention, spatial memory, and planning skills.

As already mentioned, in recent years, there has been increasing interest in understanding the role of executive processes (e.g., cognitive control, attention, working memory) in the recovery of post-stroke language deficits (Manenti et al., 2015; Pestalozzi et al., 2018). The cerebral regions involved in executive function processing have been shown to be recruited in language tasks in post-stroke aphasia and in healthy subjects (Brownsett et al., 2014). Researchers have also found that executive regions play a major role in recovery from aphasia (Geranmayeh et al., 2017). Indeed, to enact goal-directed behavior and to respond to novel and challenging tasks of everyday life, people should make use of different cognitive components, such as cognitive flexibility, working memory and attention which rely on executive functions processing. Executive functions have been linked to pragmatic abilities and to social behavior (Barkley, 2001) as they are involved in planning, monitoring, and inhibiting the discourse and in social exchanges. Moreover, intact executive functions system seems to be crucial to adaptive, motivated, and effective communication (Champagne-Lavau & Stip, 2010; Martin & McDonald, 2003). Impaired executive functions processing has been described in aphasic stroke patients and it has been shown to have a negative impact on rehabilitation outcomes (el Hachioui et al., 2014; Leśniak et al., 2008; Lipskaya-Velikovsky et al., 2018; Murray, 2012; Schumacher et al., 2019), functional communication (Olsson et al., 2019), and quality of life (Nicholas et al., 2017). However, in most of these studies, the relationship between executive control and functional communication has been investigated only by assessing the aphasic performance through neuropsychological tests, including measures of functional communication, executive functional ability, and language impairment (Baldo et al., 2005; Martin & Allen, 2008; Olsson et al., 2019, 2020). Based on these findings, it appears that higher levels of executive functioning are linked to better functional communication (Fridriksson et al., 2006) and conversational skills (Frankel et al., 2007) and greater cognitive flexibility has been significantly correlated to better strategy use in functional communication tasks (Purdy & Koch, 2006). Indeed, in Olsson and colleagues (2019, 2020) studies, most of the aphasic patients (79%) presented with executive functions deficits with the nonverbal participants more severely affected than the verbal group. Few recent studies have directly investigated if spared executive control is an important predictor of treatment gains. In Simic et al. study (2019), ten patients with mild to severe aphasia were treated three times a week for five weeks with a phonological naming therapy. Difference scores in naming accuracy of treated and untreated words served as the primary outcome measures. Results showed that individuals with better executive functions abilities showed better maintenance of treated words at four and eight- weeks follow-ups.

As far as we know, to date, only one study has emphasized the importance of strengthening executive control through prefrontal tDCS to facilitate lexical retrieval and verbal fluency in aphasia (Pestalozzi et al., 2018). However, until now, no studies have investigated the impact of executive function training combined with tDCS on functional communication.

In our study, after the training, all patients improved in their functional communication skills and in several language and executive functions tasks, indicating an improvement in executive control that enhanced functional communication. Interestingly, as also noted in previous works (see Marangolo, 2020 for a review), these generalization effects on untreated tasks were present only after anodal stimulation. Indeed, the sham condition impacted only on the cognitive treatments as such. These results might be ascribed to the severity and chronicity of the functional communication profile observed, at baseline, in all patients. Indeed, since the treatment lasted only ten days, the hypothesis might be advanced that the executive function training alone was insufficient to improve functional communication. On the contrary, interestingly, the same number of training sessions combined with anodal tDCS over the same period exerted beneficial effects on the treated functions and generalized to functional communication and to the language domain. Thus, similar to previous results (see Marangolo, 2020 for a review), combining tDCS with cognitive training boosted cognitive recovery overcoming the difficulties caused by the severity of the deficit. These findings are, thus, very promising, as ten days of tDCS produced generalization effects over untreated functions (i.e., functional communication and language) which lasted up to one month which were not obtained in the absence of stimulation.

It is well known that executive functions are dependent on the prefrontal lobes which are strongly interconnected with other cortical areas and subcortical structures

(Constantinidou et al., 2012; Suchy, 2009) among which the frontal areas. In our study, we choose to stimulate the right DLPFC due to its role in selective attention, spatial working memory and planning abilities. Indeed, most of the recent tDCS literature have found that anodal tDCS over the right DLPFC enhances these skills (Giglia et al., 2014; Harty et al., 2014; Jeon & Han, 2012; Trumbo et al., 2016; Wu et al., 2014). Moreover, since all of our patients had extensive damage to the left language areas, we reasoned that stimulation of the right DLPFC would also have positive effects on language tasks. Indeed, even if the exact underlying tDCS mechanisms in our study remain largely speculative, the hypothesis might be advanced that, due to the strong interconnections between the prefrontal and the frontal regions (Brownsett et al., 2014; Constantinidou et al., 2012; Geranmayeh et al., 2017; Suchy, 2009), anodal tDCS over the right DLPFC has enhanced activation on the right frontal cortex which, in turn, serves as a supportive area for the observed recovery. Indeed, to date, several neuroimaging studies have already shown functional connectivity changes on cortical activity within the lesioned left hemisphere (Darkow et al., 2017; Hartwigsen & Saur, 2019; Marangolo et al., 2016) and in the contralateral right homologues (Hamilton et al., 2011; Turkeltaub, 2015; Zheng et al., 2016) due to tDCS treatment.

4.3.5 Conclusion

We are aware that our study has some limitations. The major ones are the small sample size and the lack of longitudinal follow-ups and of neuroimaging recordings. However, considering these limitations, we believe that our study highlights several important aspects to be considered when making treatment decisions for people with severe aphasia. First of all, it points to the possibility of training cognitive functions other than language. Indeed, from a connectionist perspective which considers the language system as part of a network largely distributed across the brain, this allows clinicians to plan different cognitive treatments which, in turn, facilitate aphasia recovery. It also emphasizes the need to assess functional communication skills, the recovery of which, even in the most severely affected patients, will allow the patient to socially interact in everyday life contexts. Finally, it confirms several previous reports which suggest that PWA in the chronic phase can still benefit from combining the treatment with tDCS.

In conclusion, although future studies are needed to deepen our understanding of the role of executive control on functional communication and the underlying neural mechanisms by which tDCS affects verbal performance, we believe that our results are promising since, for the first time, they suggest that executive function training can positively impact functional communication in severe chronic aphasia.

CONCLUSIONS

My Ph.D. thesis was aimed at investigating new theories emerging, in these last decades, in the neuroscience of language considering their impact on planning new therapeutic approaches for aphasia recovery.

I believe that the results of the three experimental investigations reported in Chapter 4 are promising for different reasons. The first study which explored the effect of tDCS applied over the temporo-parietal region highlights its use even in persons with severe agraphia. Indeed, since the recovery of oral production in persons with aphasia might result in some cases resistant to treatment (e.g., in cases of concomitant severe apraxia of speech), the recovery of writing might result in a more realistic therapeutic goal. In recent years, due to the increasing use of the internet and mobile technologies (i.e., computers, tablets, smartphones), written production has become an increasingly important part of everyday life, providing opportunities for returning to employment, education, and greater involvement in community life (Thiel et al., 2015; Thiel & Conroy, 2022). Thus, the possibility to enhance writing skills through tDCS even in severe cases might represent an important challenge for the future.

The second experiment has its scientific relevance since it further confirms the role of the spinal cord for the recovery of some aspects of language characterized by sensorimotor properties, such as speech articulation even in severe chronic aphasia. It is well-known that the electrical conductivity of the spinal intervertebral disks is highest in magnitude than the electrical conduction along the spongy bones in the cortex. Thus, the application of electric current over the spinal cord should more easily reach the nervous fibers with respect to the application of the same amount of current over the scalp (Balmer et al., 2018). Taking these accounts into consideration, we might then suggest that tsDCS would result more effective for the recovery of the motor aspects of language compared to tDCS because an appropriate positioning of the anode over the spinal cord would induce current density which reaches homogeneously the brain network related to motor processing. This would remove the need to establish which part of the system should be targeted with tDCS. Given that action verbs and speech articulation both represent complex symptoms resistant to change in severe aphasia, the possibility of finding more effective therapeutic aids for the improvement of these abilities becomes relevant for a better prognosis.

In light of these findings, it would be also crucial for future research to investigate the therapeutic potential of tsDCS for the recovery of other cognitive abilities which rely on the motor domain, such as executive functions.

Indeed, the results of the last experiment suggest the possibility to plan for the next future potential new treatment programs for persons with severe aphasia which make use of executive trainings. As it is well known, in severe aphasia, verbal communication might result compromised in such a way to not even allow the individuals to adequately meet their communicative needs (e.g., social interaction and information transfer). Thus, a primary goal for these people is to let them recovery functional communication. The importance of gaining adequate strategic competence for successful functional communication suggests relying on the executive system in such severe cases.

In conclusion, these three Ph.D. years have been a decisive starting point for my future choices in my research career. I have learned a lot on how conceptualize experiments. I have developed several language and cognitive treatments for persons with aphasia. I have enriched my knowledge by discussing the results of my studies at national and international conferences with young and senior researchers. I have understood the importance to translate science into clinical practice considering to further pursue my research in this direction. What I have learned above all is to interface myself with human suffering. In particular, I have realized the drama of living with persons with aphasia, whose lives, families, work and social balance is forever changed due to cerebral damage. For this reason, for my next future, I feel the strong desire to carry out the “mission” to welcome these patients and encourage them to take part to treatments that could not only alleviate their symptoms but also give them moments of light-heartedness.

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