Tesi di dottorato in Scienze della Neuroplasticità e del Recupero Neurofunzionale, di Anna Fertonani, discussa presso l'Università Campus Bio-Medico di Roma in data 29/05/2012.
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Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in
Scienze della Neuroplasticità e del Recupero Neurofunzionale
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Non-invasive brain stimulation: an innovative tool to study language abilities

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To all the

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Abbreviations

AAT = Aachener aphasia test

AD = Alzheimer's dementia

BADA = battery for the analysis of the aphasic deficits

CNS = central nervous system

CPAP = continuous positive airway pressure

CRL – IPNP = Center for Research in Language – International Picture Naming Project

DLPFC = dorsolateral prefrontal cortex

EEG = electroencephalography

fMRI = functional magnetic resonance imaging

LTP = long term potentiation

LTD = long term depression

M1 = primary motor cortex

MEP = motor evoked potential

MSO = maximum stimulator output

MT = motor threshold

NIBS = non-invasive brain stimulation

NMDA = N-Methyl D-aspartate

PET = positron emission tomography

PNT = picture naming task

PWA = patient with aphasia

RT = reaction time

rTMS = repetitive transcranial magnetic stimulation

tACS = transcranial alternating current stimulation

tDCS = transcranial direct current stimulation

tES = transcranial electrical stimulation

TMS = transcranial magnetic stimulation

V1 = primary visual cortex

vRT = vocal reaction time

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Abstract

Non-invasive brain stimulation (NIBS) techniques have been to date extensively used for the investigation of the cerebral functions. Thanks to their ability to interact with the central nervous system in a non-invasive and non-painful way they have been applied to investigate not only basic motor and visual processes, but also superior cognitive functions (e.g., language, memory, attention). In the language domain, for example, repetitive transcranial magnetic stimulation (rTMS) has proved to be efficacious in shortening the vocal reaction times of young subjects during an action naming task (Cappa et al., 2002). This work has confirmed the role of the left dorsolateral prefrontal cortex (DLPFC) in action naming. The involvement of the left DLPFC in naming task has been highlighted by both neuroimaging and rTMS studies (Cappa et al., 2002, Cotelli et al., 2006, Cotelli et al., 2008, Perani et al., 1999, Shapiro et al., 2006). The aim of my research is to understand which NIBS and stimulation protocols are the most effective to obtain a facilitation in a picture naming task in healthy subjects. The final goal is to apply these protocols in aphasic patients, to support and enhance the effects of the classical logopedic rehabilitation. First of all, we created two different versions of the naming task, to adopt accordingly with the age of the experimental subjects/patients (young vs. aged). Subsequently we applied transcranial direct current stimulation (tDCS) on the left DLPFC in young healthy subjects before the execution of a picture naming task. The results highlighted a facilitation (i.e., shortening of the vocal reaction times) only after the stimulation with anodal polarity (Fertonani et al., 2010). The same task was subsequently tested in young healthy subjects with a tDCS bilateral montage (i.e., anode on the left DLPFC and cathode on the right DLPFC), but this study have not had significant results. Then we applied tDCS in healthy aged subjects, varying the timing of anodal stimulation (i.e., before vs. during the task execution). The results showed a superiority of online stimulation.

Summarizing, the most effective approach was the unilateral tDCS montage, in consequence we applied unilateral tDCS in one aphasic patient, in combination with a logopedic rehabilitation. In addition, considering the previously demonstrated efficacy of DLFPC rTMS (Cappa et al., 2002; Cotelli et al., 2006; Cotelli et al., 2008), other three aphasic patients were treated with rTMS plus logopedic

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rehabilitation (Cotelli et al., 2011b). Results are encouraging and provide additional evidence for the beneficial effects of brain stimulation in combination with targeted logopedic training in aphasic patients suffering from anomia. In particular, a long-lasting effect of combined tDCS and behavioural therapy was observed on the therapy list of stimuli still at 48 weeks after the beginning of the combined stimulation-speech therapy intervention. This result is consistent with previous reports on enhanced cognitive performance following NIBS (i.e., rTMS or tDCS) to specific cortical areas in patients with a variety of neurological diseases (Miniussi et al., 2008, Miniussi and Vallar, 2011a). Moreover, this result is also consistent with previous evidence regarding the increased efficacy of daily combined rTMS or tDCS plus cognitive rehabilitation (Baker et al., 2010, Fiori et al., 2011, Floel et al., 2011, Fridriksson et al., 2011, Kakuda et al., 2010b, Kang et al., 2011, Martin et al., 2009b, Naeser et al., 2010b, Weiduschat et al., 2011). The possibility of non-invasively interacting with the functioning of the brain and its plasticity mechanisms, leading to cognitive and behavioural modifications, opens new and exciting scenarios in the cognitive neurorehabilitation field.

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1.

INTRODUCTION

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This thesis describes the research activity carried out during the three years of PhD in "Scienze della Neuroplasticità e del Recupero Neurofunzionale". This activity has been focalized on the study of the cognitive functions, i.e., the language, using non-invasive brain stimulations (NIBS). The objective of my research was to understand which stimulation protocols were the most effective in healthy people in inducing naming facilitation thinking about the future application in the neurorehabilitation of patients with language deficits.

1.1 The language

The language is the more complex, flexible and exclusive system of communication used by the humans. It permits the communication between us and our similes, and it defines in their truth reality the being of the men and of the society. As all the communication system, it is constructed by the possibility of producing a signal and of decoding it.

In this chapter, after a brief review about the discover of the relationship between the language and the brain and the historical development of the conceptualization of this relation, I'll present the principal form of disease of oral language (i.e., aphasic syndromes) and the rationale underlying their treatment.

1.1.1 The language and the brain

After the imaginative descriptions of Gall, a concrete relationship between the language and the brain was clearly established from 1861, with Broca's studies on his famous patient called "Tan". When this patient died, Broca dissected his brain finding a lesion in the left frontal lobe. In consequence of his discovery this area is now named "Broca's area". A second important discovery was carried out by Carl Wernicke, that in 1874 described patients that in consequence of a left posterior temporal cortex presented a fluent but non-sense speech. Indeed, most of all we know today about the involvement of certain brain areas in the linguistic process, it's due to studies on aphasia, known as "language disease" yet at the last of the eighty (Cacciari, 2001). At this time date back also the idea of a functional asymmetry between the two hemispheres, with the predominance of the left one for the linguistic functions. In this conceptualization the area of Broca was related to the production of language whereas the area of Wernicke was deputized to its comprehension. In the

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associationist and neo-associationist current, lesions of one of these areas or of the connections between them yield to the different forms of aphasia.

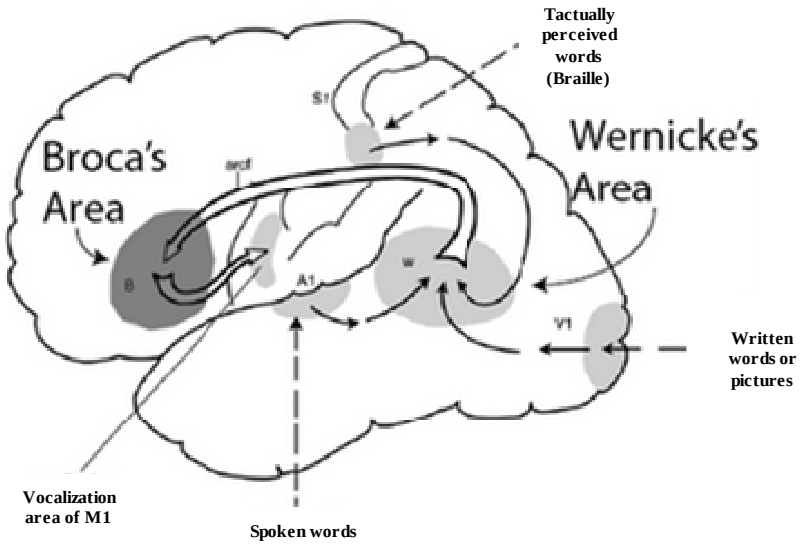

Figure 1 – Principal brain structures involved in the production and comprehension of language – From http://mybrainnotes.com/memory-language-brain.html

Really, this kind of conceptualization was too simple to explain both the complexity of language organization in the brain and the different combinations of aphasic symptoms. Today, with the adoption of the modern neuroimaging techniques, it seems clear that Broca's and Wernicke's areas are part of a complex network of cortical and sub-cortical structures that interact for the adoption of a linguistic behavior (See Figure 1).

From the 1970s, with the cognitive neuropsychological approach, we assisted at a shift from clinical and anatomical concerns to an emphasis on functional architecture of language. In this viewpoint, numerous models have been elaborated to explicate the different stages of language processing, from the auditory speech perception and word recognition to the speech production, from the basic reading processes to the more complex comprehension of syntactic and semantic aspects (Eysenck and Keane, 2010).

The ability of naming pictures is a very complex one, involving distinct cognitive processes or representations (see Figure 2). First of all the sight of a picture activates

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the semantic system and the corresponding lexical node. Moreover, to name the picture, the activation of the simple and compounds phonological nodes is required. At last the motor program must be transferred to the buccofacial muscles to be executed. As a consequence of this complexity, a large network of brain regions is activated during a picture naming test. Nevertheless, separate components of this network are differentially required for distinct cognitive processes underlying the task (DeLeon et al., 2007).

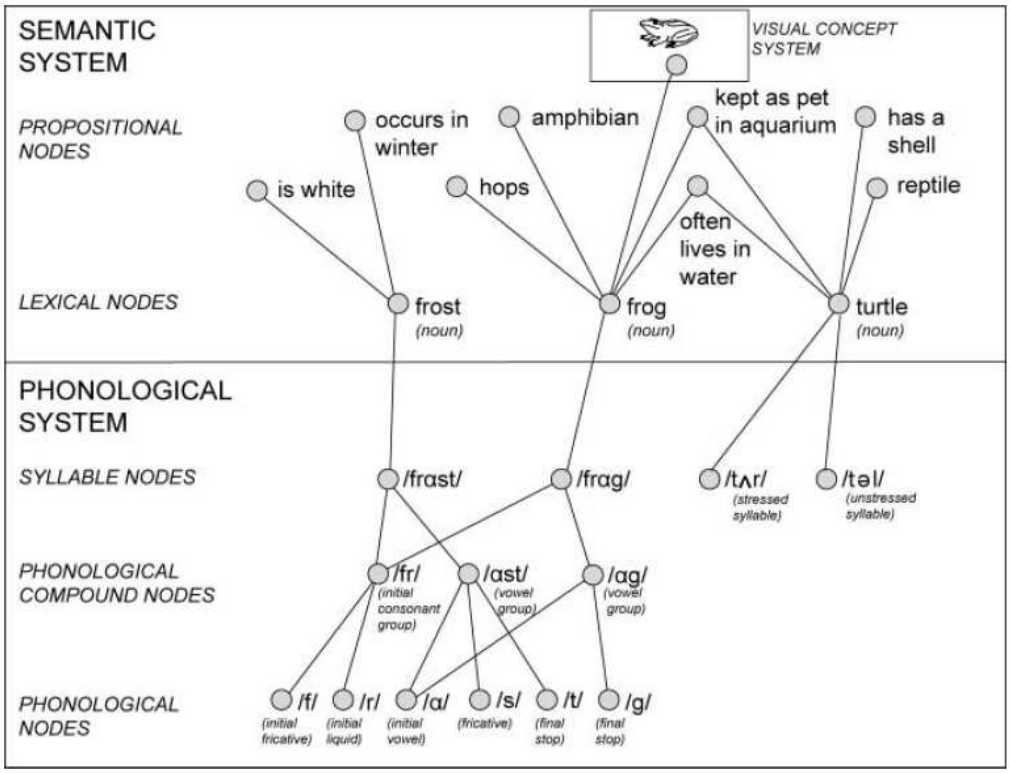

Figure 2 – Example of representation of some semantic, syntactic and phonological information in an interactive activation model of the language (Burke and Shafto, 2008).

1.1.2 Aphasia

Aphasia is an acquired language disorder following brain damage. The most common cause of aphasia is a cerebrovascular accident, mainly to the left hemisphere. About one-third of all people who experience a stroke develop aphasia (Engelter et al., 2006, Laska et al., 2001). Classically several syndromes of aphasia

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have been identified, characterized by different kind of language impairment (e.g., fluent or non-fluent speech, preserved or not comprehension, etc.), related to different cerebral lesions. The principal aphasic syndromes are Broca's Aphasia, Wernicke's Aphasia, Conduction Aphasia, Global Aphasia, Transcortical Motor Aphasia, Transcortical Sensory Aphasia, and Anomic Aphasia.

Despite the reasonable clinical validity of these syndromes, and their utility for clinical communication, there are numerous limitations to this type of conceptualization. For example the noteworthy variable degree of impairment in language comprehension or production is not very amenable to dichotomous judgments, necessary to do a syndrome diagnosis. Furthermore, a problem is that the same signs not ever have the same patophysiologic mechanisms in different patients. Another difficulty is that these syndromes are defined by numerous criteria, and so it's problematic to decide what to conclude if only some of the criteria are met (Alexander, 1997).

1.1.3 Can aphasia be treated?

After a cerebral lesion the cognitive recovery can be subdivided in temporal stages, in which act different neurophysiologic mechanisms that could account for the clinical improvement (Cappa, 2011). In a first time, during the acute (1-2 weeks post-onset) and subacute (up to 6 months post-onset) state, the mechanisms are for example the disappearance of cerebral edema, the normalization of hemodynamic in ischemic penumbra areas and the resolution of inflammation. It makes sense to speak about aphasia rehabilitation also in its chronic stages thanks to the important discoveries of the last teens relative to the presence of phenomena of neuro-plasticity also in the adult brain. In the healthy brain, we can assist at reorganization phenomena with sensorial deprivation, or simply when we learn a new skill or ability (Hyde et al., 2009, Kambi et al., 2011, Karni et al., 1995, Rossini et al., 1996). In the injured brain evidences of post-lesional plasticity has been reported both in animals and humans (Nudo, 2006, Vibert et al., 1999). The recovery could occur thanks to the expansion of a particular representational map, or to the reactivation of the peri-lesional areas, or thanks to the involvement of homologues areas (Turkeltaub et al., 2011).

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According to the cognitive neuropsychology, to impost a treatment for an aphasic patient is first of all necessary to have an accurate functional diagnosis based on the cognitive model of reference. Consequently the treatment will be focused on the specific deficits of that patient, e.g., phonologic and articulatory deficits, or lessical deficits, or morphosyntactic deficits (Mazzucchi, 2006).

Regarding the characteristics that should have the aphasia therapy, a recent study has determined that intense aphasia therapy over a short period of time has greater impact on recovery than less intense therapy over a longer period (Bhogal et al., 2003). Cappa and colleagues (2003, 2005) have written on European Federation of Neurological Societies guidelines on cognitive rehabilitation concluding that there is enough evidence to award a grade A, B or C of recommendation to some forms of cognitive rehabilitation included aphasia therapy. A recent Cochrane review (Kelly et al., 2010) shows emerging evidence from randomized trials that suggests that there may be a benefit from speech and language therapy. Unfortunately, there is insufficient evidence in order to indicate the best approach in delivering speech and language therapy. In this context born the possibility to support the classic logopedic treatment with new techniques of NIBS, to optimize the success of the treatment (see next chapters for more details on this issue).

1.2 Non-invasive brain stimulation (NIBS)

During the centuries we can found a lot of examples in which electromagnetic current was applied to the brain to try to treat a variety of neurological disorders (Priori, 2003, Walsh and Cowey, 2000). Recently, thanks to the advancement in both theories and devices, the electric and electromagnetic stimulation of the nervous system has become a real possibility. In the next paragraphs I'll present the principal and most widely used forms of NIBS (i.e., repetitive transcranial magnetic stimulation - TMS and transcranial direct current stimulation - tDCS, see Figure 3).

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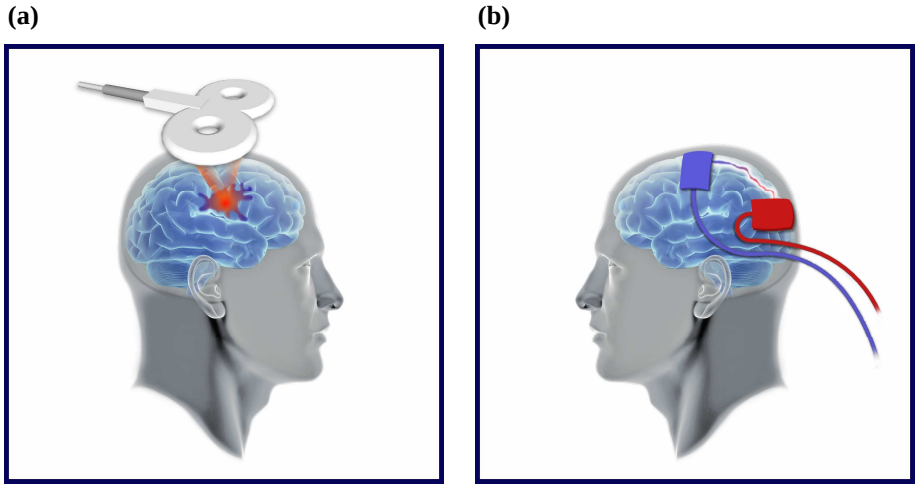

Figure 3 – The devices for the application of TMS (a) and tDCS (b).

1.2.1 TMS

TMS is the better known NIBS (See Figure 3a). Today TMS is a standard stimulation technique for the noninvasive investigation of motor and cognitive functions (Hallett, 2007, 2011b, Sandrini et al., 2011, Wassermann et al., 2008). TMS allows the stimulation of the brain thanks to the principles of electromagnetic induction (Barker et al., 1985). In more details, TMS delivers a large current in a short period of time: the current flowing in the TMS coil produces a magnetic field that lasts very briefly (about 1 ms). This rapidly changing magnetic field is able to penetrate the scalp and skull and to induce an electrical field sufficient to stimulate neuronal activity and to induce in the stimulated neurons action potentials. TMS is thought to activate neuronal axons in the cortex and subcortical white matter, rather than the cell bodies of cortical neurons (Ridding and Rothwell, 2007), also if its precise mechanisms of action are still unclear.

TMS can be applied with a single pulse (spTMS) or with a train of pulses (repetitive TMS – rTMS), according to the desired effects. Indeed TMS has many application fields, from neuroscientific research to clinical practice. In particular, when delivered over primary motor area (spTMS) it gives rise to peripheral responses that allow an evaluation of excitability and viability of corticospinal system both in normal and pathologic conditions. TMS has been widely used also as mapping tool for studying perceptual, motor and cognitive functions in the human brain, due to its unique

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possibility to investigate the causality of an area in a specific task (Sack and Linden, 2003). In addition, in the last years there is a growing interest in the therapeutic use of rTMS, as it is well known that its effects on cortical activity persist after the end of the stimulation, possibly involving plastic mechanisms (Miniussi et al., 2008, Siebner and Rothwell, 2003).

Regarding the latter case, rTMS has been applied for the rehabilitation of several kind of cognitive impairment (e.g., language, memory and attention, see for a review 2011b). In these rehabilitation protocols usually rTMS is applied for several minutes (on average 10-15 minutes) before the subject is tested on the task of interest. A wide discussion on the application of TMS for the investigation and treatment of language can be found in chapter 1.3.

1.2.2 tDCS

tDCS allows the non invasive stimulation of the central nervous system (CNS). A current of low level intensity (usually comprised between 1 and 2 mA) crosses the brain thanks to the application of two electrodes on the scalp (see Figure 3b). This current is able to modulate the frequency rate of firing of the neural populations underneath (Nitsche and Paulus, 2000). Also if the major intensity of the current is under the electrodes, studies of neuroimaging have demonstrated the modulation of the neural activity also of distant connected regions (Jang et al., 2009, Zheng et al., 2011). In the anodal stimulation, the anode is collocated on the scalp corresponding to the cerebral area of interest, whereas the cathode is collocated on a reference site. This can be cephalic or not (e.g., the right shoulder or the neck) (Priori et al., 2008). In the cathodal stimulation the electrodes positioning is reversed.

If applied on the motor cortex, anodal tDCS (a-tDCS) has a general facilitation effect and causes membrane depolarisation, whereas cathodal tDCS (c-tDCS) has a general inhibitory effect and causes membrane hyperpolarisation (c-tDCS, see Liebetanz et al., 2002). In the investigation of cognitive functions the effects are not so clear: generally we can observe the anodal facilitation whereas the effects of cathodal stimulation are contrasting or also absent (Jacobson et al., 2011).

The size of the electrodes is usually between 15 and 60 cm^2. A positive consequence is the non painfulness and the safety of the technique (Iyer et al., 2005, Poreisz et al., 2007), but the negative aspect is its low spatial resolution (Wagner et al., 2007).

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Behavioural facilitatory tDCS effects have been highlighted (see Vallar and Bolognini, 2011) with respect to implicit motor learning (Nitsche et al., 2003a, Reis et al., 2009), working memory (Fregni et al., 2005, Ohn et al., 2008), pitch memory (Vines et al., 2006), perception (Antal et al., 2004) and language (Fertonani et al., 2010, Iyer et al., 2005, Sparing et al., 2008). Interestingly and particularly relevant to the neurorehabilitation field, these tDCS-induced modifications of cortical excitability and behaviour can outlast the stimulation period itself. Hence, there is growing interest in applying these methodologies therapeutically to potentiate the effects of cognitive rehabilitation and to reduce cognitive deficits in patients with chronic and neurodegenerative diseases.

Regarding the mechanisms of action, studies on slices and animal models demonstrated that the online effect is due to the de/hyper-polarization of the neuronal membrane in the underlying cortical areas. The consequence of these variations is the modification of the neuronal excitability (Bindman et al., 1964, Nitsche et al., 2003a).

The long-term effects are less understood but could be mediated by different mechanisms, i.e., long term potentiation-like phenomenon (LTP-like) or long term depression-like phenomenon (LTD-like). In particular different studies point out on the involvement of the N-Methyl D-aspartate (NMDA) ionic channels (Bindman et al., 1962, Gartside, 1968b, Liebetanz et al., 2002).

1.3 NIBS and language

Recently NIBS (i.e., TMS, and tDCS) have been applied in healthy subjects and patients to enhance the performance in various language tasks.

1.3.1 Healthy subjects –State of the art

TMS has been widely applied in the researches on language (see e.g., Devlin and Watkins, 2007). Indeed with a single magnetic pulse, the processing of information in a certain area of the brain can be interrupted with a high spatiotemporal precision. Consequently, the causal role of that area in a process of interest can be investigated. TMS was used, for example, to study the effects of speech perception on the motor system underlying speech production (Fadiga et al., 2002, Sundara et al., 2001,

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Watkins et al., 2003), the functional organization of Broca's area (Aziz-Zadeh et al., 2005, Devlin et al., 2003), and the link between grammatical processing and left prefrontal cortex (Sakai et al., 2002), in particular the different neural substrates for processing nouns and verbs (Cappa et al., 2002, Shapiro et al., 2001). Cappa and colleagues (2002) reported that high frequency rTMS of left dorsolateral prefrontal cortex (DLPFC) significantly reduced the vocal reaction times for naming of action pictures, but not of object pictures. These data, subsequently confirmed in patients (Cotelli et al., 2006, Cotelli et al., 2008), strongly suggest that the left DLPFC is preferentially involved in processing verbs relative to nouns.

tDCS has been introduced in the scientific research more recently than TMS and so there are only few studies on this topic. Iyer and colleagues (2005) were the firsts to find an improvement of verbal fluency after anodal stimulation of the left prefrontal cortex in healthy subjects. This result has been recently confirmed by Cattaneo et al. (2011). Following, Sparing and colleagues (2008) demonstrated a transient improvement in a naming task after anodal stimulation of Wernicke's area. In the work reported in chapter 2.1 we demonstrated an analogous facilitation after anodal stimulation of the left DLPFC (Fertonani et al., 2010). A faster naming in anodal condition was found also by Holland et al. (2011) with the stimulation of the left inferior frontal cortex. The same results, reached with the DC stimulation of different areas belonging to the language network, could be explained by the low spatial resolution of this stimulation technique. Furthermore, it is possible that the current diffuse itself in the brain in a non completely predictable way.

Other results obtained with tDCS are the improvement in the recall of famous names, highlighted by Ross and colleagues in young and in middle aged subjects (Ross et al., 2011, Ross et al., 2010), the facilitation in associative verbal learning (de Vries et al., 2009, Fiori et al., 2011, Floel et al., 2008) and the demonstration of the motor cortex involvement in the learning of action word (Liuzzi et al., 2010).

1.3.2 Aphasic patients –State of the art

In the context of the research of the best approach to deliver speech and language therapy, there is increasing interest in the potential enhancement of performance with NIBS, i.e., rTMS tDCS, applied to specific cortical areas (Miniussi et al., 2008). Facilitation effects have been observed in patients with stroke and dementia when

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performing a variety of cognitive tasks. These effects have been related to TMS-induced changes in cortical excitability resulting in functional reorganisation and improved cognitive performance. Specifically, the potential of rTMS or tDCS to trigger adaptive neuroplasticity in neurological patients has been related to three main mechanisms: a) the reactivation of canonical networks, b) the recruitment of compensatory networks, mostly contralateral homologue cortical regions and c) the additional recruitment of perilesional sub-optimally functioning areas (see Miniussi and Vallar, 2011a for a discussion). The mechanisms responsible for the induced changes in neural activity remain largely unknown. There is, however, evidence that rTMS and tDCS techniques can modify neuronal excitation through different mechanisms: TMS elicits action potentials in neurons, whereas tDCS does not (see Paulus, 2011). Nevertheless, tDCS effectively modifies both the evoked cortical response to afferent stimulation and the postsynaptic activity level of cortical neurons, presumably by inducing a shift in intrinsic neuronal excitability (Bindman et al., 1962). In other words, both techniques can modify cortical plasticity by increasing excitability in cortical neurons within a specific network and, in doing so, improve the cognitive ability sustained by the stimulated network.

Specifically, regarding rTMS, there is evidence that the frequency of stimulation modulates neural activity. High-frequency rTMS (≥5 Hz), has been shown to increase cortical excitability, whereas low-frequency rTMS (≤1 Hz) can inhibit "maladaptive" plasticity, which prevents recovery from aphasia (Martin et al., 2009a). The administration of low-frequency rTMS to the anterior portion of the right homologue of Broca's area (pars triangularis) improves picture naming in patients with non-fluent aphasia (Barwood et al., 2011a, Barwood et al., 2011b, Hamilton et al., 2010, Naeser et al., 2010a, Naeser et al., 2005a). The same authors reported language results following treatment with continuous positive airway pressure (CPAP) for sleep apnoea in a stroke patient with chronic non-fluent aphasia as well as language results following CPAP plus slow-rTMS to suppress pars triangularis in the same patient (Naeser et al., 2010a). The patient showed a language improvement after CPAP alone and improvement following CPAP plus rTMS. Researchers (Naeser et al., 2010b) argue that low-frequency rTMS over the right pars triangularis suppresses maladaptive right hemisphere frontal activations and thus

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allows for the activation of left hemisphere perilesional and perisylvian areas, as well as the left supplementary motor area, which support recovery in non-fluent aphasia. However, in the study by Martin and co-authors (2009a), only one of two patients with chronic non-fluent aphasia showed language improvement following low-frequency rTMS on the right pars triangularis. The authors argue that the shift to left hemisphere activation post-rTMS observed in the functional magnetic resonance imaging (fMRI) scans of the good responder supports the idea that restoration of the left hemisphere language network is linked, at least in part, to better recovery of naming in non-fluent aphasia. Moreover, in a subsequent study, Martin et al. (2009b) reported improved naming performance following a combined behavioural and rTMS treatment in a pilot single-case study, in which rTMS was immediately followed by constraint-induced language therapy. These pilot data suggest that a combined behavioural-rTMS treatment could be more efficient than behavioural treatment alone.

In this vein, Kakuda et al. (2010a) demonstrated that the application of low-frequency rTMS to an area that is homologous to the most activated area, as evaluated in a pre-treatment fMRI acquisition, resulted in improvement of the language abilities in three chronic stroke patients. In a subsequent study, the authors applied rTMS over the left Wernicke's area combined with language therapy in two post-stroke patients with sensory-dominant aphasia (Kakuda et al., 2010b). Ten sessions of treatment were provided throughout 6-day hospitalization, followed by weekly outpatient rTMS treatment for 3 months. The study showed an improvement of comprehension abilities in both patients at the end of the sixth day, maintained also after the 3-month post-discharge period.

A recent randomized, controlled, blinded pilot study has investigated the effect of low-frequency rTMS over right-hemispheric pars triangularis portion of the Broca's area homologue in ten patients with post-stroke aphasia (Weiduschat et al., 2011). The patients received, in addition to conventional speech and language therapy, multiple sessions of rTMS. Using positron emission tomography (PET) this research revealed an activation shift toward the right hemisphere in the placebo group which was absent in the real rTMS group of patients. Furthermore, only the real rTMS group shows a performance improvement in the Aachener aphasia test (AAT) global

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score. The authors suggested that low-frequency rTMS applied on the right Broca's area homologue prevents right-hemispheric lateralization resulting in a better clinical improvement.

Furthermore, Szaflarski and co-authors (2011) provide preliminary evidence regarding safety and efficacy of fMRI-guided high-frequency rTMS (intermittent theta burst stimulation) applied to the residual left hemispheric Broca's area in eight patients with post-stroke aphasia. The study showed an improvement in semantic fluency after two weeks of stimulation that was associated with a significant shift of fMRI signal to the affected hemisphere.

Finally, Jung and co-workers (2010) reported a significant improvement of naming and comprehension performances in a post-stroke patient affected by crossed aphasia following the application of low-frequency rTMS over the left parietal cortex.

tDCS is another way of promoting neuroplasticity to enhance cognitive performance. Monti and co-authors (2008) reported naming facilitation following cathodal stimulation over the damaged left frontotemporal areas in eight patients with chronic, non-fluent, post-stroke aphasia. In addition, Baker and co-authors (2010) performed a combined behavioural tDCS study with patients receiving 5 days of computerised anomia therapy concurrently with tDCS over the damaged left hemisphere or sham stimulation. This study revealed significantly improved naming accuracy in patients treated with anodal tDCS compared with the sham tDCS patients. In addition, the treatment effect persisted for at least one week after treatment.

In their study, Fridriksson et al. (2011) applied the same procedure used by Baker et al. (2010) in eight patients with chronic fluent aphasia and showed that anodal tDCS administered during language treatment decreased verbal reaction times during naming as assessed immediately post-treatment and three weeks later. Another recent study conducted by Fiori and colleagues (2011) highlights the beneficial effects of five days of anodal tDCS in three aphasia patients. The stimulation was applied to Wernicke's area while the patients were executing a naming task. This procedure produced an improvement in naming accuracy that lasted for three weeks.

In a randomized, double-blind, sham controlled crossover trial, Floel and co-workers (2011) explored whether anodal tDCS compared to cathodal tDCS and placebo

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stimulation applied over the right temporo-parietal cortex would improve the success of anomia training in a group of twelve post-stroke aphasia patients. The finding suggests that all treatment conditions led to significant increase of naming ability, with a greater effect of anodal tDCS as compared to cathodal and placebo tDCS.

Kang and colleagues (2011) evaluated the hypothesis that cathodal tDCS applied on the right Broca's homologue could improve picture naming in patients with post-stroke aphasia. The patients received five consecutive days of cathodal tDCS followed or preceded (minimum interval of one week) by five days of placebo tDCS and simultaneous language therapy. The results demonstrated that cathodal tDCS applied over the right Broca's homologue combined with language therapy can improve picture naming task performance in post-stroke aphasia.

Furthermore, You and co-workers (2011), in a prospective, double-blind, sham-controlled study assessed whether anodal to the left superior temporal gyrus or cathodal tDCS to the right superior temporal gyrus in comparison with sham tDCS could ameliorate the symptoms of aphasia. The authors found that cathodal tDCS over right superior temporal areas showed significantly greater improvements in auditory verbal comprehension as compared to the other two groups.

In summary, recent studies report enhanced cognitive performance following rTMS or tDCS, to specific cortical areas in a variety of patients with neurological diseases. Specifically in chronic aphasia patients, NIBS has been shown to increase the number of correct responses and to reduce response times. Moreover, recent studies suggest that these effects can persist over time (Baker et al., 2010, Barwood et al., 2011a, Fiori et al., 2011, Floel et al., 2011, Fridriksson et al., 2011, Hamilton et al., 2010, Kakuda et al., 2010a, Kakuda et al., 2010b, Martin et al., 2009a, Martin et al., 2009b, Naeser et al., 2010a, Naeser et al., 2005a, Naeser et al., 2005b, Naeser et al., 2010b).

1.4 Work organization

The work that I developed during the Ph.D. contributed to a wider research line to better understand NIBS effects in clinical applications. In the field of language, I have started from the works of Cappa and colleagues (2002) and Cotelli et al. (2006),

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that adopting the rTMS investigated the possibility to obtain an enhancement of naming abilities in young subjects and in patients affected by Alzheimer's dementia (AD). My work had the aim to extend these results to different types of brain stimulation (i.e., electric stimulations). First of all I have prepared two different versions of a naming task, to adopt accordingly with the age of the experimental subjects (young vs. aged) and patients. Then I have applied tDCS in healthy young subjects (unilateral and bilateral montage) and in healthy aged subjects. The more effective approach was the unilateral tDCS montage, in consequence I have applied unilateral tDCS in one aphasic patients, in combination with a logopedic rehabilitation. Considering the promising results obtained by Cappa and colleagues (2002) and Cotelli et al. (2006, 2008) with the application of rTMS, other three aphasic patients were treated with rTMS plus logopedic rehabilitation (Cotelli et al., 2011b).

As a general conclusion, I can say that at present the knowledge about the effects of NIBS on language is more extended than before, nevertheless many questions remain to be answer, to establish the best way to go for future researches. For example: what is the best timing to apply the stimulation, before or during the execution of the task? What is the optimal site to apply the reference electrode? After the clarification of these and other issues, there is the strong need to test the rehabilitation protocols in an adequate number of patients, to arrive at clear and possibly definite conclusions. Once demonstrated the efficacy of these technique on aphasia rehabilitation it will be possible to extend these protocols also to other cognitive deficits (e.g., treatment of memory or attention).

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2.

RESEARCHES ON HEALTHY SUBJECTS

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2.1 "Naming facilitation induced by tDCS"

2.1.1 Abstract

tDCS is able to generate a long-term increase or decrease in the neuronal excitability that can modulate cognitive tasks, similar to rTMS. The aim of this study was to explore the effects of tDCS on a language task in young healthy subjects. Anodal, cathodal and sham tDCS were applied to the left DLPFC before two picture naming experiments, a preliminary study (i.e., experiment 1) and a main study (i.e., experiment 2). The results show that anodal tDCS of the left DLPFC improves naming performance, speeding up verbal reaction times after the end of the stimulation, whereas cathodal stimulation had no effect. We hypothesize that the cerebral network dedicated to lexical retrieval processing is facilitated by anodal tDCS to the left DLPFC. Although the mechanisms responsible for facilitation are not yet clear, the results presented herein implicate a facilitation lasting beyond the end of the stimulation that imply cortical plasticity mechanisms. The opportunity to non-invasively interact with the functioning of these plasticity mechanisms will surely open new and promising scenarios in language studies in basic and clinical neuroscience fields.

2.1.2 Introduction

A large number of neuroimaging studies highlight that the ability to name actions or objects is achieved by a wide and complex cerebral network. This system involves, among other areas, the left prefrontal and temporal areas (Liljestrom et al., 2008, Perani et al., 1999), as demonstrated by neuroimaging (Perani et al., 1999, Shapiro et al., 2006) and brain lesion (DeLeon et al., 2007, Luzzatti et al., 2002) studies. The crucial role of the left DLPFC in action naming has also been confirmed by rTMS studies (Cappa et al., 2002, Cotelli et al., 2006, Cotelli et al., 2008). Cappa and colleagues (2002) reported that high frequency rTMS of left DLPFC significantly reduced the vocal reaction times for naming of action pictures. This interesting result has been subsequently confirmed in AD patients (Cotelli et al., 2006), extending the effect to object naming (Cotelli et al., 2008) and in a patient affected by primary progressive aphasia (Finocchiaro et al., 2006).

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Recently, a lot of interest has been captured by the rediscovery of a cerebral stimulation technique that acts through the application of a very low direct current (Nitsche et al., 2008, Priori, 2003). tDCS seems to act by modulating the resting membrane potential, in an opposite direction depending on the polarity (anodal vs. cathodal) of the electrode placed on the chosen area. A very interesting characteristic is the duration of these neuromodulatory effects. The first studies on the human motor cortex (Nitsche et al., 2003b, Nitsche and Paulus, 2001) have shown that 13 minutes of anodal stimulation induce 90 minutes of increased cortical excitability (enhanced resting motor evoked potentials - MEPs amplitude) or that, in a similar way, but with opposite results, cathodal stimulation causes 60 minutes of diminished cortical excitability (reduced resting MEPs amplitude).

The mechanisms underlying these effects have been first studied in animals, in the sixties (Bindman et al., 1964, Creutzfeldt et al., 1962, Gartside, 1968a, Purpura and McMurtry, 1965). In humans, Liebetanz and colleagues (2002) demonstrated that short-term tDCS effects are related to membrane depolarisation (anodal stimulation) or hyperpolarisation (cathodal stimulation), while long-term tDCS effects involve the participation of glutamatergic NMDA receptors. We now know that synaptic plasticity, i.e., modulation of the strength of synaptic connections on the basis of experience, is dependent on NMDA receptors, as we know that plasticity is the basis for learning and memory (Morris et al., 1986). If we consider that a brain injury, such as stroke or a neurodegenerative disease, can damage this system, the opportunity to non-invasively modulate the function of these mechanisms can open new prospects for the neurorehabilitation of brain-damaged patients (see Miniussi et al., 2008, Serruya and Kahana, 2008).

In the past years, several studies have sought to durably modify cortical excitability. Behavioural facilitatory effects have been highlighted with regard to implicit motor learning (Nitsche et al., 2003c), associative learning (Floel et al., 2008), working memory (Fregni et al., 2005, Ohn et al., 2008), pitch memory (Vines et al., 2006), perception (Antal et al., 2004) and language (Iyer et al., 2005, Monti et al., 2008, Sparing et al., 2008). This facilitatory function may be very important, not only in establishing the role of the stimulated area, but also because it can be used to enhance reduced function in cognitive neurorehabilitation.

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Our work aims to explore the effects of tDCS on picture naming, making use of a task that was previously studied with rTMS in normal (Cappa et al., 2002) and Alzheimer's patients (Cotelli et al., 2006, Cotelli et al., 2008). We hypothesise that anodal stimulation of the DLPFC can generate a facilitatory effect, namely a decrease of the vocal reaction times in action and/or object naming.

2.1.3 Methods

Two picture naming experiments were conducted with normal young subjects after the end of a tDCS period over the DLPFC.

2.1.4 Subjects

Twelve healthy subjects (4 males, mean age 24.1 years, standard deviation 3.7, range 19-32) took part in the experiment 1 and twelve other healthy subjects participated in the experiment 2 (6 males, mean age 21.8 years, standard deviation 1.0, range 20-23). Each subject participated in only one of the two experiments.

Subjects were native Italian speakers, right-handed and with normal or corrected-to-normal vision. We did not include subjects with a history of seizures, implanted metal objects, heart problems or any other neurological disease. The study was approved by the Ethics Committee of IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Informed consent was obtained from participants prior to the beginning of the experiment.

2.1.5 Experimental Tasks

2.1.5.1 Picture Naming Task

Stimuli for the picture naming task were presented on a personal computer screen using the software Presentation v. 12.0 (http://www.neurobs.com). All of the stimuli were black and white 2-dimensional line drawings taken from the corpus of the CRL-IPNP (Center for Research in Language – International Picture Naming Project; http://crl.ucsd.edu/~aszekely/ipnp), a broad set of 795 action and object pictures. These items have been tested in healthy and patient populations across seven different international sites and languages. Items are coded for a number of variables known to influence naming difficulty, including initial word frequency, age of

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acquisition and picture image ability scores. These variables have been tested to assess their influence on the participants' naming performance (Bates et al., 2000).

The picture naming task used in the two experiments was made up of three experimental blocks and a practice block. In the experiment 1, each experimental block included 15 object and 15 action images. While in the experiment 2 each block included 14 object and 14 action images accurately selected from a larger data set, tested in a behavioural experiment not reported here. The selection of a subset of stimuli from a larger set was done to obtain a congruent subset of stimuli balanced for all variables and verbal reaction time responses. In both experiments, the practice block included nine object and nine action images.

The subjects were required to accurately name, as fast as possible, the stimuli appearing on the computer screen. The trial structure for experiment 1 is illustrated in Figure 4a. In experiment 2, we added the indication "action" or "object" immediately before the picture presentation in order to disambiguate lexical selection. This second trial structure is illustrated in Figure 4b.

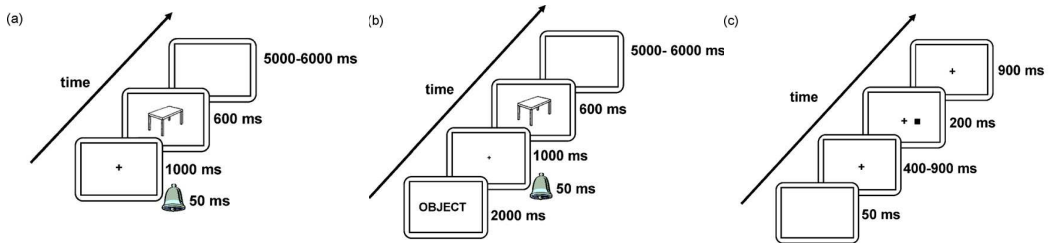

Figure 4 - Trial structure of the picture naming task in the two experiments: a) experiment 1 and b) experiment 2. c) Trial structure in the attentive control task.

2.1.5.2 Attentive task

To exclude the possibility that the tDCS effect could be ascribed to a general enhancement of arousal by anodal stimulation, we introduced an attentive control task using the same computer and software as used for the picture naming task. The attentive task comprised two equal blocks. There were 44 trials in each block. The structure of each trial is depicted in Figure 4c. After 50 ms of white screen, a fixation cross appeared at the centre of the screen for a time varying from 400 to 900 ms. A

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small black square was presented for 200 ms at the right or left of the fixation cross. After the disappearance of the square, the fixation cross remained on the screen for another 900 ms. In every block, there were 20 trials in which the square was presented to the right of the fixation cross and 20 with the square to the left; the remaining four trials were catch trials (no square appearance). We asked the subjects to respond as fast as possible, by pressing the space bar at the appearance of the stimulus. They used the left hand in one block and the right hand in the other, in an inter-subject counterbalanced manner.

2.1.6 Transcranial direct current stimulation

The stimulation was delivered by a battery-driven, constant current stimulator (neuroConn GmbH, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (7 cm x 5 cm). A constant current of 2 mA was applied for eight (experiment 1) or ten (experiment 2) minutes, with a ramping period of 10 s both at the beginning and at the end of the stimulation. The current density was maintained below the safety limits (Nitsche et al., 2008, Poreisz et al., 2007). The electrodes were kept firm by elastic bands and an electroconductive gel was applied under the electrodes before the montage, to reduce contact impedance. The so-called active electrode was placed on the left DLPFC, moving 8 cm frontally and 6 cm laterally with respect to the scalp vertex, which had been identified as Cz in 10-20 nomenclature for EEG electrode positioning (Cappa et al., 2002). The reference electrode was fixed on the right shoulder. We preferred an extracephalic reference to avoid unwelcome interference effects from brain areas underlying the reference electrode (Monti et al., 2008).

The study was a single-blind experiment: the individual subjects do not know the type of stimulation they received while the experimenter knew it. We applied three different stimulations on the left DLPFC: anodal, cathodal and sham (i.e., placebo). In the sham stimulation, the current was turned off 30 seconds after the beginning of the stimulation (duration of fade in and fade out period = 10 s) and was turned on for the last 30 seconds of the stimulation period. In this way, the subjects felt the itching sensations below the electrodes at the beginning and at the end of the stimulation, making this condition indistinguishable from the real stimulation (Gandiga et al., 2006).

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Moreover, to detect differences in the perception of sensation, we asked all of the subjects taking part in the experiment 2 to compile a questionnaire about the sensations experienced during the different types of stimulations (anodal, cathodal and sham). The questionnaire (see Appendix) was partially based on a previous questionnaire presented by Poreisz et al. (2007). We chose to use this questionnaire to evaluate whether unspecific stimulation effects related to different experimental conditions could account for differences in behavioural performance.

2.1.7 Procedure

In the two experiments, subjects were seated in front of a computer screen, in a quiet room in semi-darkness. In the experiment 1, they performed the picture naming task immediately after anodal, cathodal and sham stimulation. The three sessions and, therefore, three experimental blocks were separated by a one-hour pause (i.e., washing-out) period. Their order of execution was accurately balanced. The procedure is shown in Figure 5a.

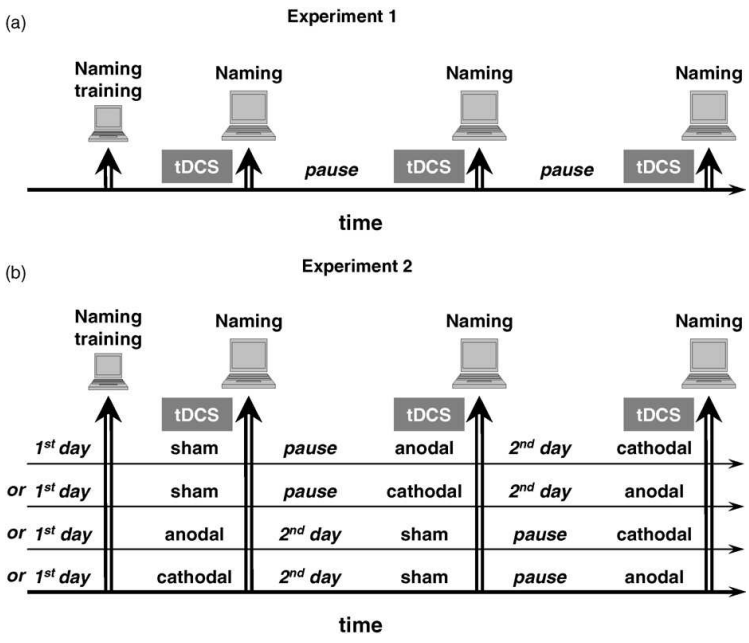

Figure 5 - a) Procedure for experiment 1. b) Procedure for experiment 2.

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In experiment 2, the subjects performed the picture naming task directly after anodal, cathodal and sham stimulation, as in experiment 1. The active stimulations (i.e., anodal, cathodal) were executed on two different days, thus minimising the probability of interference effects. In this case, a complete balance of the stimulation order was not possible. The presentation order was semi-balanced. The sham stimulation was always the first stimulation performed on the first or second day (see Figure 5b).

In addition, to exclude the possibility that the tDCS effect could be ascribed to non-specific stimulation effects or to a general enhancement of arousal, four subjects performed the attentive task four times, i.e., at the beginning and at the end of each of the two sessions each day.

2.1.8 Data analysis

The subjects' performances were recorded with a microphone placed in front of the participant. Vocal responses were digitised with the GoldWave v. 5.15 (GoldWave, Newfoundland, Canada) software, with a sampling rate of 11025 Hz.

We measured accuracy, giving 1 point to each error (no response, semantic error, visual error) and then calculating the mean for each subject in each condition.

The latency of the verbal response (vocal reaction time – vRT) was measured manually on the screen, marking the start of the wave corresponding to the vocal response. We eliminated from the analysis all incorrectly performed trials. In addition, we removed all data falling above or below two standard deviations with respect to the mean for each subject in each condition.

In the attentive control task, we analysed the manual RT. In this task Wilcoxon test was used for the small numerousness of the sample. For all the other data (vRT, accuracy), the Kolmogorov–Smirnov test confirmed the normality of the distribution, therefore data were subsequently analysed using repeated measures analysis of variance (ANOVA).

The data sphericity was tested using the Mauchly test where appropriate. When the test results were statistically significant, the data were corrected using the Huynn-Feldt correction. Moreover for multiple comparisons the p-values were corrected using Bonferroni correction.

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2.1.9 Results of Experiment 1

All of the subjects tolerated the stimulation well; no subjects reported adverse effects or asked to interrupt the experiment.

2.1.9.1 Accuracy

A repeated measures ANOVA tDCS (anodal, cathodal, sham) by type of stimulus (object, action) did not show any significant difference between conditions for accuracy [tDCS: $F_{(2, 22)} = 1.219$; $p > .05$ – type of stimuli: $F_{(1, 11)} = 3.973$; $p > .05$ – tDCS by type of stimuli: $F_{(2, 22)} = 0.288$; $p > .05$].

2.1.9.2 Response times

A repeated measures ANOVA tDCS (anodal, cathodal, sham) by type of stimulus (object, action) did not show a significant difference between conditions (mean vRT ±standard deviation (SD) for actions: sham = 907 ±104 ms, anodal = 871 ±78 ms, cathodal = 916 ±129 ms; and objects: sham = 739 ±81 ms, anodal = 731 ±99 ms, cathodal = 761 ±84 ms).

Even if cathodal and anodal tDCS induce an opposite pattern of behaviour, data were highly variable between subjects overall. Considering this large data variability, we normalised the data. For each subject, we calculated the difference between the vRT in each stimulation condition (anodal or cathodal) and the sham vRT (vRT_{sham}), divided by vRT_{sham}. The repeated measures ANOVA tDCS (anodal, cathodal) by type of stimuli (objects, actions) revealed a main effect of the tDCS factor [$F_{(11, 37)} = 6.015$; $p = .032$]. Subjects denominated the stimuli faster after anodal stimulation than after cathodal stimulation (see Figure 6a).

2.1.10 Results of Experiment 2

We inferred that all of the subjects tolerated the stimulation by interpreting the spontaneous report as well as the questionnaire completed by each subject at the end of the experiment (see appendix). The questionnaire results are reported in Table 1. Itch and irritation were the most commonly reported sensations (87% and 77% of the subjects, respectively), with light to moderate intensity. None of the subjects were able to distinguish sham from real stimulation.

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A multiple paired t-test did not show any significant difference in the subjects' perception of sensation between the real (anodal or cathodal) and the sham stimulation conditions.

	Irritation	Pain	Burning	Heat	Itch	Iron taste	Fatigue	Effect on performance
SHAM								
Intensity	**0.9**	**0.0**	**0.4**	**0.3**	**1.3**	**0.4**	**0.0**	**0.2**
Subjects (%)	77	0	31	15	85	15	0	15
ANODAL								
Intensity	**1.4**	**0.2**	**0.7**	**0.4**	**1.8**	**0.8**	**0.0**	**0.3**
Subjects (%)	77	15	38	38	85	38	0	23
CATHODAL								
Intensity	**0.9**	**0.0**	**0.6**	**0.3**	**1.3**	**0.8**	**0.0**	**0.3**
Subjects (%)	77	0	38	23	92	38	0	15

Table 1 - Mean intensity of the sensations reported by the subjects after tDCS stimulation in experiment 2 and the percentage of subjects that reported a certain sensation. The sensation intensity is presented on a 5-point scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Considerable, 4 = Strong. The column "Effect on performance" indicates the subjective feeling of the participant relative to how much did the tDCS induced sensations affect his performance.

2.1.10.1 Accuracy

A repeated measures ANOVA tDCS (anodal, cathodal, sham) by type of stimulus (object, action) shows only a significant main effect of the type of stimulus factor [$F_{(1,\ 11)} = 11.712$; $p < .05$]: participants made significantly fewer errors in object naming as compared to action naming.

2.1.10.2 Response times

A repeated measures ANOVA with tDCS (anodal, cathodal, sham) by stimulus factor type (objects, actions), shows a significant main effect of tDCS [Epsilon = .680, p = .014 – Huynh-Feldt – $F_{(1.359,\ 14.950)} = 4.194$; $p < .05$] and stimulus factor type [$F_{(1,\ 11)} = 253.916$; $p < .05$]. The interaction was not statistically significant [$F_{(2,\ 22)} = 1.608$; $p > .05$]. In regards to the main effect of the factor tDCS, multiple post-hoc comparisons revealed a statistically significant difference between sham (mean vRT ±SD = 703 ±117 ms) and anodal (mean vRT ±SD = 666 ±92 ms) stimulation (see Figure 6b).

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Participants were faster after anodal stimulation. Cathodal stimulation (mean vRT ±SD = 687 ±90 ms) did not differ significantly from sham stimulation.

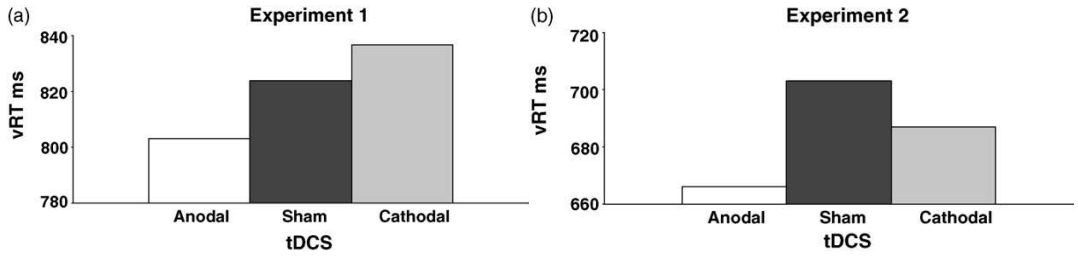

Figure 6 - vRTs of the two experiments: a) experiment 1 and b) experiment 2. Along the ordinate, data are expressed in milliseconds.

The main effect of the stimulus type shows that subjects were faster at object naming than at action naming (Mean vRT ±SD for actions: sham = 789 ±100 ms, anodal = 741 ±58 ms, cathodal = 757 ±60 ms; and objects: sham = 617 ±51 ms, anodal = 590 ±47 ms, cathodal = 616 ±51 ms). The lack of a statistically significant interaction indicates that the facilitation after anodal stimulation was present for both action and object naming.

As in experiment 1, data were normalised and a repeated measures ANOVA with tDCS (anodal, cathodal) by type of stimulus (object, action) underscored a main effect of the tDCS factor [$F_{(11, 37)} = 8.130$; $p = .016$]. As revealed by the previous analyses, subjects were faster at naming the stimuli in the anodal as compared to the cathodal condition.

Regarding the attentive control task, we calculate the difference in the RT before and after the anodal (pre-post anodal) and the cathodal (pre-post cathodal) stimulation. The text of Wilcoxon did not show a significant difference between the pre-post anodal and the pre-post cathodal condition ($Z = -.535$; $p > .05$). We conclude that the performance in the attentive control task was not influenced by the different types of stimulation (mean RT ±SD in each condition: pre-anodal = 293 ±17 ms, post-anodal = 290 ±20 ms, pre-cathodal = 293 ±13 ms, post-cathodal = 291 ±13 ms).

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2.1.11 Discussion

In this study, we show that anodal stimulation of the left DLPFC exerts a facilitation effect on picture naming in healthy subjects. The absence of a significant differential stimulation effect on the attentive task or on the perception of sensations questionnaire ruled out the possibility of facilitation due to non-specific effects, such as enhancement of arousal or attention. Moreover, the observation of a facilitatory effect in both experiments indicates robustness of the result.

Our experiments do not highlight any effect of cathodal stimulation, since reaction times in the cathodal conditions are not different from those in the sham conditions. In animal (Bindman et al., 1964, Purpura and McMurtry, 1965) and human motor cortex (Nitsche et al., 2003b, Nitsche and Paulus, 2000) studies, general cathodal effects are described, as opposed to those induced by anodal stimulation (inhibition vs. facilitation). Nevertheless, there are several studies in the cognitive domain that report the absence of inhibitory effects after cathodal stimulation (Floel et al., 2008, Fregni et al., 2005, Kincses et al., 2004, Sparing et al., 2008), which is consistent with our results.

On the other hand, the experiments presented herein highlight the facilitatory effect of anodal stimulation, namely faster vocal reaction time. The facilitation effect that we observed is similar to that described by Sparing and co-workers (2008) with anodal stimulation of Wernicke's area. Nevertheless, many differences between our study and theirs make comparison of the results difficult. In contrast to our study, their study focused strictly on object naming and the stimuli were over-trained to obtain stable reaction times with regard to naming. Furthermore, they adopted a cephalic collocation of the reference electrode. Analogous difficulties are present when comparing these findings with the results of Monti and co-workers (2008). The cathodal facilitation that they highlight is surely difficult to explain, although the current distribution in brains with diffuse atrophy is certainly different from that in a healthy brain (Wagner et al., 2007).

The facilitation observed in our study is consistent with previous data showing that high frequency rTMS on the left DLPFC shortens the time necessary for naming in young healthy subjects (Cappa et al., 2002) and in patients with Alzheimer's disease (Cotelli et al., 2006, Cotelli et al., 2008). A notable difference to the Cappa et al.

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(2002) rTMS study, which was performed on young normal subjects, is the reduced specificity of the obtained effect in our study. In the present tDCS experiment, the facilitation was for action as well as for object naming, while the facilitation was present only for action naming during an on-line protocol in the Cappa et al. (2002) study. A possible explanation for this distinction is the amplitude of the area of the electrodes used for tDCS (i.e., 35 cm^2) as compared to the smaller TMS stimulation area of the figure-eight coil (i.e., ~2 cm^2 around the intersection point of the coil) (Wagner et al., 2008). Therefore, it seems that our stimulation had a more general influence on the network involved in the naming task. In addition, the differential effects on behavioural response might be dependent upon the timing of stimulation (i.e., on-line vs. off-line). The effects induced by on-line stimulation are generally short-lived, probably on the order of a few hundred milliseconds to a few seconds, while use of the off-line approach allows for transient modulation of long-term neural excitability. This difference in duration may be related to a differential modulation of the neural network that controls language.

Another difference related to studies with rTMS involves the mechanism underlying behavioural performance. While rTMS is a neurostimulation technique that is able to induce action potentials in the stimulated area, tDCS is a neuromodulation technique (Nitsche et al., 2008, Wagner et al., 2007). Therefore, short-term effects of tDCS are due respectively to a decrease (anodal) or an increase (cathodal) of the resting neuronal threshold (Liebetanz et al., 2002). Nevertheless, in our study, behavioural facilitatory effects after the end of the stimulation period (i.e., off-line), are very likely induced by long-term modulatory effects on the activation state of the target area. This could appear in disagreement with the rules of the homeostatic plasticity, which sustain that low background activity would enhance facilitatory plasticity, whereas high background activity would inhibit it. Nevertheless this kind of assumption has been demonstrated in tDCS studies only on the human motor cortex and with conditioning protocols employing rTMS (Lang et al., 2004, Siebner et al., 2004). Nitsche and collaborators (2007), with another conditioning paradigm, obtains results coherent with the homeostatic plasticity only when this paradigm was applied simultaneously with the tDCS, and not when it was applied, like in our experiment, after the stimulation. This data seems confirmed also by a number of cognitive

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studies, that highlight facilitation when a cognitive task is performed after the anodal stimulation (Boggio et al., 2009, Ohn et al., 2008, Sparing et al., 2008).

We conclude that polarisation by anodal tDCS of the underlying brain tissue and of the remote connected areas has had a more general influence on the network involved in the naming task. More specifically, since it has been demonstrated that language operations mediated by prefrontal cortex are involved in word retrieval (Alexander et al., 1989, Kerns et al., 2004), and that word retrieval includes searching and monitoring as well as selecting the appropriate word from among competing alternatives (Alexander et al., 1989, Kerns et al., 2004), we suggest that the cerebral network dedicated to lexical retrieval processing is facilitated by anodal tDCS to left DLPFC. Although the detailed mechanisms responsible for facilitation are not completely understood, they seem to involve long-term potentiation (Liebetanz et al., 2002, Nitsche et al., 2003c). Since it has been demonstrated that short-term tDCS effects are related to membrane depolarisation (anodal stimulation) while long-term tDCS effects involve the participation of glutamatergic NMDA receptors and that synaptic plasticity is dependent on NMDA receptors, we can hypothesize that the result obtained might depend from these mechanisms.

This finding suggests that behavioural improvements may be induced in patients with cognitive deficits through stimulation/facilitation of the adequate network to solve a given task. Further, in a ideal neurorehabilitation approach, these improvements could become long-lasting effects through the strengthening effects of neural learning by cognitive training (Miniussi et al., 2008).

In conclusion, we found that anodal stimulation of the left DLPFC modulates the behavioural performance of healthy subjects in a picture naming task, demonstrating that left DLPFC is part of cerebral network dedicated to lexical retrieval/selection processing in naming. Moreover this study has revealed promising results in terms of the potential effectiveness of inducing a tDCS facilitatory effect in a linguistic elaboration process that is surely able to open new and promising scenarios in the field of language rehabilitation.

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2.2 A behavioural study: "Naming action and objects – Young subjects".

2.2.1 Introduction and objective

Results reported in Experiment 1 described in the chapter 2.1.9 highlighted a problem in the balancing of the blocks of the orientation discrimination task. Even if the items of the three blocks were accurately balanced regarding characteristics such as frequency, length and imaginableness they weren't for vRTs.

The aim of this behavioural experiment was to create a naming task accurately balanced, qualified for testing the linguistic abilities of both healthy subjects and aphasic patients. We started from the naming task used by Cappa et al. (2002) and Cotelli et al. (2006) and we increased the number of stimuli included in the task. Then for each stimulus we obtain the mean of vocal reaction times, its standard deviation, the percentage of correct naming and the correct answer alternatives elicited.

The experiment was proposed to a group of young subjects (21-40 years). The objective was to collect for each stimulus a large dataset of data, with information differentiated by the age of interest. Afterwards the same experiment was carried out by our research group also on elderly subjects (60-80 years) (Cotelli et al., 2011c).

2.2.2 Materials and methods

In this experiment we used 54 objects and 54 actions taken from the CRL-IPNP database (see previous chapter for details). None of the action stimuli included in the task were associated with the selected objects. The nouns and verbs corresponding to the set of objects and actions used were matched for target word frequency and length. The frequency, length of the target word, visual complexity and imaginableness of the pictures were matched and counterbalanced between the experimental blocks. Eighteen additional objects and actions were used for a practice block (9 actions and 9 objects). Subjects sat in front of a 17-inch monitor controlled by a personal computer running Presentation software. The trial structure is illustrated in Figure 7. After a frame that indicated the category of the stimulus to the subject ("ACTION" or "OBJECT"), a sound 50 ms in duration was presented at the

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onset of a centrally located fixation cross that was present for 1000 ms. After the disappearance of the fixation cross, the stimulus was presented and remained on the screen for 600/1000 ms (respectively for young and for elderly). A blank screen followed for a time varying from 3000-4000 (young) to 4000-5000 ms (elderly). The time of presentation was longer for the elderly subjects to maintain a similar level of difficulty in the two tasks. The subject's task was to accurately name as fast as possible the stimuli appearing on the computer screen. Verbal responses were recorded and digitized at 44.1 kHz using the program GoldWave (V. 5.12). The responses were then analyzed off-line for accuracy and vRTs. For each stimulus, we calculated the mean vRT and the mean response accuracy percentage.

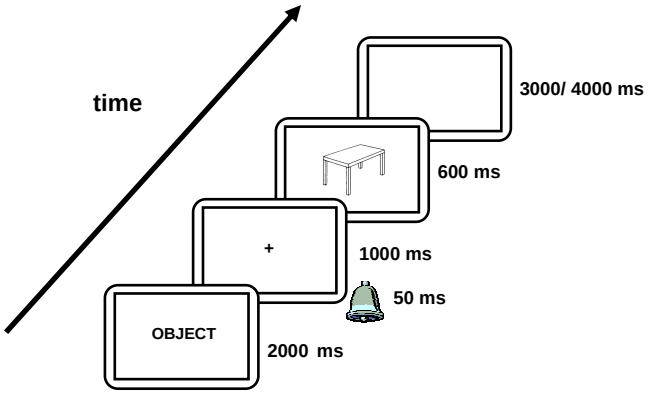

Figure 7 – Trial structure of the picture naming task in the behavioural study: "Naming action and objects – Young subjects". The timing in the picture is the one adopted for young subjects.

2.2.3 Subjects

20 healthy young subjects (10 male, age 21–34 years, mean 25.5 years, education mean = 15.0 years) participated in the experiment. All participants were native Italian speakers and had normal or corrected-to-normal vision. All participants were right-handed (Oldfield, 1971). The study was approved by the local ethics committee, and informed consent was obtained from all participants prior to the beginning of the experiment.

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2.2.4 Analysis and Results

The responses were analyzed off-line for accuracy and vRTs. We excluded from analysis vRTs falling above or below two standard deviations from the mean.

The 54 actions were, on average, named after 908 ms (±171), whereas the 54 objects required 746 ms (±147) to be correctly named. The mean accuracy was 91% (±13) for actions and 96% (±10) for objects.

Based on these results, we decided to exclude the actions that required a vRT higher than 1200 ms (i.e., mean vRT plus 1 standard deviation) or with a mean accuracy lower than 80%. We excluded objects with vRTs higher than 850 ms (i.e., mean vRT plus 1 standard deviation) or with a mean accuracy lower than 90%.

The obtained subset of stimuli comprised 42 actions and 42 objects. Within this final set, actions were named after 863 ms (±124), whereas objects required 716 ms (±73) to be correctly named. The mean accuracy was 95% (±6) for actions and 99% (±2) for objects. The new sets of stimuli were still matched for frequency and length.

2.2.5 Conclusions

This experiment let us to create a very accurately balanced orientation discrimination task. With this behavioural experiment we have collected a broad dataset for each stimulus (i.e., picture) included in the task (vTR, standard deviation, accuracy, correct alternative answers).

The same experiment was proposed by our research group (Cotelli et al., 2011c) to 30 older adults (8 male, age 60–81 years, mean 64.1 years, education mean = 13.8 years). These are the results: the 54 actions were, on average, named after 1132 ms (±280), whereas the 54 objects required 823 ms (±154) to be correctly named. The mean accuracy was 90% (±14) for actions and 97% (±4) for objects.

Based on these results, they decided to exclude the actions that required a vRT higher than 1692 ms (i.e., mean vRT plus 2 standard deviations) or with a mean accuracy lower than 85%. We excluded objects with vRTs higher than 1131 (i.e., mean vRT plus 2 standard deviations) or with a mean accuracy lower than 90%.

The obtained subset of stimuli comprised 42 actions and 42 objects. Within this final set, actions were named after 1070 ms (±252), whereas objects required 777 ms (±108) to be correctly named. The mean accuracy was 95% (±5) for actions and 99%

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(±2) for objects. The new sets of stimuli were still matched for frequency and length. (Cotelli et al., 2011c).

Considering also these data on healthy aging people, a particularly interesting result has been the construction of two different tasks to adopt accordingly to the age of the experimental subjects (young, or elderly).

2.3 "Naming facilitation induced in healthy aging subjects by tDCS"

2.3.1 Abstract

tDCS is able to generate a long-term increase or decrease in the neuronal excitability that can modulate cognitive tasks, similar to repetitive transcranial magnetic stimulation. The aim of this study was to explore the effects of tDCS on a language task in healthy-aging subjects. Anodal tDCS was applied to the left DLPFC before or during a picture naming task and the results were compared to that obtained in a placebo condition. The results show that anodal tDCS of the left DLPFC applied during the task improves naming performance, speeding up verbal reaction times, whereas anodal stimulation applied before the task hasn't a significant effect. We hypothesize that the cerebral network dedicated to lexical retrieval processing could be more facilitated if anodal tDCS to the left DLPFC is applied on an "active" neural network.

2.3.2 Introduction

Naming actions or objects is a complex ability, that requires the involvement of a wide cerebral network to be executed. Neuroimaging and brain lesion studies have highlighted that this system involves, among other areas, the left prefrontal and temporal areas (DeLeon et al., 2007, Liljestrom et al., 2008, Luzzatti et al., 2002, Perani et al., 1999, Shapiro et al., 2006). The crucial role of the left DLPFC in action naming has also been confirmed by rTMS studies (Cappa et al., 2002, Cotelli et al., 2006, Cotelli et al., 2008, Cotelli et al., 2011c) and tDCS studies (Fertonani et al., 2010). Cappa and colleagues (2002) reported that high frequency rTMS of left DLPFC significantly reduced the vRT for naming of action pictures. This interesting

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result has been subsequently confirmed in AD patients (Cotelli et al., 2006), extending the effect to object naming (Cotelli et al., 2008), in a patient affected by primary progressive aphasia (Finocchiaro et al., 2006) and in healthy-aging people (Cotelli et al., 2011c). These results were also confirmed with the application of tDCS. When young subjects were stimulated for ten minutes with anodal tDCS before the execution of the task, the vocal reaction times were significantly reduced in respect to sham, for both action and object naming (see chapter 2.1, published in Fertonani et al., 2010).

In the past years, several studies have sought to durably modify cortical excitability with the application of transcranial direct current stimulation. Behavioural facilitatory effects have been highlighted with regard to implicit and explicit motor learning (Nitsche et al., 2003c, Stagg et al., 2011), associative learning (Floel et al., 2008), working memory (Fregni et al., 2005, Ohn et al., 2008), pitch memory (Vines et al., 2006), perception (Antal et al., 2004) and language (Fertonani et al., 2010, Iyer et al., 2005, Sparing et al., 2008). This facilitatory function may be very important, not only in establishing the role of the stimulated area, but also because it can be used to enhance reduced function in cognitive neurorehabilitation.

Nevertheless, before to apply this technique in rehabilitative protocols, some issues remains to be considered. For example, some previous studies suggest that timing could be an important variable in influencing the effects of tDCS.

Nitsche et al. (2003c) have demonstrated that anodal tDCS applied during the execution of an implicit learning task lead to an improvement in the rate of learning of that task. On the other hand, if the same task is performed after ten minutes of stimulation, there isn't an enhancement in the rate of learning (Kuo et al., 2008). Similar results have been reported by Stagg et al. (2011), in an explicit sequence-learning task. Whereas the online stimulation bring the subjects to a faster learning, the offline stimulation has the opposite effect, slowing the rate of learning.

These results on motor cortex are consistent with the idea that anodal tDCS interacts with subsequent motor learning in a metaplastic manner, inducing a worsening, or no enhancement in the performance when applied before the task.

Thus, it seems that timing is a really crucial variable for obtaining the desired behavioural modulation by tDCS. For this reason the present work aims to explore

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the effects of tDCS on picture naming in healthy aging, investigating what is the best timing to apply anodal stimulation (i.e., during vs. before the execution of a naming task). To realize this study, we have used a task that was previously studied with rTMS and tDCS in normal (Cappa et al., 2002, Cotelli et al., 2011c, Fertonani et al., 2010) and Alzheimer's patients (Cotelli et al., 2006, Cotelli et al., 2008).

We hypothesise that online anodal stimulation of the DLPFC can generate a facilitatory effect, namely a decrease of the vocal reaction times in action and object naming. We don't expect a different effect in the naming of actions and objects, analogously to the results of tDCS stimulation in young subjects (Fertonani et al., 2010).

2.3.3 Methods

2.3.4 Subjects

Twelve healthy-aging subjects (7 males, mean age 68.7 years, standard deviation 6.3, range 62-83, mean education 11.5 years) took part in the experiment.

Subjects were native Italian speakers, right-handed and with normal or corrected-to-normal vision. We did not include subjects with a history of seizures, implanted metal objects, heart problems or any other neurological disease. The participants underwent a complete and accurate neuropsychological evaluation investigating the domains of memory, language, attention, prassic abilities and the general cognitive status. The study was approved by the Ethics Committee of IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Informed consent was obtained from participants prior to the beginning of the experiment.

2.3.5 Picture Naming Task

Stimuli for the picture naming task were presented on a personal computer screen using the software Presentation v. 12.0 (http://www.neurobs.com). All of the stimuli were black and white 2-dimensional line drawings taken from the corpus of the CRL-IPNP (http://crl.ucsd.edu/~aszekely/ipnp), a broad set of 795 action and object pictures. These items have been tested in healthy and patient populations across seven different international sites and languages. Items are coded for a number of variables known to influence naming difficulty, including initial word frequency, age

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of acquisition and picture image ability scores. These variables have been tested to assess their influence on the participants' naming performance (Bates et al., 2000).

The picture naming task used was made up of three experimental blocks and a practice block. Each block included 14 object and 14 action images accurately selected from a larger data set, tested in a behavioural experiment reported in the previous chapter. The practice block included nine object and nine action images.

The subjects were required to accurately name, as fast as possible, the stimuli appearing on the computer screen. The trial structure is illustrated in Figure 8.

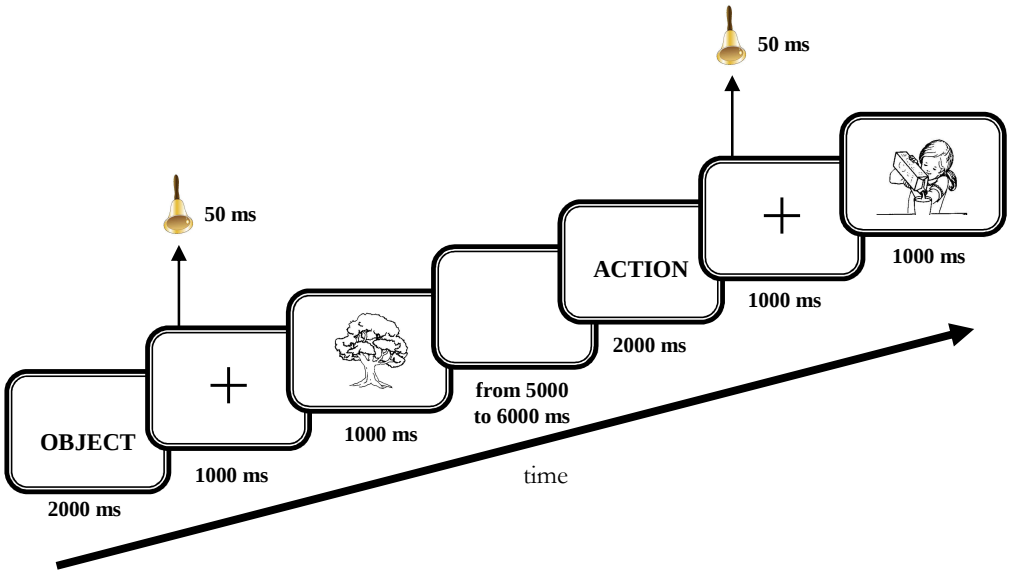

Figure 8 - Trial structure of the picture naming task in the experiment "Naming facilitation induced in healthy-aging subjects by transcranial direct current stimulation".

2.3.6 tDCS

The stimulation was delivered by a battery-driven, constant current stimulator (neuroConn GmbH, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (7 cm x 5 cm). A constant current of 2 mA was applied for ten (offline condition) or five (online condition) minutes, with a ramping period of 10 s both at the beginning and at the end of the stimulation. The current density was maintained below the safety limits (Nitsche et al., 2008, Poreisz et al., 2007). The electrodes

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were kept firm by elastic bands and an electroconductive gel was applied under the electrodes before the montage, to reduce contact impedance. The so-called active electrode was placed on the left DLPFC, moving 8 cm frontally and 6 cm laterally with respect to the scalp vertex, which had been identified as Cz in 10-20 nomenclature for EEG electrode positioning (Cappa et al., 2002). The reference electrode was fixed on the right shoulder. We preferred an extracephalic reference to avoid unwelcome interference effects from brain areas underlying the reference electrode (Fertonani et al., 2010).

The study was a single-blind experiment: the individual subjects do not know the type of stimulation they received while the experimenter knew it. We applied three different stimulations on the left DLPFC: anodal online (duration of five minutes), anodal offline (duration of ten minutes), and sham (i.e., placebo). In the sham stimulation (duration of seven minutes), the current was turned off 10 seconds after the beginning of the stimulation (duration of fade in and fade out period = 10 s) and was turned on for the last 10 seconds of the stimulation period. In this way, the subjects felt the itching sensations below the electrodes at the beginning and at the end of the stimulation, making this condition indistinguishable from the real stimulation (Gandiga et al., 2006).

Moreover, to detect differences in the perception of sensation, we asked all of the subjects taking part in the experiment to compile a questionnaire (see appendix) about the sensations experienced during the different types of stimulations (anodal online, anodal offline and sham).

2.3.7 Procedure

Subjects were seated in front of a computer screen, in a quiet room. In the anodal online condition the subjects performed the picture naming task during the stimulation, in the anodal offline condition the subject performed the task immediately after the stimulation, and in the sham condition the placebo stimulation was started about three minutes before of the start of the stimulation. The active stimulations (i.e., anodal online, anodal offline) were executed on two different days, thus minimising the probability of interference effects (see Figure 9).

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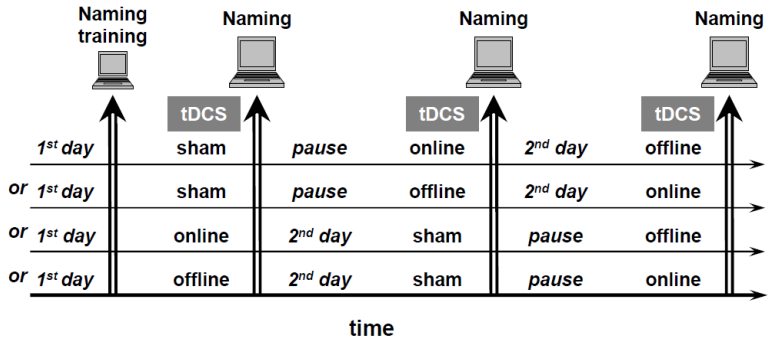

Figure 9 - Procedure of the experiment "Naming facilitation induced in healthy aging subjects by transcranial direct current stimulation". The three stimulation conditions (sham, anodal online and anodal offline) were executed on two different days. Each line represent the procedure for one subject.

In this case, a complete balance of the stimulation order was not possible. The presentation order was semi-balanced. The sham stimulation was always the first stimulation performed on the first or second day.

2.3.8 Data analysis

The subjects' performances were recorded with a microphone placed in front of the participant. Vocal responses were digitised with the GoldWave v. 5.15 (GoldWave, Newfoundland, Canada) software, with a sampling rate of 11025 Hz.

We measured accuracy, giving 1 point to each error (no response, semantic error, visual error) and then calculating the mean for each subject in each condition.

The latency of the vRT was measured manually on the screen, marking the start of the wave corresponding to the vocal response. We eliminated from the analysis all incorrectly performed trials. In addition, we removed all data falling above or below two standard deviations with respect to the mean for each subject in each condition.

For all the data (vRT, accuracy), the Kolmogorov–Smirnov test confirmed the normality of the distribution, therefore data were subsequently analysed using repeated measures ANOVA.

The data sphericity was tested using the Mauchly test where appropriate. When the test results were statistically significant, the data were corrected using the Huynn-

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Feldt correction. Moreover for multiple comparisons the p-values were corrected using Bonferroni correction.

2.3.9 Results

We inferred that all of the subjects tolerated the stimulation by interpreting the spontaneous report as well as the questionnaire completed by each subject at the end of the experiment (see appendix). The questionnaire results are reported in Table 2. Itch and burning were the most commonly reported sensations (64% and 36% of the subjects, respectively), with light intensity. None of the subjects were able to distinguish sham from real stimulation.

A multiple paired t-test did not show any significant difference in the subjects' perception of sensation between the real (anodal or cathodal) and the sham stimulation conditions.

	Irritation	Pain	Burning	Heat	Itch	Iron taste	Fatigue	Effect on performance
SHAM								
Intensity	**0.3**	**0.0**	**0.5**	**0.0**	**0.6**	**0.1**	**0.0**	**0.0**
Subjects (%)	33	0	47	0	53	7	0	0
ANODAL ONLINE								
Intensity	**0.1**	**0.0**	**0.5**	**0.0**	**0.9**	**0.1**	**0.0**	**0.1**
Subjects (%)	13	0	40	0	73	7	0	7
ANODAL OFFLINE								
Intensity	**0.4**	**0.0**	**0.3**	**0.0**	**0.9**	**0.1**	**0.0**	**0.1**
Subjects (%)	33	0	20	0	67	7	0	7

Table 2 - Mean intensity of the sensations reported by the subjects after tDCS and the percentage of subjects that reported a certain sensation. The sensation intensity is presented on a 5-point scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Considerable, 4 = Strong. The column "Effect on performance" indicates the subjective feeling of the participant relative to how much did the tDCS induced sensations affect his performance.

2.3.9.1 Accuracy

Overall the level of accuracy was very high. A repeated measures ANOVA with stimulation condition (sham, anodal online, anodal offline) by type of stimulus (object, action) underscored only a main effect of the type of stimulus factor [$F_{(1, 10)}$ =

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5.941; p = .034]. Subjects were more accurate in the object naming (mean = 0.17 errors/block) than in the action naming (mean = 0.78 errors/block).

2.3.9.2 Response times

A repeated measures ANOVA on vRT with stimulation condition (sham, anodal online, anodal offline) by type of stimulus (object, action) underscored a main effect of the stimulation condition factor [$F_{(2, 20)}$ = 4.584; p = .023] and type of stimulus factor [$F_{(1, 10)}$ = 105.490; p < .05]. In regards to the main effect of the stimulation condition, multiple post-hoc comparisons revealed a statistically significant difference between sham (mean vRT ±SD = 808 ±145 ms) and anodal online (mean vRT ±SD = 770 ±127 ms) stimulation (see Figure 10). Participants were faster during anodal online stimulation. Anodal offline stimulation (mean vRT ±SD = 796 ±149 ms) did not differ significantly from sham stimulation.

The main effect of the type of stimulus shows that subjects were faster at object naming than at action naming (mean vRT ±SD for actions: 898 ±109 ms; and objects: 685 ±66 ms).

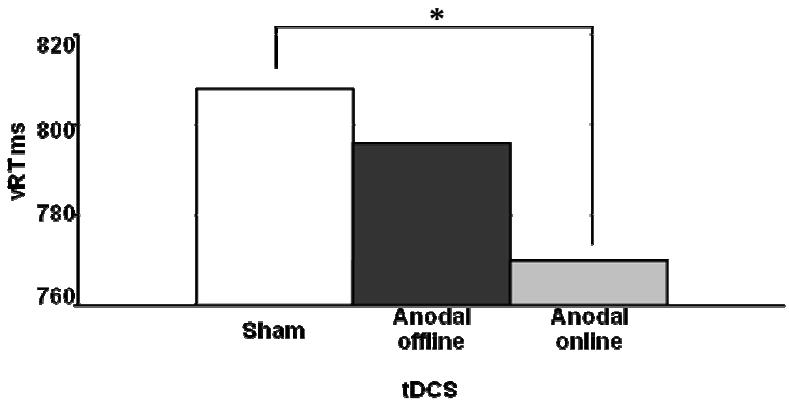

Figure 10 - vRTs of the experiment "Naming facilitation induced in healthy aging subjects by transcranial direct current stimulation". Along the ordinate, data are expressed in milliseconds. Asterisk indicates p value < 0.05.

2.3.10 Discussion

In this study, we show that anodal stimulation of the left DLPFC exerts a facilitation effect on picture naming in healthy aging subjects. In particular this speeding up in

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the vRT was significant only if the stimulation was carried out during the execution of the task, and not if the stimulation was executed before the execution of the task. This is a very interesting result, that highlight the importance of the timing of stimulation. Such variable has been considered by few studies to date, particularly with stimulation of motor cortex (Kuo et al., 2008, Nitsche et al., 2003c, Stagg et al., 2011). These studies demonstrate that online anodal stimulation over the motor cortex induce a higher facilitation effect. Regarding the cognitive domain, in literature we can found both data that seem to confirm the presence of facilitation effects when a cognitive task is performed after the anodal stimulation (e.g., Boggio et al., 2009, Ohn et al., 2008, Sparing et al., 2008) and data that highlight analogous facilitations when the task is performed during the stimulation (e.g., Chi et al., 2010, Fregni et al., 2005). Nevertheless these studies don't investigate both the conditions and so it's impossible to know if the two timing of stimulations simply differed in the degree of induced facilitation.

Our study, comparing two different kind of anodal stimulation (i.e., online vs. offline) in the same subjects, performing the same task, permit to have a clearer result. In healthy aging subjects, online stimulation is better than offline when performing a picture naming task. This datum seems to be in contrast with our previous study on young subjects (Fertonani et al., 2010), in which we highlighted a facilitation in an offline condition (i.e., ten minutes of stimulation before the task). Nevertheless, in that study we didn't tested the online condition, so it's possible that in that last condition the facilitation would be even more strong. This hypothesis should certainly be tested.

Another point to be noted is that the facilitation was for action as well as for object naming, while the facilitation was present only for action naming during an rTMS on-line protocol in the Cappa et al. (2002) study. The more plausible explanation for this distinction is the amplitude of the area of the electrodes used for tDCS (i.e., 35 cm^2) as compared to the smaller TMS stimulation area of the figure-eight coil (i.e., ~2 cm^2 around the intersection point of the coil) (Wagner et al., 2008). Therefore, it seems that our stimulation had a more general influence on the network involved in the naming task. This generalization of the effect to object naming has been found also in young subjects (Fertonani et al., 2010).

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The lack of a facilitation effect after offline stimulation may be due to the short period of stimulation (i.e., ten minutes). Really, this shouldn't be the case since with a stimulation of the same duration we were able to obtain a facilitation in young subjects performing the same task (Fertonani et al., 2010). Nevertheless we have to remember that neural networks of young and aged people are different, and the minor responsiveness of healthy-aging neural networks could account for the absence of offline facilitation.

We conclude that polarisation by anodal tDCS of the underlying brain tissue and of the remote connected areas has had a more general influence on the network involved in the naming task. More specifically, since it has been demonstrated that language operations mediated by prefrontal cortex are involved in word retrieval (Alexander et al., 1989, Kerns et al., 2004), and that word retrieval includes searching and monitoring as well as selecting the appropriate word from among competing alternatives (Alexander et al., 1989, Kerns et al., 2004), we suggest that the cerebral network dedicated to lexical retrieval processing is facilitated by online anodal tDCS to left DLPFC. Since it has been demonstrated that online anodal tDCS effects are related to membrane depolarisation, we can hypothesize that the result obtained might depend from this mechanism.

This finding suggests that behavioural improvements may be induced in patients with cognitive deficits through stimulation/facilitation of the adequate network to solve a given task. Further, in a ideal neurorehabilitation approach, these improvements could become long-lasting effects through the strengthening effects of neural learning by cognitive training (Miniussi et al., 2008).

In conclusion, we found that anodal stimulation of the left DLPFC modulates the behavioural performance of healthy aging subjects in a picture naming task, confirming that left DLPFC is part of cerebral network dedicated to lexical retrieval/selection processing in naming. Moreover this study has revealed important results in terms of the optimal timing to execute tDCS. To clarify the best parameters of application is fundamental to improve tDCS effectiveness in inducing facilitatory effect in a linguistic elaboration process, opening new and promising scenarios in the field of language rehabilitation.

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2.4 "Naming in young healthy subjects: bilateral tDCS"

2.4.1 Introduction and objective

This experiment was implemented to verify if a bilateral stimulation of the DLPFC could induce stronger facilitation results than the unilateral one in young healthy subjects.

In the experiment previously described we have highlighted a facilitatory effect of anodal tDCS stimulation in healthy subjects with a unilateral montage. In aphasic patients could however be particularly promising the adoption of a bilateral montage. In this last case, we could simultaneously enhance the excitability of an area and diminish the excitability of the contralateral one. The objective of this experiment was to study the effect of tDCS applied on both left and right DLPFC in healthy subjects. In the literature a facilitatory effect has been obtained both in memory (Chi et al., 2010, Penolazzi et al., 2010) and decision making tasks (Fecteau et al., 2007, Hecht et al., 2010).

2.4.2 Materials, methods and procedure

The picture naming task used was made up of three experimental blocks and a practice block. Each block included 14 object and 14 action images. The practice block included nine object and nine action images. Stimuli for the picture naming task were presented on a personal computer screen using the software Presentation v. 12.0 (http://www.neurobs.com). All of the stimuli were black and white 2-dimensional line drawings taken from the corpus of the CRL-IPNP (http://crl.ucsd.edu/~aszekely/ipnp), a broad set of 795 action and object pictures (Bates et al., 2000).

Subjects were required to accurately name, as fast as possible, the stimuli appearing on the computer screen. The trial structure is illustrated in Figure 7. The subjects' performances were recorded with a microphone placed in front of the participant. Vocal responses were digitised with the GoldWave v. 5.15 (GoldWave, Newfoundland, Canada) software, with a sampling rate of 11025 Hz.

The stimulation (intensity 2 mA, ten minutes duration) has been delivered before the execution of the task. The so-called active electrode was placed on the left DLPFC, moving 8 cm frontally and 6 cm laterally with respect to the scalp vertex, which had

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been identified as Cz in 10-20 nomenclature for EEG electrode positioning (Cappa et al., 2002). The "reference" electrode was placed on the contralateral DLPFC (i.e., the right one). The stimulation condition were three: anodal on the left hemisphere and cathodal on the right one (A-C), cathodal on the left hemisphere and anodal on the right one (C-A) and placebo stimulation (sham).

In the sham condition the stimulation was delivered only for 30 s at the beginning of the stimulation. The electrodes area was 35 cm^2.

Twelve young healthy participants were recruited (6 males; mean age: 22.1 years; range 19-29 years; mean education: 13.5 years), all native speakers of Italian. We screened the subjects adopting the exclusion criteria described for the magnetic and electrical stimulation (Nitsche et al., 2008, Rossi et al., 2009). The study was approved by the Ethics Committee of IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Informed consent was obtained from participants prior to the beginning of the experiment.

The experiment has been conducted in two consecutive days, with the order of stimulations partially counter-balanced (the structure of the experiment was similar to the one adopted in the experiment 2, reported in chapter 2.1.7). The two active stimulations were administered in two different days, whereas the sham stimulation was always executed as first stimulation. The sham was executed in the first day in half of the subjects, in the second day in the other half. Before of the beginning of the experiment the subjects were instructed with a brief training in the picture naming task, to familiarize with the task.

2.4.3 Results

All the subjects tolerate well the stimulation and no one asked to interrupt the experiment.

We analyzed the vRT and the percentage of accuracy of each subjects in each stimulation condition.

A repeated measures ANOVA on accuracy with condition (sham, A-C, C-A) and gender (male, female) as between subjects factors and type of stimulus (action, object) as within subjects factors shows only the main effect of stimulus [$F_{(1, 20)} = 13.154$; $p < .05$]. Subjects made more mistakes naming action pictures than naming object pictures.

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We eliminated from vRT analysis all incorrectly performed trials. In addition, we removed all data falling above or below two standard deviations with respect to the mean for each subject in each condition (see Figure 11). The repeated measures ANOVA condition (sham, A-C, C-A) by type of stimuli (objects, actions) by gender (male, female) shows only the main effect of stimulus [$F_{(1, 20)} = 19.103$; $p < .05$]. Subjects were slower naming action pictures than naming object pictures. Subjects don't differ in their naming abilities in the three conditions of stimulation (mean vRT ±SD for sham: 735 ±131 ms; A-C: 730 ±116 ms; and C-A: 748 ±136 ms).

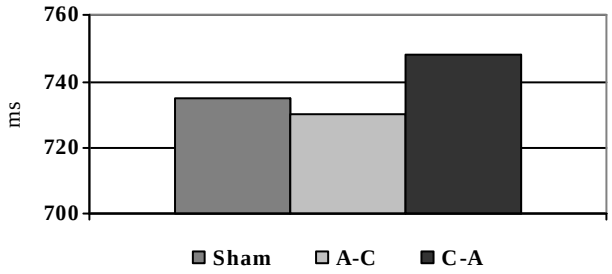

Figure 11 - Results: mean vRTs in the three condition of "Naming in young healthy subjects: bilateral tDCS" experiment.

2.4.4 Conclusions

In this study we have failed to show an enhancement effect in a naming task with a tDCS bilateral DLPFC stimulation. There are different reason to explain this result. The principal probably is that the stimulation with bilateral tDCS seems particularly suitable for a brain in which exists an imbalance between the two hemispheres activity. Nevertheless it seems the case that in young people, in which this imbalance doesn't exists, this montage don't bring any advantage for the task execution. Another problem should be the closeness of the two electrodes, and the consequent considerable amount of shunting of the current outside the brain. In this way the effectiveness of the stimulation may be considerable diminished.

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3.

RESEARCHES ON APHASIC PATIENTS

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3.1 Cognitive rehabilitation and NIBS treatment

This project is focused on the application of NIBS in aphasic patients with the aim to ameliorate their naming abilities.

The facilitatory effect of TMS and tES in cognitive tasks has been widely proved in literature, in studies in both healthy subjects and patients (see chapter 1.2 and 1.3, de Vries et al., 2009, Ferrucci et al., 2008, Jo et al., 2009, Ohn et al., 2008).

Studies on healthy subjects have demonstrated that, generally, the effect of the stimulations is short-living. Nevertheless it can be hypothesized that stimulation sessions repeated daily could amplify its effects. Our hypothesis is that the enhancement effects could become even more wide and stable if, at the same time of the stimulation, the patient undergo a classical cognitive rehabilitation session (i.e., logopedic therapy in the case of language). The reason is this: the stimulation acts on a neural network enhancing its excitability, if at the same time the patient perform a cognitive task that involves the stimulated network, then the connections activated by the task will be presumably more strengthened than the non-activated ones. In this way the effect of the stimulation should be more incisive for the brain functional reorganization. Results that seem to go in this direction have been obtained in the motor ambit (Khedr et al., 2005).

The aim of this project is that of evaluate the possible therapeutic application of the NIBS, coupled with the traditional logopedic therapy, in chronic aphasia patients (i.e., aphasia must be the consequence of a focal cerebral injury). In detail, we proposed the application of rTMS or tDCS sessions immediately before the logopedic rehabilitation. Our aim is to promote a functional reorganization of the damaged linguistic network to achieve a better performance in linguistic tasks.

Patients with chronic aphasia, arisen in consequence of a focal cerebral lesion (hemorrhagic or ischemic event), will be included in this project. All the patients will undergo a deep neuropsychological evaluation of linguistic and cognitive abilities. The essential requirement will be the presence of a residual naming deficit, in the context of preserved comprehension and repetition abilities.

All the exclusion criteria for NIBS will be carefully considered (Nitsche et al., 2008; Rossi er al., 2009).

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3.2 Post-stroke aphasia and rTMS plus language training

The present chapter reports the results of a combined rTMS anomia training approach administered to three patients with post-stroke chronic aphasia (PWAs).

3.2.1 Participants

Three patients with post-stroke chronic aphasia (PWAs) were recruited for the present study. The time after aphasia onset varied from 1 year to 4.5 years (see Table 3). Two PWAs had suffered a left middle cerebral artery infarction [PWA 1 (P1) and PWA 3 (P3)], whereas one PWA had a left capsulo-thalamic haemorrhage [PWA 2 (P2)]. Two of the three patients were right-handed (P2 and P3). A clinical assessment showed full awareness of the deficits in each of the three patients.

PWAs were selected on the basis of a neurological assessment, complete neuropsychological assessment (see Table 3) and neuroimaging diagnostic procedures. Each patient underwent a structural brain MRI. They all presented non-fluent speech but no verbal dyspraxia. The ability to understand single words was preserved. They could repeat and read single words but had a naming deficit.

Exclusion criteria included clinical evidence of depression, clinical signs of hearing or vision impairment, a past history of epilepsy, implanted metal objects, psychosis or major depression and alcohol abuse and drug addiction. These parameters are consistent with the safety recommendations for rTMS (Rossi et al., 2009). The use of psychopharmacological agents that could interfere with the test performance or diagnosis and MRI evidence of relevant cerebrovascular changes unrelated to the main diagnosis of the patient were additional exclusion criteria.

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	P1	**P2**	**P3**
Age at Entry into this study, y	41	45	71
Male/Female	F	M	M
Education, y	13	13	5
Etiology (Ischemic/Hemorrhagic)	I	H	I
Time post onset, y	4.5	1	3.5
Length of a phrase (words)	5	4	1
Neurological Symptoms	Hemiparesis	Hemiplegia	Hemiparesis
Handedness	Left	Right	Right
Aachener Aphasie Test (AAT)			
Token Test (Errors)	**19/50**	**38/50**	**27/50**
Repetition	**132/150**	**106/150**	**83/150**
Writing	86/90	**62/90**	**8/90**
Naming	105/120	**94/120**	**13/120**
Comprehension	109/120	**82/120**	**42/120**
Battery for the Analysis of the Aphasic Deficits (BADA)			
Object comprehension subtest	40/40	40/40	38/50
Action comprehension subtest	18/20	20/20	20/20
Object naming subtest	25/30	18/30	4/30
Action naming subtest	21/28	12/28	1/28
Sentence Comprehension	58/60	40/60	44/60

Table 3 - Clinical features and baseline language assessment of the three PWAs. Bold data indicate scores below normal cut-off.

3.2.2 Methods

3.2.2.1 TMS

Patients were randomly assigned to one of two conditions: i) Real-Real (RR), in which the patient received four weeks of rTMS stimulation of the DLPFC combined with the speech therapy (P1); and ii) Placebo-Real (PR), in which patients received left DLPFC placebo stimulation combined with the speech therapy during the first two weeks followed by two weeks of real stimulation combined with the speech

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therapy (P2 and P3). Each week of rTMS treatment consisted of 5 sessions that comprised a total of 50 minutes/day (25 minutes of rTMS plus 25 minutes of speech therapy). rTMS was delivered using a Magstim unit featuring a double 70 mm air-cooled coil. Before starting the rTMS treatment, the right motor cortex excitability stimulation threshold was established for each subject (mean ±SD: 54 ±10%). The stimulation intensity used during the experiment was set to 90% of each subject's motor threshold. Trains of high-frequency (20 Hz) rTMS were delivered in short periods (2 sec duration) separated by longer periods (28 sec) of no stimulation, for each 25-minute daily rTMS session. The total number of pulses for each session was 2000 (40 stimuli/train, 50 trains). These parameters are consistent with safety recommendations for rTMS (Rossi et al., 2009). Furthermore, all participants tolerated rTMS well and did not report any adverse effects. In the placebo condition, a sham coil was used. We localised the target areas using the SofTaxic neuronavigator system (www.emsmedical.net) on an MRI template. Based on these estimated MRIs, the average location of the stimulating points was centred on Talairach coordinates X=-35, Y=24, Z=48, corresponding to the left DLPFC (Brodmann Area 8/9). To stimulate the DLPFC, the coil was placed with the junction of the two coil wings above the target point. During the experiment, the coil was fixed with a mechanical support.

3.2.2.2 Rationale for choosing the left DLPFC as the rTMS target area

Previous studies showed that high-frequency rTMS to the left DLPFC results in reduced action naming latencies in young subjects (Cappa et al., 2002) and an increased number of correct responses for action naming in patients with mild AD and for both classes of stimuli (actions and objects) in moderate to severe AD (Cotelli et al., 2006, Cotelli et al., 2008). Moreover, in an off-line study, a significant effect of left DLPFC stimulation (25 minutes/day for 5 days/week for 4 weeks) on language functioning, together with a lasting benefit at six months, was also found in an AD patient sample (Cotelli et al., 2011a). Based on these previous observations, we hypothesised that high-frequency rTMS stimulation over the left DLPFC would result in improved naming in cases of post-stroke chronic aphasia. An additional hypothesis was that combining this rTMS treatment with speech therapy could enhance the improvement effect.

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3.2.3 Behavioural assessment

Participants were assessed before therapy (baseline), after the first two weeks of the therapy and at the end of all four weeks of therapy with a series of tests including the following: a neuropsychological battery for testing reasoning and verbal fluency (Lezak et al., 2004); the AAT (Luzzatti et al., 1994) and the object and action naming subtests, comprehension and sentence comprehension subtests of the battery for the analysis of the aphasic deficits (BADA) (Miceli et al., 1994). See Table 3 for details.

3.2.3.1 Stimuli selection

To select stimuli for the therapy and to test for generalisation effects, all patients completed two oral naming tasks and one oral comprehension task. The oral naming task was repeated twice, on two consecutive days, to ensure a stable baseline before introducing therapy and to select the therapy items. Stimuli for the oral naming task were 340 black-and-white 2-dimensional line drawings representing objects, which were taken from the 795 corpus of objects and nouns of the CRL-IPNP (http://crl.ucsd.edu/~aszekely/ipnp) (Bates et al., 2000). These stimuli were normalised with healthy and brain damaged populations across 7 international sites and languages and items are coded for a number of variables known to influence naming difficulty (e.g., word frequency, age of acquisition, degree of imageability, etc.). In total, 349 pictures of objects were displayed twice (on two consecutive days) on a computer screen using Presentation software v. 12.0 (neurobehavioural systems: http://www.neurobs.com), with each picture being presented for a maximum of ten seconds. The participant was asked to name each picture as accurately as possible and oral responses were recorded.

In addition, because we aimed to focus the therapy on word production, all misnamed pictures were included in a comprehension task to make sure that the participants understood the word. In the comprehension task, participants were asked whether a picture presented for a maximum of ten seconds corresponded or not to the word spoken. The participant was questioned about the picture's name during three consecutive trials, including the target's correct name, a semantic distractor and an unrelated distractor (e.g., for the picture of a bottle, the questions were "Is it a bottle?", "Is it a glass?" or "Is it a calendar?", respectively). The presentation of the

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items and the order of the distractors were randomised. Only the items for which no errors were made in any of the three trials were selected for the rehabilitation list.

The rehabilitation list was further split into two sets: the therapy list, including the items to be treated and the control list, with items not to be treated (untreated items). The two lists were balanced for a number of variables related to the participant's performance during the assessment of naming abilities. More specifically, these variables included the percentage of correct picture naming across assessment sessions (one time or never across two sessions), target word frequency, number of syllables and number of letters, as the semantic category (i.e., living or non-living). Furthermore, the two sets were split into two balanced sub-sets to be used during the first and the second week of treatment or to be used during the third and the fourth week, respectively (first and second vs. third and fourth).

Given the type of procedure used to select the therapy and control lists, each participant ended with a personalised set of items, which ensured the within and across subject validity of the design.

3.2.3.2 Therapy protocol

Participants underwent 25 minutes of speech therapy immediately following each rTMS treatment on a daily basis and for 4 weeks. In general, the procedure included repetition and reading of the target word to facilitate naming (see Figure 12) and an articulatory suppression task (see below). For every error, the trial was repeated again (at the end of the list). The patient was seated in front of a computer screen in a quiet room while the therapy protocol was displayed using Presentation software v. 12.0 (neurobehavioural systems: http://www.neurobs.com). The pictures showing the items to be treated and the written words used during the treatment were presented on the computer screen. The treatment involved several steps to elicit the production of a target noun, specifically:

Step 1: repetition of the target word (the target word was spoken by the therapist and the participant was asked to repeat it three times);

Articulatory suppression task: interference with articulatory codes caused by the uttering of an irrelevant speech sound (i.e., bla, bla, bla).

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In the suppression condition, the participants received instructions to start uttering the syllable 'bla' before the first stimulus of the oral picture naming task (steps 2 and 4).

Step 2: oral picture naming (the target picture was presented on the computer screen and the participant was asked to retrieve its correct name);

Step 3: reading of the target word (the target written word was presented on the computer screen and the participant was asked to read it);

Articulatory suppression task: interference with articulatory codes caused by the uttering of an irrelevant speech sound (i.e., bla, bla, bla).

Step 4: oral picture naming (the target picture was presented on the computer screen and the participant was asked to retrieve its correct name and say it aloud).

The complete procedure was repeated when at least one of the two requested naming responses was incorrect.

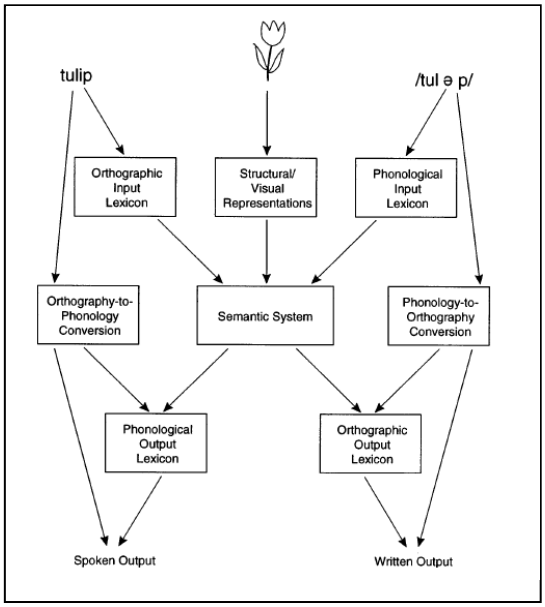

Figure 12 – A model of language organization. In the logopedic rehabilitation the visual representation of an object was accompanied by both its written noun (orthographic input lexicon) and its spoken noun (phonological input lexicon) to facilitate the recovery of the association between visual representation and noun.

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At the end of the therapy, action and object naming were reassessed, with their respective lists prepared during the pre-therapy assessment. At the end of the first two weeks of treatment, an equal number of treated and untreated items corresponding to the first two weeks were tested, whereas at the end of the treatment and at follow-up visits, all treated and untreated items corresponding to the four weeks of the experiment were tested.

3.2.4 Results

No changes were recorded in the standard neuropsychological assessment including formal language assessment (AAT and BADA) after the therapy. In contrast, significant improvements were found for object naming in the experimental stimuli set. For each participant, we calculated the baseline for the therapy and control lists. The percentage correct at baseline for each participant corresponds to the number of items correctly named in 1 of the 2 naming assessment sessions, divided by two and further divided by the total number of items in the therapy and control lists (both the therapy and control lists included the same number of items) multiplied by 100. For each PWA, a χ^2 comparison, with the Yates correction, was applied to compare performance scores after 2, 4, 12, 24 and 48 weeks, with respect to baseline and for both the treated and untreated items.

For treated items, the three PWAs showed improvement after 2 weeks of combined rTMS-behavioural therapy weeks, as compared to baseline and this significant improvement persisted at 4, 12, 24 and 48 weeks. Moreover, the improvement was also significant with untreated items after 2 weeks of combined rTMS and behavioural therapy and at weeks 4, 12, 24 and 48 (see Figure 13 and Table 4).

Additionally, to examine the generalisation of effects to untreated items, we compared the accuracy scores for trained and untrained items for each PWA and for each time-point using Yates-corrected χ^2 comparisons. The results showed a significant effect on treated items (vs. untreated items) at the 2- and 4-week post-treatment measurement points, in all 3 cases, whereas the difference between the naming treated and untreated images decreased over time, and in most cases, vanished at follow-up visits beginning at 12 weeks post-entry/baseline in 2 of the 3 cases (see Table 4 for details).

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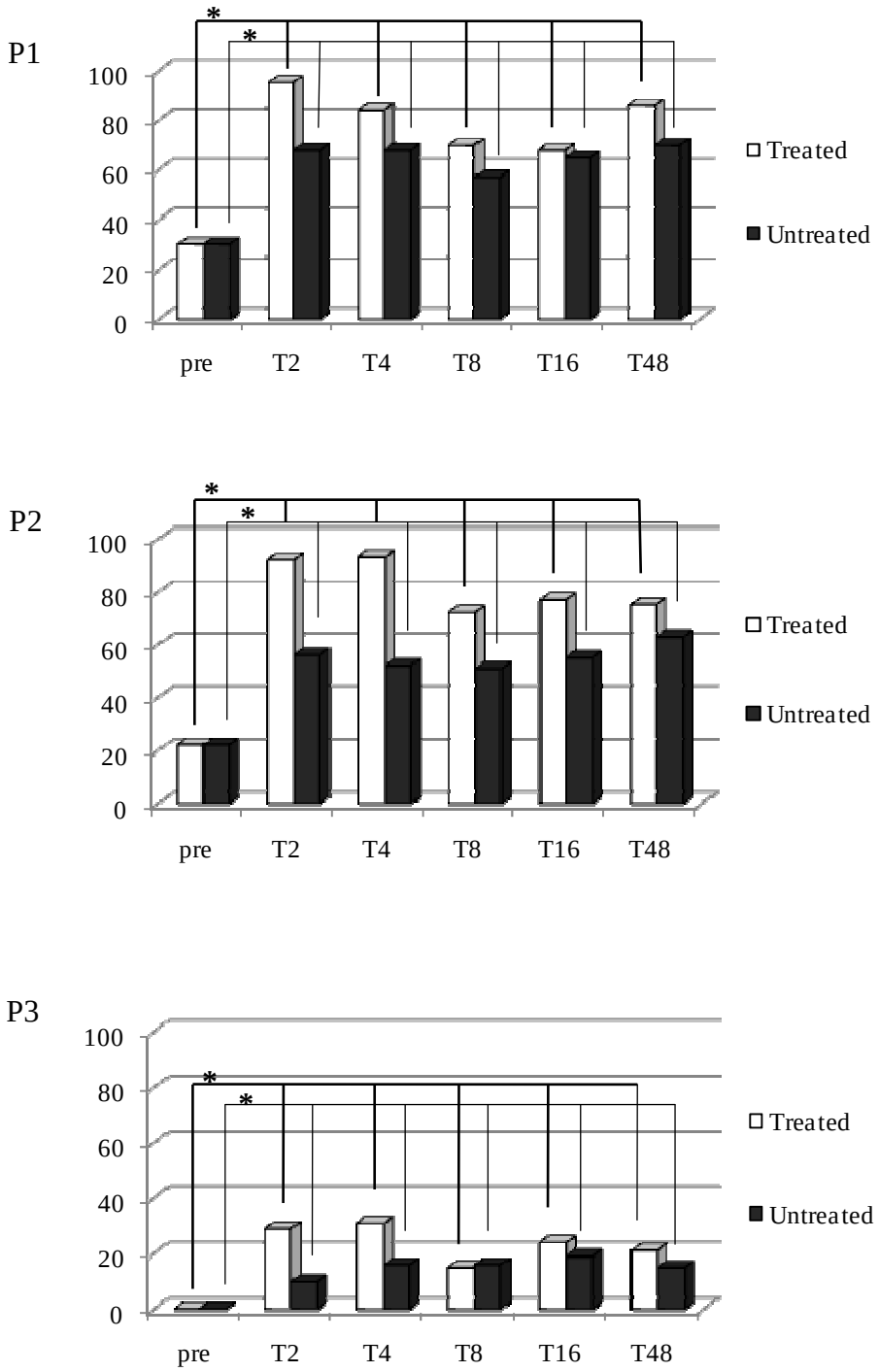

Figure 13 - Percentage of correct responses in the picture-naming task for treated and untreated items at baseline and 2, 4, 12, 24 and 48 weeks after the beginning of treatment for patients P1 (A), P2 (B) and P3 (C). Asterisks indicate p values < 0.05.

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		Treated Items		Untreated Items		
	Timing	**Correctness %**	**Comparison with baseline**	**Correctness %**	**Comparison with baseline**	**Treated vs. Untreated**
P1 4 Weeks of Real rTMS plus Speech Therapy	baseline	30		30		
	2 weeks	95	χ^2=87.4, p<0.001	68	χ^2=27.4, p<0.001	χ^2=22.4, p<0.001
	4 weeks	84	χ^2=57.3, p<0.001	68	χ^2=27.4, p<0.001	χ^2=6.2, p=0.013
	12 weeks	70	χ^2=30.4, p<0.001	57	χ^2=13.8, p<0.001	ns
	24 weeks	68	χ^2=27.4, p<0.001	65	χ^2=23.2, p<0.001	ns
	48 weeks	86	χ^2=62.1, p<0.001	70	χ^2=30.4, p<0.001	χ^2=6.6, p=0.011
P2 2 Weeks of Sham rTMS plus Speech Therapy followed by 2 Weeks of Real rTMS plus Speech Therapy	baseline	22		22		
	2 weeks	92	χ^2=97.1, p<0.001	56	χ^2=22.9, p<0.001	χ^2=31.8, p<0.001
	4 weeks	93	χ^2=100.3, p<0.001	52	χ^2=18.0, p<0.001	χ^2=40.1, p<0.001
	12 weeks	72	χ^2=48.2, p<0.001	51	χ^2=16.9, p<0.001	χ^2=8.5, p=0.004
	24 weeks	77	χ^2=58.3, p<0.001	55	χ^2=21.6, p<0.001	χ^2=9.8, p=0.002
	48 weeks	75	χ^2=54.1, p<0.001	63	χ^2=32.7, p<0.001	ns
P3 2 Weeks of Sham rTMS plus Speech Therapy followed by 2 Weeks of Real rTMS plus Speech Therapy	baseline	0		0		
	2 weeks	29	χ^2=31.6, p<0.001	10	χ^2=8.5, p<0.001	χ^2=10.3, p=0.001
	4 weeks	31	χ^2=34.4, p<0.001	16	χ^2=15.3, p<0.001	χ^2=5.5, p=0.020
	12 weeks	15	χ^2=14.1, p<0.001	16	χ^2=15.3, p<0.001	ns
	24 weeks	24	χ^2=25.1, p<0.001	19	χ^2=18.8, p<0.001	ns
	48 weeks	21	χ^2=21.3, p<0.001	15	χ^2=14.1, p<0.001	ns

Table 4 - Oral object naming at all time points for treated and untreated items for the three patients (P1, P2, P3). Statistical data (χ^2, Yates correction) are reported too. ns= not statistically significant.

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3.3 Post-stroke aphasia and tDCS plus language training

The present section reports the results of a combined tDCS anomia training approach administered to one patient with post-stroke chronic aphasia (PWA).

3.3.1 Patient AA

AA was a sixty year old engineer that suffered of a left middle cerebral artery infarction 8 years before the enrolment in the study. He was right-handed. A clinical assessment showed his full awareness of the deficits.

AA was selected on the basis of a neurological assessment and complete neuropsychological assessment (see Table 5). He presented non-fluent speech but no verbal dyspraxia. The ability to understand single words was preserved. He could repeat and read single words but had a naming deficit.

Age at Entry into this study, y - Education, y	60 - 18
Male/Female	M
Etiology (Ischemic/Hemorrhagic)	H
Time post onset, y	8
Neurological Symptoms	Hemiparesis
Handedness	Right
Aachener Aphasie Test (AAT)	
Token Test (Errors)	5/50
Repetition	144/150
Writing	87/90
Naming	110/120
Comprehension	107/120
Battery for the Analysis of the Aphasic Deficits (BADA)	
Object comprehension subtest	39/40
Action comprehension subtest	20/20
Object naming subtest	**25/30**
Action naming subtest	**25/28**
Sentence Comprehension	**55/60**

Table 5 - Clinical features and baseline language assessment of patient AA. Bold data indicate scores below normal cut-off.

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Exclusion criteria included clinical evidence of depression, clinical signs of hearing or vision impairment, a past history of epilepsy, implanted metal objects, psychosis or major depression and alcohol abuse and drug addiction. These parameters are consistent with the safety recommendations for tDCS (Nitsche et al., 2008). The use of psychopharmacological agents that could interfere with the test performance or diagnosis and MRI evidence of relevant cerebrovascular changes unrelated to the main diagnosis of the patient were additional exclusion criteria.

3.3.2 Preliminary experiment: online evaluation

Initially we tested the presence of a tDCS facilitatory effect applying the stimulation with an "online" protocol, similar to the protocol applied in healthy subjects .

The patient was required to accurately name, as fast as possible, the stimuli appearing on the computer screen. Trial structure is illustrated in Figure 8. The only difference with the task used with healthy-aging subjects was that the picture remained on the screen for 10 seconds. The experiment was made up of three block, each containing 15 trials. Each block was performed after a different kind of stimulation: anodal, cathodal or sham on the left DLPFC.

Stimulation was applied for ten minutes before each block of the task (I= 2 mA) by the mean of two 35 cm^2 electrodes. The reference electrode was collocated on the right shoulder. The three sessions and, therefore, three experimental blocks were separated by a one-hour pause (i.e., washing-out) period.

The results shown a facilitation in the action naming (vRT sham = 1752 ms; vRT cathodal = 1424 ms) after the cathodal stimulation. With anodal stimulation the results was a worsening of the performance (vRT anodal = 2219 ms). For this reason AA enter the off-line rehabilitation protocol, including the sub-ministration of repeated sessions of stimulation (cathodal) and a classic daily cognitive rehabilitation protocol.

3.3.3 Methods

AA received four weeks of tDCS of the left DLPFC combined with the speech therapy. Each week of tDCS treatment consisted of 5 sessions that comprised a total of 50 minutes/day (25 minutes of tDCS plus 25 minutes of speech therapy). tDCS (Eldith, Neuroconn, Germany) was applied with a 2mA intensity with two electrodes

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of 35 cm^2 for 25 minutes. These parameters are consistent with safety recommendations for tDCS (Nitsche et al., 2008). The cathodal electrodes was applied on the left DLPFC based on the results of "online" evaluation. The left DLPFC was individuated moving 8 cm frontally and 6 cm laterally with respect to the scalp vertex, which had been identified as Cz in 10-20 nomenclature for EEG electrode positioning (Cappa et al., 2002). AA tolerated tDCS well and did not report any adverse effects.

For the rationale for choosing the left DLPFC as the tDCS target area, see section 3.2.2.2.

3.3.4 Behavioural assessment

All the characteristics of the behavioural assessment were identical to the rTMS protocol exposed in the previous chapter (for details see chapter 3.2.3).

3.3.5 Results

No changes were recorded in the standard neuropsychological assessment including formal language assessment (AAT and BADA) after the therapy. In contrast, significant improvements were found for object naming in the experimental stimuli set. We calculated the baseline for the therapy and control lists. The percentage correct at baseline corresponds to the number of items correctly named in 1 of the 2 naming assessment sessions, divided by two and further divided by the total number of items in the therapy and control lists (both the therapy and control lists included the same number of items) multiplied by 100. A χ^2 comparison, with the Yates correction, was applied to compare performance scores after 2, 4, 8, 16 and 48 weeks, with respect to baseline and for both the treated and untreated items.

For treated items, AA showed improvement after 2 weeks of combined tDCS-behavioural therapy weeks, as compared to baseline and this significant improvement persisted at 4, 8, 16 and 48 weeks. Moreover, the improvement was also significant with untreated items after 2 weeks of combined tDCS and behavioural therapy and at weeks 4, 8, 16 and 48 (see Figure 14 and Table 6 for details).

Additionally, to examine the generalisation of effects to untreated items, we compared the accuracy scores for trained and untrained items for each time-point using Yates-corrected χ^2 comparisons. The results showed a significant effect on

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treated items (vs. untreated items) at the 2-week post-treatment measurement point, whereas the difference between the naming treated and untreated images decreased over time and vanished beginning at 4 weeks post-entry/baseline.

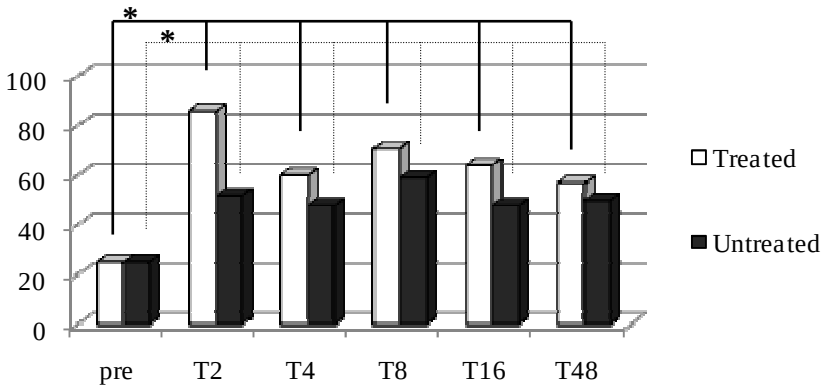

Figure 14 – Percentage of correct responses in the picture-naming task for treated and untreated items at baseline and 2, 4, 8, 16 and 48 weeks after the beginning of treatment for patients AA. Asterisks indicate p values < 0.05.

		Treated Items		Untreated Items		
	Timing	**Correctness %**	**Comparison with baseline**	**Correctness %**	**Comparison with baseline**	**Treated vs. Untreated**
AA 4 Weeks of Real tDCS plus Speech Therapy	baseline	25		25		
	2 weeks	86	χ^2=26.0, p<0.001	52	χ^2=4.6, p=0.031	χ^2=6.5, p=0.014
	4 weeks	60	χ^2=12.7, p<0.001	48	χ^2=5.3, p=0.021	ns
	8 weeks	71	χ^2=21.6, p<0.001	59	χ^2=11.5, p<0.001	ns
	24 weeks	64	χ^2=15.4, p<0.001	48	χ^2=5.3, p=0.021	ns
	48 weeks	57	χ^2=10.3, p=0.001	50	χ^2=6.2, p=0.013	ns

Table 6 - Oral object naming at all time points for treated and untreated items for AA. Statistical data (χ^2, Yates correction) are reported too. ns= not statistically significant.

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3.4 Discussion

Our preliminary findings provide additional evidence for the beneficial effects of brain stimulation in combination with targeted behavioural training in PWAs suffering from anomia. In particular, a long-lasting effect of combined NIBS and behavioural therapy was observed; this effect was still present at 48 weeks after the beginning of the combined NIBS-speech therapy intervention on the therapy list, but not on the standardized tests. This result is consistent with previous reports on enhanced cognitive performance following NIBS (i.e., rTMS or tDCS) to specific cortical areas in patients with a variety of neurological diseases (Baker et al., 2010, Berthier and Pulvermuller, 2011, Cotelli et al., 2006, Cotelli et al., 2008, Fiori et al., 2011, Martin et al., 2004, Monti et al., 2008, Naeser et al., 2005a, Naeser et al., 2005b). Moreover, the results of our study are also consistent with previous evidence regarding the increased efficacy of daily combined rTMS or tDCS plus cognitive rehabilitation (Baker et al., 2010, Fiori et al., 2011, Floel et al., 2011, Fridriksson et al., 2011, Kakuda et al., 2010b, Kang et al., 2011, Martin et al., 2009b, Naeser et al., 2010b, Weiduschat et al., 2011).

The present study provides additional evidence supporting the use of combined behavioural and brain stimulation approaches to achieve successful outcomes in aphasia therapy. The heterogeneity of the approaches used to date - i.e., 1) low-frequency rTMS over the unaffected hemisphere to suppress the presence of over-activation in the right frontal area due in part, to lack of transcallosal inhibition from the damaged left frontal area; and 2) high-frequency rTMS over the damaged hemisphere aiming at the facilitation of the spared regions surrounding the lesional areas - makes comparison of rTMS studies complex.

Regarding tDCS, both anodal and cathodal stimulation applied over the lesional hemisphere improved language in post-stroke aphasia patients. What are the possible mechanisms responsible for these effects? It has been hypothesised that both tDCS and rTMS can affect the cortical plastic changes following stroke in a positive way and that these effects may outlast the stimulation period (Ridding and Rothwell, 2007).

Several studies support the idea that a favourable recovery from post-stroke aphasia is associated with a predominant reactivation of ipsilateral areas (Heiss et al., 1993,

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Thiel et al., 2001, Winhuisen et al., 2005, 2007). Recent reviews highlighted that several recruitment mechanisms occur, including persistent function in spared areas, compensatory recruitment of alternate nodes and involvement of areas that may hinder recovery (Miniussi and Vallar, 2011a, Turkeltaub et al., 2011). Based on the same idea, we applied high-frequency rTMS over the left DLPFC to increase cortical excitability and our results are consistent with this perspective. No adverse effects have been reported, supporting the safety of this approach (Rossi et al., 2009).

These facilitation effects may be related to changes in cortical excitability and plasticity (Ridding and Rothwell, 2007). One possible explanation for these stimulation effects is that they may be mediated by the enhancement of compensatory modifications in functional networks associated with a specific function (Fridriksson et al., 2011). These modifications of cortical activity through the use of stimulation may re-adjust the pathological patterns of brain activity, thus providing an opportunity to normalise activity patterns within the affected functional networks (Thut and Miniussi, 2009).

The present findings suggest that NIBS-induced modulation of short- and/or long-range cortical synaptic efficacy and connectivity, which potentiates the system within the language network, leads to increased effects of speech therapy (see Miniussi and Vallar, 2011a).

The major limitations of this preliminary study were the small number of patients (only one with the application of tDCS) and the lack of a placebo stimulation group, for 2 and 4 weeks, with and without speech therapy. Thus, the main findings of this study - i.e., that combined behavioural-NIBS treatment induced a long-lasting effect on treated items and contributed to a generalisation of therapy effects to untreated items - needs to be confirmed using a larger sample. The inclusion of a control group receiving only language therapy is required to separate the respective contribution of language therapy alone, and in combination with real or placebo NIBS treatments.

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4.

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS OF RESEARCH

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In these three years I've studied the application of NIBS to enhance the performance of healthy people and aphasic patients in a language task. The adoption of these NIBS techniques, in particular of tDCS, is very recent and has provoked great interest in the scientific community for their easiness of use and their potential in the rehabilitation field. During these years several research group all over the world has independently worked to ameliorate our knowledge about these techniques, with studies of modeling (Miranda et al., 2006, Sadleir et al., 2010, Wagner et al., 2007), neuroimaging (for a review see Siebner et al., 2009), studies on animals and on human subjects (see for reviews Brunoni et al., 2011, Nitsche and Paulus, 2011). tDCS effects have been studied on primary motor and visual cortex (for reviews see Nitsche et al., 2008, Nitsche and Paulus, 2011) but also on superior cortices, such as parietal cortex, temporal cortex and prefrontal cortex (see e.g., Andrews et al., 2011, Boggio et al., 2009, Fertonani et al., 2010, Stone and Tesche, 2009, Straube et al., 2011). As happened twenty years ago for TMS, all these studies have carried important proofs of the tDCS effects, but they have also demonstrated that a simplistic vision of their functioning is incongruous. The initial conception of a "facilitating" anodal stimulation and a "worsening" cathodal stimulation is indeed well-grounded only for motor cortex stimulation (Jacobson et al., 2011). Moreover, also for motor stimulation, there are important parameters of application, such as the duration of the stimulation (and the potential presence of homeostatic phenomena, see e.g., Fricke et al., 2011, Monte-Silva et al., 2010) or the positioning of the reference electrode (and consequently the direction of the flux of current, see Moliadze et al., 2010, Nitsche and Paulus, 2000) that can dramatically change the measured effects of tDCS. These concepts emerge also from my researches on the facilitation effects of tDCS and TMS on a picture naming task. First of all, only anodal stimulation has an effect. Thus the opposition of anodal/cathodal effects seems not to be true for this more complex task, that requires a wide network to be executed and so it's more difficult to worsen (see Jacobson et al., 2011, for analogous considerations in literature). Second, a particularly important variable to considerate seems to be the timing of stimulation. In the study on healthy-aging people only the anodal stimulation was effective only if it was delivered simultaneously to the task execution. This is a precious indication for the planning of

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rehabilitation protocols, and surely would have to be confirmed also in young subjects. Another interesting, also if negative, result, is the lack of effect of bilateral tDCS. The stimulation with bilateral tDCS seems particularly suitable for a brain in which exists an imbalance between the two hemispheres activity. Nevertheless it seems the case that in young people, in which this imbalance doesn't exists, this montage don't bring any advantage for the task execution.

In the second part of my thesis I've presented the results of a project that had the objective of evaluate the possible therapeutic application of TMS and tES, coupled with the traditional logopedic therapy, in chronic aphasia patients. These preliminary results seem very promising, providing additional evidence for the beneficial effects of brain stimulation in combination with targeted behavioural training in patients with aphasia suffering from anomia. Nevertheless it should be considered that these are preliminary results, due to the small number of patients involved. Therefore the next step will be necessary to increase the patient sample. In particular the inclusion of a control group receiving only language therapy will be required to separate the respective contribution of language therapy alone, and in combination with real or placebo NIBS treatments.

Whit this research we expect to advance the understanding of the mechanisms by which tDCS impacts on brain function as progress in neuroscience and expansion of tDCS applications to the clinic. Therefore the obtained data will result in a further step towards the building of an innovative and more effective therapeutic strategy with important potential. If standard cognitive treatment effects could be maximized, the time needed to rehabilitate the patients will be reduced, with definite implications in assessing benefits of these approaches. Transferring knowledge from bench to clinical domains is indeed an important aspect of research. Benefits will extend to the well-being of patients and families and will improve public health, reducing long-term disability in these patients.

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Appendix

Survey of sensations related to transcranial direct current stimulation (Published in Fertonani et al., 2010)

a) English version

Subject code: _____ **Date:**____/____/____

Experiment: _____

Have you experienced any sensation during the direct current stimulation? Please answer to the following questions regarding the different sensations, indicating the degree of intensity of your perception according to the following scale:

- ***None*** **= I have not felt the described sensation**
- ***Mild*** **= I have mildly felt the described sensation**
- ***Moderate*** **= I have felt the described sensation**
- ***Considerable*** **= I have felt the described sensation to a considerable degree**
- ***Strong*** **= I have strongly felt the described sensation**

In the first stimulation block

Itchiness:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Pain:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Burning:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Warmth/Heat:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Pinching:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Iron taste:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Fatigue:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Other_____:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong

When did the sensations begin?

□ At the beginning of the block □ About the middle of the block □ Towards the end of the block

How long did they last?

□ They stopped soon □ They stopped in the middle of the block □ They stopped at the end of the block

How much did these sensations affect your performance?

□ Not at all □ A little □ Considerably □ Much □ Very much

In the second stimulation block

…

If you want to provide more details, please briefly describe the experimented sensations in relation to:

- Itchiness:
- Pain:
- Burning:
- Warmth/Heat:
- Pinching:
- Iron taste:
- Fatigue:
- Other:

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b) Italian version

Codice Soggetto: _____ **Data:**____/____/____

Esperimento/Sperimentatore:_____

Che sensazioni ha percepito durante la stimolazione elettrica a corrente continua? Risponda alle seguenti domande indicando il grado di intensità con il quale ha percepito ognuna delle sensazioni elencate, utilizzando una scala come la seguente:

- ***Nessuno*** **= non ho avvertito alcuna sensazione del tipo descritto**
- ***Lieve*** **= la sensazione descritta è stata appena avvertita**
- ***Moderato*** **= la sensazione descritta è stata avvertita**
- ***Abbastanza*** **= la sensazione descritta è stata avvertita in grado considerevole di intensità**
- ***Molto*** **= la sensazione descritta è stata avvertita come forte**

Nel primo blocco di stimolazione

Prurito:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Dolore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Bruciore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Calore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Pizzicore:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Sapore Ferroso:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Affaticamento:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto
Altro_____:	□ Nessuno	□ Lieve	□ Moderato	□ Abbastanza	□ Molto

Quando sono insorte le sensazioni?

□ All'inizio □ Verso la metà del blocco di stimolazione □ Verso la fine

Per quanto tempo sono durate?

□ sono subito svanite □ sono svanite verso la metà del blocco □ sono durate fino alla fine del blocco

Quanto le sensazioni provate hanno influenzato la qualità della sua prestazione in questo blocco?

□ Per Nulla □ Poco □ Abbastanza □ Molto □ Moltissimo

Nel secondo blocco di stimolazione

...

Se lo ritiene opportuno, descriva brevemente le sensazioni da lei provate riguardo a:

- Prurito:
- Dolore:
- Bruciore:
- Calore:
- Pizzicore:
- Sapore ferroso:
- Affaticamento:
- Altro:

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Published papers

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