UNIVERSITY OF MILANO BICOCCA
DEPARTMENT OF PSYCHOLOGY

DOCTORAL PROGRAM IN EXPERIMENTAL PSYCHOLOGY,
LINGUISTICS AND COGNITIVE NEUROSCIENCE
XXV CYCLE

INVESTIGATING THE NEURAL CORRELATES OF LANGUAGE PRODUCTION BY MEANS OF tDCS

Tutor: Professor COSTANZA PAPAGNO

Doctoral thesis by:
ALBERTO PISONI

ACADEMIC YEAR 2012/2013

Table of contents

Abbreviations list

- a-tDCS: Anodal tDCS
- c-tDCS: Cathodal stimulation
- EEG: Electroencephalography
- GMFP: Global mean field power
- LDLPFC: Left dorsolateral prefrontal cortex
- LIFG: Left inferior frontal gyrus
- LITG: Left inferior temporal gyrus
- LMFG: Left middle frontal gyrus
- LMFP: Local mean field power
- LPMC: Left premotor cortex
- LSPL: Left superior parietal lobe
- LSTG: Left superior temporal gyrus
- LTD: Long term depression
- LTP: Long term potentiation
- MEP: Motor evoked potential
- NiBS: Non-invasive brain stimulation
- NSE: Neuron specific enolase
- PF: Phonological facilitation
- PFC: Prefrontal cortex
- PPC: Posterior parietal cortex
- PWI: Picture word interference
- RIFG: Right inferior frontal gyrus
- RT: Reaction times
- SI: Semantic interference
- tDCS: Transcranial direct current stimulation
- TEP: TMS evoked potential
- TMS: Transcranial magnetic stimulation
- TOT: Tip of the tongue

1 Introduction

Language production is one of the most complex cognitive – motor skills developed by *homo sapiens* throughout evolution to allow inter-personal and intra-personal communication (Indefrey and Levelt, 2000). A great number of cortical regions have adapted to support this high-speed combination of muscular and mental processes, in order to correctly generate the intended utterances in different contexts and situations. The neural organization of language processing is a thorny matter, that in the last decades has been investigated with a number of different methods ranging from functional imaging (fMRI, PET; see Gernsbacher & Kashack, 2003; Price, 2010; 2012 for reviews) neurophysiology (EEG, ERP, MEG, see Ganushchak et al., 2011 for a review), lesion studies (for a review see Turkeltaub et al., 2011) and non-invasive brain stimulation (such as transcranial magnetic stimulation, TMS, and transcranial direct current stimulation, tDCS, Devlin and Watkins, 2007; Monti et al., 2012 for reviews). Overall these studies have identified specific areas differently involved in language sub-processes (for a review see Price, 2012; Indefrey, 2011). As a new methodology to investigate the relationship between cortical areas and behavioural performance in cognitive tasks, including language, tDCS has been increasingly used in the last decade (Vallar & Bolognini, 2011). This technique relies on a sub-threshold polarization or de-polarization of neurons that leads to a modulation of cortical excitability and plasticity (Nitsche & Paulus, 2011). Due to its ease of application even in clinical settings, the potential of this tool in neuro-scientific investigation seems wide, but there is no precise knowledge of its mechanisms and effects on cognitive functions. The aim of the present study is to test tDCS effects on language production, to explore when this technique can be applied and to deeply investigate the mechanisms that lead to behavioural changes. In particular, since one of the classification criteria in aphasia is verbal fluency, in study

1 I investigated the effects of anodal tDCS on a verbal fluency task, aiming at developing a possible protocol to apply on clinical populations. To assess whether stimulation could modulate language production, healthy subjects performed a verbal fluency task both on phonemic and semantic cue immediately after real or sham stimulation. Since this requires the activity of a distributed network, including, among others, the left inferior frontal gyrus (LIFG), the left pre-motor cortex (LPMC), the left inferior and superior temporal gyri (LITG, LSTG) and the bilateral occipital-temporal sulci (Birn et al., 2010), and given that widespread effects of tDCS on functional networks need further clarification, in study 2 I investigated how electrical non-invasive brain stimulation affects cortical excitability by means of a TMS- EEG and tDCS combination, assessing how tDCS modulates cortical excitability and, accordingly, behavioural performance on verbal fluency. An open issue, indeed, is how stimulation enhances the activity of functional networks during task execution. Few recent studies addressed this question, but they generally rely on imaging data (Meinzer et al., 2012, 2013; Holland et al., 2011;). Hence, I tested how cortical excitability is modified after anodal tDCS applied over the LIFG in a functionally connected area, namely the LPMC (BA6) and in a region not involved in verbal fluency, the left superior parietal lobe (LSPL, BA7), and whether these changes could explain the effects of tDCS on task performance. Then, in study 3 and 4 and 5, I tested whether tDCS could be a useful tool to investigate language processes in healthy subjects. In particular, in study 3 and 4 I focused on semantic and phonological interference in picture naming tasks. The functional locus of the semantic interference (SI) effect, indeed, is still not clear (Finkbeiner and Caramazza, 2006; Schnur et al., 2006; 2009; Schnurr and Martin, 2012) and the role of the LIFG and LSTG in this effect is still under debate (Schnur et al., 2006; 2009). To test the different hypotheses underlying SI effect, I investigated the effects of anodal stimulation on the two aforementioned areas in a naming task in which

semantic context was manipulated ("blocked naming task", Belke et al., 2005). Similarly, frontal and temporal regions seem to be involved in the phonological facilitation (PF) effect observed in naming (De Zubicaray et al., 2002; De Zubicaray and McMahon, 2009; Zhao et al., 2012; Damian & Bowers, 2009; Meyer and Schriefers, 1991; Scrhiefers et al., 1990). A picture word interference paradigm (PWI) was then administered after anodal stimulation of the LIFG and LSTG, and the effect of stimulation on PF was assessed. Finally, since proper name retrieval decreases with aging (Evrard et al., 2002), it would be of high interest to develop protocols improving this ability: this is the topic of study 5.

1.1 The functional and neural correlates of word production

In the last decades, several different models of word production have been developed, which differ one from another in several aspects (see for example Dell, 1986; Levelt 1999; Pickering and Garrod, 2013; Dell, 2013). A model that sums up the findings of psycholinguistic and neuro-linguistic research is the one proposed by Kay, Lesser and Coltheart (1996, Fig. 1.1).

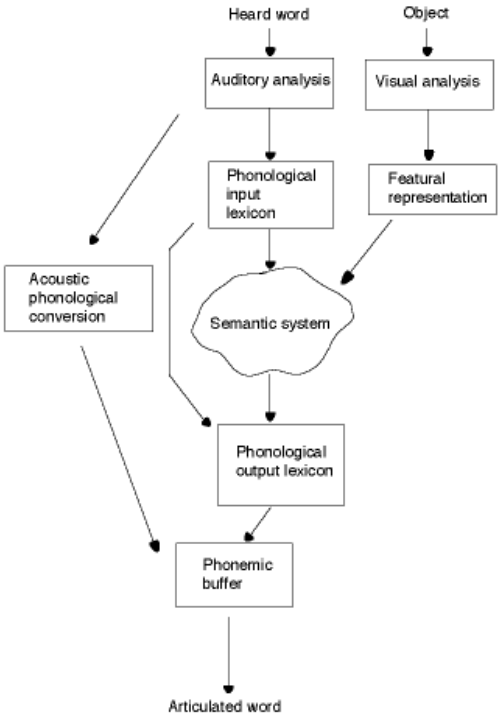


Fig. 1.1: Model of word processing. Adapted from Kay, Lesser and Coltheart, 1996.

According to this model, word processing and production rely on different subcomponents, which differ depending on the input and output modalities in which they are triggered. Namely, input modalities are the auditory form, the visual object presentation (as in picture-naming) and the written form. Since the studies here reported do not involve reading or writing, I will focus my description on the stages of picture

naming and auditory word presentation. With regard to auditory word processing, a preliminary step in word comprehension is the acoustic analysis, in which sounds are recognized and processed as verbal material. After analysis, verbal sounds enter the phonological input lexicon, in which phonemes configurations are recognized as words. At this level no information about word meaning is present, but the input phonemes sequence is compared with stored auditory word form representations. When the match is achieved, activation spreads from the identified lexical form to the corresponding semantic node. This contains knowledge about the concept linked to the target word, and is part of a broader network in which connections represent semantic relation between different concepts. Besides providing semantic information, nodes are directely linked to lemmas, representations carrying the grammatical and syntactic properties of the word. In the case of picture naming, access to semantic concepts can be achieved through object visual analysis. In this case, the presented picture is analyzed and recognized as an element of a specific semantic node. To name a picture, after semantic and lemma selection, representations in the phonological output lexicon are activated. This lexicon contains word forms as a sequence of phonemes, which will be retrieved as separate units and transformed into motor plans in the phonological buffer in order to correctly articulate the target word.

Regarding the neural correlates of word production, Price (2012) in a meta-analysis and Indefrey (2011) in a review, reported a summary of more than 20 years of imaging studies on language processing, highlighting the different neural patterns associated to each stage of word production. Briefly, the left middle frontal gyrus (LMFG) and the LIFG, the posterior portions of LSTG and anterior cingulate zone seem to be involved in word retrieval; the LSTG, the left ventral pars opercularis and LPMC seem crucial for phonological encoding and the pre-post central regions as well as subcortical

structures (putamen) for overt articulation. Nevertheless, this simplified summary of word production-related areas becomes more complicated when language tasks are performed in combination with different context demands, as for example when naming is required during the simultaneous presentation of distracters, or word production is constrained by phonologic or semantic characteristics.

1.1.1 Verbal fluency

In verbal fluency the participant is asked to produce in one minute as many words as possible, sharing a common feature (Novelli et al., 1986). In verbal fluency on phonemic cue, words must be retrieved on the basis of their initial letter, while on semantic cue words must belong to the same semantic category. Both tasks involve similar linguistic (lexical selection, phonological retrieval and encoding, and articulation) and executive (sustained attention, creating a retrieval strategy, competitors inhibition and working memory) processes. What differs is the lexical retrieval focus: in one case it relies on orthography and phonology, while for semantic fluency it requires access to conceptual knowledge (Birn et al., 2010). These similarities and differences are reflected in the neural activations linked to both fluency tasks (e.g., Birn et al., 2010; Grogan et al., 2009; Gourovitch et al., 2000; Heim et al., 2008; Perani et al., 2003). In particular, semantic compared to phonemic fluency is associated to a greater activation of the LITG, probably related to the retrieval of stored conceptual information (e.g., Mummery et al., 1996; Gourovitch et al., 2000; Heim et al., 2008), while phonemic fluency engages the LPMC and LIFG, as well as discrete bilateral foci in the occipital-temporal cortices, possibly linked to word-form retrieval. Nonetheless, the LIFG is likely to subserve common processes that, in someone's opinion, are crucial for both

semantic and phonemic tasks (for a review, see Costafreda et al., 2006), as also suggested by patients with frontal lesions occasionally showing deficits in both situations (Baldo and Shimamura, 1998; Schwartz and Baldo, 2001) even if some studies report clear dissociation between areas involved in phonological and semantic fluencies (e.g. Baldo et al., 2006).

1.1.2 Picture naming

As previously described, naming a picture requires at least the following processes: recognition of the visual stimulus, access to the meaning, access to the phonological word form, and the motor programming and planning of articulation (Levelt et al., 1998; Maess et al., 2002). This complex task requires a rather sequential processing, even if backward feedback inputs cannot be excluded (see Dell, 2013). Fig. 1.2 sums up the most recent updates in this regard. Lexical and phonological retrieval are of course crucial for picture naming. These processes are indeed related to phonologic and semantic context in which they have to be performed, and could work on a spread of activation way (Weaver ++ model, Roelofs, 1997; Levelt, 1999; Fig. 1.3).

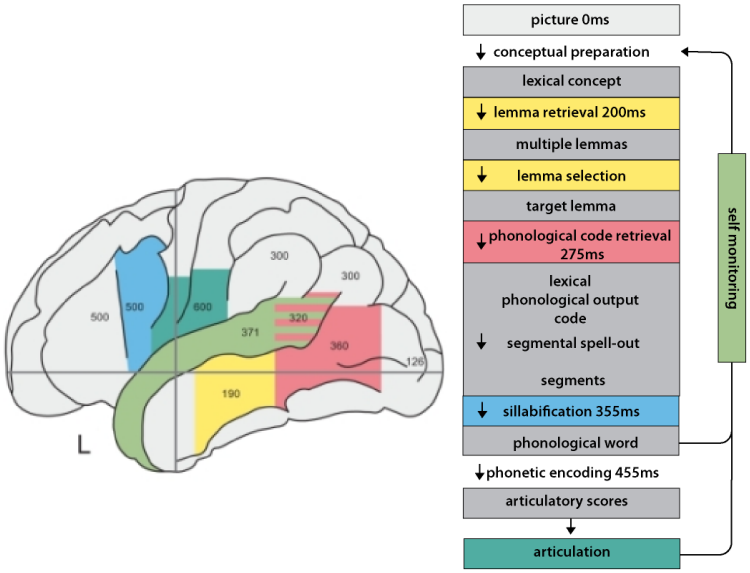


Fig. 1.2: Anatomical and temporal signatures of picture naming. Adapted from Indefrey, 2011.

According to this model, concepts are interconnected nodes of a network, hierarchically organized in different levels. The more general level is the conceptual stratum, where nodes are connected by semantic associations and where semantic knowledge is stored; then, at the lemma level, syntactic/lexical information is available. Finally, there is the form stratum), where nodes are represented by phonemes and where the selection of sounds forming a word takes place. Selecting a target concept (representing a node of the conceptual network), and then its word-form, ends in a slight activation of closely related lemmas and phonemes (Fig. 1.3).

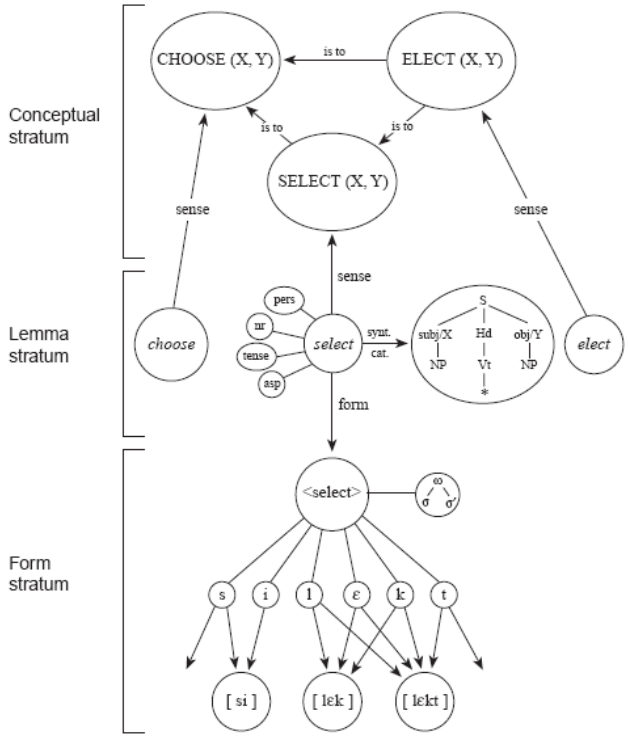


Fig. 1.3: Weaver ++ model. Adapted from Levelt, 1999.

These side-activations are considered to be responsible of the SI and the PF effects, often reported in studies with different naming protocols (Schnur et al., 2006; 2009; 2012; Damian & Bowers, 2009; Belke et al., 2005; Costa et al., 2005; Damian et al., 2001; Damian and Bowers, 2003; Maess et al., 2002; De Zubicaray et al., 2001; 2002; Caramazza & Costa, 2000; Schriefers et al., 1990). The SI effect refers to the increase

of reaction times (RTs) in naming an object in a semantically related context with respect to a non-related one (Damian et al., 2001; Belke et al., 2005; Schnur et al., 2006; 2009; Abdel Rahman and Melinger, 2011; Ganushchak and Schiller, 2008). Spread of activation is considered the mechanism underlying this effect (but see Caramazza & Costa, 2000; Schnur et al., 2012 for different positions), but it is not yet clear why this interference arises. It has been suggested that spreading activation may cause a "refractory state" ending in a higher competition between items (Forde and Humphreys, 1997, Schnur et al., 2006), or may produce an "over-inhibition" of the system due to the repeated suppression of non-target items (Dell, 1986). Similarly, the phonological context has been found to affect picture naming. Indeed, naming latencies are reduced by phonological similarity in a picture-word interference paradigm compared to phonological un-relatedness, but only if the intervening word is presented within 200ms from picture presentation (Schriefers et al., 1990), when the phonological activation has already occurred.

The neural correlates of picture naming include a variety of regions highly dependent on task demands. Recent reviews of more than 20 years of imaging research (Indefrey, 2011; Price, 2012) have highlighted that the most common pattern of activation related to lexical retrieval includes the LIFG, LMFG and posterior regions in the LITG , with more dorsal superior temporal lobe involvement when retrieval becomes more difficult. Word form retrieval, instead, has been linked to the LMTG and LSTG activations. Phonological encoding, on the other hand, seems to be related to LSTG, the left pars opercularis and LPMC activity.

Overt articulation, the last stage of picture naming, has been linked to the activity in the pre- and post-central regions responsible for orofacial muscles control, as well as

subcortical areas involved in motor activity timing and control (Indefrey, 2011; Price, 2012).

Regarding the previously described SI and PF effects, it seems that the degree of LSTG activity relates to the increased or decreased difficulty of the task. Greater activation of this area has been found in tasks eliciting a SI effect (De Zubicaray et al., 2001, but it may be also related to internal self-monitoring and control of the selected output, see Maess et al., 2002), while it shows less activation in PF contexts (De Zubicaray et al., 2002).

Converging evidence suggests also an involvement of the LIFG in lexical-semantic selection (Devlin et al., 2003; Moss et al., 2005; Hirshorn and Thompson-Schill, 2006; Schnur et al., 2006, 2009; Oztekin et al., 2009), possibly reflecting demanding selection processes and/or detection of response conflicts.

1.1.3 Lexical retrieval and proper names

Lesion studies have demonstrated that the neural organization of domain specific knowledge is differently organized in the brain (for an overview see Warrington & Shallice, 1984; Hillis & Caramazza, 1991; Damasio et al., 1996). Proper names, in particular, can be selectively impaired (or spared) after brain injury (for a recent review see Semenza, 2009). From a linguistic point of view, the main difference between common and proper names is that common names refer to a number of exemplars sharing common features, while proper names are “pure referring expression” (Kripke, 1980), meaning that exemplars with the same name usually do not have similar characteristics (not all Andreas, for example, have the same hair or eyes colour). Since persons with the same name cannot be distinguished from the others from recognizable

characteristics, a direct association is needed in order to link the conceptual knowledge of an individual with his/her name. At a neural level, converging evidence indicates that the left temporal pole might be involved in proper name retrieval, while the right temporal pole seems involved in people semantic knowledge (Gainotti, 2007), even if evidence is still under debate (Semenza, 2011). Since proper names establish a single, direct link with the correct exemplar they refer to, this ability is easily compromised in brain damaged patients (Semenza, 2009), and even in normal aging, a difficulty in retrieving proper names is one of the most reported inconvenience (Evrard, 2002). Upon these premises, it would be useful to develop a protocol effective in improving proper name retrieval in the elderly. Recently, tDCS studies have been devoted to this aim (Ross et al., 2010; 2011), but results are far from being convincing.

1.2 Transcranial Direct Current Stimulation (tDCS)

1.2.1 The technique

tDCS is a non-invasive brain stimulation (NiBS) technique that can be used to modulate spontaneous cortical activity in the human brain (e.g., Been et al., 2007; Hamilton et al., 2011; Fregni and Pascual-Leone, 2007; Miniussi et al., 2008; Nitsche et al., 2008; Paulus, 2003; Priori, 2003; Nitsche & Paulus, 2011 for reviews). The stimulation is usually applied via a chargeable battery driven current generator connected to two rubber electrodes (Fig. 1.4) with a ramp up/down period to gently increase or decrease current intensity, a procedure that reduces discomfort sensations in participants (Ambrus et al., 2012). One electrode (Anode) represents the positive pole of the circuit, while the other (Cathode) the negative one.

Fig. 1.4: A tDCS battery driven stimulator.

The electrode montage, according to whether one or both electrodes are placed over a target scalp area, can be unipolar or bipolar. In unipolar montages, the stimulating electrode (or active electrode) is placed over a site corresponding to the target brain region while the other one (usually referred to as return, inactive or reference electrode) is placed over a control site. The stimulation target may be localised with different methods, like neuro-navigation with individual or template MRI, by means of TMS (mainly when targeting M1 to find the motor hotspot) or following the international EEG 10-20 method for electrode positioning. On the contrary, the location of the return electrode is arbitrary, and can be located outside the head (referred to as extra-cephalic reference, usually placed over the deltoid, the neck, the arm or the tibia), or over a head area in which no modulation is supposed to occur, like the chin, the cheekbone, or the supraorbital region (Nitsche et al., 2008; but see Bikson et al., 2010 for further considerations over the reference electrode role in tDCS). Bipolar montages, instead, are used mainly in rehabilitation protocols in which one area has to be enhanced and another, usually the contralateral homologue, needs to be inhibited to restore the normal functional balance between the two hemispheres (Ferrucci e tal., 2009; Brunoni et al., 2012). Electrode size can range from 9 to 50 cm^2, and it has been proven that diminishing active electrode area can improve tDCS focality (Nitsche et al., 2007). New montages with a different number and placement of very small electrodes (HD tDCS, Kuo et al., 2012; Borckardt et a., 2012; Datta et al., 2009) are under investigation, but reducing electrode size may also affect the depth of stimulation (Miranda et al., 2009). Current intensities ranging from 0.5 to 2 mA have been found effective for inducing a modulation of cortical excitability (Nitsche et al., 2008), even if current density (J) is more relevant than intensity. Current density is defined as

$$J=\frac{I}{A}$$

where I is stimulation intensity and A the area of the active electrode. The same is true for charge density (Q), defined as

$$Q=\frac{tI}{A}$$

where I is stimulation intensity, t is stimulation duration and A the area of the active electrode. Current density is thus depending both on intensity of stimulation and electrode size, while charge density includes also stimulation duration; these two variables must be taken in account when designing a stimulation protocol. Safety limits of tDCS applications are, indeed, referred to current and charge densities rather than intensity (Liebetanz et al., 2009). Animal studies investigating deleterious effects of different stimulation protocols in rat samples indicate that lesions appear at a current density of 142.9 A/m^2 (0,5 mA over an electrode area of 3.5 mm^2) and charge density of 57.143 C/m^2 (corresponding to 3.33 min 1 mA over an electrode area of 3.5 mm^2)(Liebetanz et al., 2009). In the majority of studies in human subjects the current is applied up to 2 mA with an electrode size of 25/35 cm^2 and a duration up to 20 min (see Nitsche & Paulus, 2011 for a review), with a theoretical maximum current density of 0,8 A/m^2 and charge density of 960 C/m^2, thus two orders of magnitude below the risk threshold. Moreover, these protocols do not induce any pathological changes in healthy subjects in EEG recordings (Iyer et al., 2005), skin temperature (Nitsche & Paulus, 2000), MR sensitive to oedema onset (Nitsche et al., 2004c) and neuron specific enolase (NSE) values (Nitsche & Paulus, 2001, Nitsche et al., 2003b). Besides safety aspects, stimulation intensity is related to procedural feelings associated to tDCS, higher

stimulation intensities being related to stronger itching and discomfort sensations under the electrode area, as well as a better discrimination between real and sham sessions (Ambrus et al., 2010; 2012). In order to reduce discomfort, mainly due to the resistance that the current encounters passing from the electrode to the scalp, a conductive medium is usually interposed between these two surfaces. Typically, electrodes are placed in sponges soaked in NaCl solution, or a conductive paste can be spread under the electrodes in order to improve conductance and decrease discomfort in participants (Nitsche et al., 2008). Regarding placebo procedures, it is important that real and sham stimulation are not clearly discernible, in order to avoid that expectancy or stimulation side effects could affect subjects' performance (referred to as subject blinding, Ambrus et al., 2012). Among the methods used to prevent subjects from perceiving differences in stimulation sessions (blinding procedures), the fade-in/fade-out approach is the most frequently used (Ambrus et al., 2012). This procedure includes in sham sessions a short lasting stimulation (30s) introduced by a 30s ramp up and followed by a 30s ramp down period (Ambrus et al., 2012). In this way, participants feel a sensation similar to the one induced during real sessions; it has been shown that even such a short stimulation can produce procedural feelings lasting up to 10 min from its end (Ambrus et al., 2012).

1.2.2 tDCS and cortical excitability modulation

The effects of stimulation depend on the polarity of the current flow, with brain excitability being usually increased by anodal tDCS (a-tDCS) and decreased by cathodal tDCS (c-tDCS; Nitsche and Paulus, 2000; Liebetanz et al., 2002), although the effects of c-tDCS are more controversial (see for instance Jacobson et al., 2012). The on-line stimulation-induced functional changes are supposed to be due to membrane slight polarization or depolarization, ending in an enhancement or decrement of

spontaneous firing rate of the neurons (Nitsche & Paulus, 2000); long term after effects may rely on long term potentiation (LTP) and long term depression (LTD) –like calcium dependent effects (Nitsche & Paulus, 2011). In pioneering animal studies, indeed, Bindman and colleagues (1964) showed that applying a current flow for a few minutes on a rat brain preparation, increased or decreased neurons firing rate (according to flow direction), and these effects lasted beyond the end of stimulation. The authors concluded that on-line effects of stimulation could be induced by the membrane polarization, while after effects could depend on different long-term plastic changes (Bindman et al., 1964). Results from early pharmacological studies investigating neurophysiological mechanisms of tDCS long-term after effects on the cerebral cortex, indicate a crucial role of membrane channels. Blocking voltage-dependent sodium and calcium channels by administering NMDA glutammate (GLU) receptors antagonist dextromethorphan abolishes a-tDCS effects, while the partial agonist d-cycloserine lengthens its after effects (Nitsche et al., 2003a, 2004b). Since NMDA receptor activity is strictly related to intra cellular calcium concentrations, these findings support the role of the glutamatergic system in tDCS after-effects, and suggest that this modulation might rely on LTP and LTD–like plasticity changes, as reported in animal experiments (Malenka & Bear, 2004). Moreover, GABA, dopaminergic, cholinergic and serotoninergic system modulations have prominent impact on tDCS after effects (for a review see Nitsche & Paulus, 2011). As a caveat, when applying tDCS, one has to consider all the possible central nervous system-acting drugs that participants are assuming, since they can modify stimulation effects on cortical excitability and plasticity.

tDCS modulation of cortical excitability is thus time dependent, and it can outlast stimulation duration. In humans, early studies indicated that Motor Evoked Potentials

(MEPs) amplitude is enhanced by a-tDCS for 5 min after 5 min of 1 mA stimulation of the primary motor cortex (M1) and similarly decreased after c-tDCS (Nitsche & Paulus, 2000). With longer stimulation durations, namely 13 min, tDCS can induce detectable after effects up to 90 min post stimulation (Nitsche & Paulus, 2001). However, this apparent relationship between stimulation duration and after effects (the longer the stimulation the longer the after effects period) does not apply for longer stimulation durations (26 min or more), for which modulatory effects seem to reverse their direction, with a-tDCS reducing excitability (Monte-Silva et al., 2012). On the other hand, it seems more efficient, in order to lengthen tDCS after effects, to apply 2 stimulation blocks, starting the second tDCS period after 13 or 20 min from the end of the first one (Monte-Silva et al., 2012).

Therefore, in order to establish a tDCS protocol it is crucial to pay attention to the duration of stimulation, current density, electrode montage and definition of the shamming procedure. All these parameters can influence the effect of stimulation on brain excitability.

1.2.3 tDCS and cognition

In the last decade, tDCS has been increasingly applied to evaluate the neural correlates of cognitive functions. Specifically, tDCS has been successfully applied on healthy subjects during spatial attention orienting (Bolognini et al., 2010a, b), executive functions (Dockery et al., 2009; Cerruti & Schlaug, 2009), language (see Monti et al., 2012 for a review), episodic memory (Javadi and Walsh, 2012a) and working memory tasks (Sandrini et al., 2011, Andrews et al., 2012). A recent meta-analysis has investigated the reliability of a-tDCS and c-tDCS effects on cognitive tasks (Jacobson et al., 2012). Qualitatively results indicate that the anodal excitatory effect is confirmed in

most of the reviewed papers, while the cathodal inhibitory effect often fails to be reported. The authors speculate that the down-regulating effect of c-tDCS is not strong enough to effectively contrast task-driven cortical excitation. In the present thesis, the excitatory effect of a-tDCS will be confirmed on language production, but the final effect on behaviour is strictly related to task demands. Concerning language studies involving tDCS, previous research has shown how this technique can be useful to improve performance. For instance, a-tDCS over both Wernicke's area (Sparing et al., 2008) and the left dorsolateral prefrontal cortex (LDLPFC see Fertonani et al., 2010) reduces naming latencies in healthy subjects. Moreover, a-tDCS over Wernicke's area facilitates associative learning as compared to sham stimulation in neurologically unimpaired individuals (Floel et al., 2008, for a complete review of the latest findings see Monti et al., 2012). It is still unclear, however, how tDCS acts on the functional network involved in language production (and generally in cognitive task execution). Few direct neurophysiological proofs of its effect on cortical activity seem to indicate a reduction of slow wave activity in EEG recordings performed after a-tDCS and task execution compared to sham sessions (Wirth et al., 2011), or in a decreased BOLD signal in the stimulated areas (Holland et al., 2011; Meinzer et al., 2012), both related to an improvement in language performance.

Since a-tDCS usually improves performance in language tasks, it has been applied in rehabilitation of aphasia (for reviews see Monti et al., 2012; Holland & Crinion, 2012). These first attempts to introduce tDCS, as an additional tool in language disorders treatment, assessed whether one (Monti et al., 2008) or multiple (Fiori et al., 2010; Baker et al., 2010; Fridriksson et al., 2011) sessions of tDCS could improve patients' performance in language tasks, mainly on picture naming. Generally, improvements in aphasia have been evaluated as a better learning of the linguistic material or as a faster

rate of acquisition at which patients achieve behavioural benefits. Similarly, generalization of the rehabilitation protocol, i.e. an improvement of performance with stimuli that were not included in the treated material administered during the stimulation sessions, seems to be enhanced by stimulation. Monti et al. (2008), investigated the effects of one single session of anodal, cathodal and sham stimulation on a sample of 8 chronic aphasic patients on picture naming. Surprisingly, the only effective intervention was 20 min 2 mA cathodal stimulation of the damaged hemisphere, while sham and a-tDCS had no effect. The authors speculate that an inhibition of the inhibitory inter-neurons in the affected hemisphere could have enhanced language areas activity, thus ending in a behavioural benefit. Multiple session studies, instead, reported a general improvement after anodal stimulation (Fiori et al., 2010; Baker et al., 2010; Fridriksson et al., 2011). The rationale behind multiple session studies is not to induce a permanent status of high excitability, but rather to produce an optimal condition for learning, so that rehabilitation protocols performed during this period could last longer (or produce better results) than in normal language treatment settings (Holland & Crinion, 2012). Overall, application of tDCS in aphasia rehabilitation seems to be potentially useful, but there are some methodological and theoretical aspects that still need to be elucidated. For instance, the location of the stimulation site has been differently chosen across studies. Overall, regardless of the method used to localize the optimal stimulation site, it seems that the best results are achieved by applying a-tDCS over the peri-lesional areas, thus indicating the importance of sites near the lesion in language recovery (Fridriksson et al., 2010; Monti et al., 2008). Moreover, tDCS focality does not allow clearly determining the electrical field peak. Indeed, it has been proposed that, since current is applied trans-cranially, only half of the delivered current reaches the brain, the rest being shunted across the scalp (Miranda et al., 2006), and in the case of stroke patients the presence of the lesion

complicates the modelling of current spread. This raises the question on how it is possible to obtain any effect by applying tDCS over a lesion site (as found in Fiori et al., 2010). Furthermore, it is still unclear whether inhibiting the right hemisphere homologues of language areas may result in an improvement (Naeser et al., 2005; but see Winhuisen et al., 2005 for different results highlighting the importance of post-onset timing when designing stimulation protocols). A theoretical background is then required in order to understand when and where to stimulate. Current data on stroke patients with motor deficits may not be directly transferred to aphasic ones (Vines et al., 2008; Lindenberg et al., 2010).

Beyond the ease of application in different contexts and the increasing evidence of its solidity as a research tool, tDCS has some critical drawbacks. One is its low spatial resolution, in the range of several cm^2; then, the actual spreading of current flow is still under investigation, by testing in experimental settings the results from mathematic models (for example see Bikson et al., 2012a, b; Datta et al., 2013). Finally, tDCS has no temporal resolution: stimulation can be applied online or offline, but its duration, in order to find a clear modulatory effect, should not be less than 5 min, preventing a possible use of tDCS as an event-related stimulation technique like TMS (but see Javadi et al., 2012 for a first attempt in this direction). Further research is needed to clarify the neural mechanisms on which tDCS effects rely, and with which functional and spatial specificity electrical stimulation should be applied.

2 Study 1: The role of LIFG in verbal fluency

2.1 Introduction

As previously outlined, recent studies have shown that tDCS can modulate language functions. In particular, it has been consistently reported that a-tDCS over the LIFG may improve production, both in healthy subjects and aphasic patients (Monti et al., 2012). These results converge with those obtained using TMS (for a review, see Devlin and Watkins, 2007) and demonstrate that NiBS is effective in modulating language functions, highlighting the potential clinical applications of TMS and tDCS for post-stroke language rehabilitation. TMS has allowed clarifying the role of different sub-regions of Broca's area in phonological, semantic and syntactic processing (Chouinard et al., 2009; Devlin et al., 2003; Gough et al., 2005; Lauro et al., 2010; Nixon et al., 2004; Sakai et al., 2002) as well as some function of Wernicke's area: low-frequency repetitive TMS (rTMS) over the posterior parts of LSTG speeded up RTs in a task tapping on native language perception in healthy volunteers (Andoh et al., 2006) while single-pulse TMS over the same area significantly reduced picture naming latencies (Mottaghy et al., 2006). In chronic post-stroke aphasic patients, excitatory rTMS applied near the damaged parts of the LIFG improved language skills (Szaflarski et al., 2011) while it is controversial whether suppressing the right-hemispheric Broca's homologue through low frequency rTMS facilitates recovery of language functions in prost-stroke aphasic patients (e.g., Barwood et al., 2010; Weiduschat et al., 2011; see Naeser et al., 2010, for a review).

This first experiment aims at assessing whether a-tDCS over the LIFG (Broca's region: left BA 44/45) can modulate verbal fluency in healthy subjects. Earlier findings suggest that stimulation over the LIFG may improve performance in verbal fluency on

phonemic cue (Iyer et al., 2005), but no study so far investigated the effect of a-tDCS on semantic fluency.

Specifically, the effect of a-tDCS over the LIFG was compared within the same group of neurologically unimpaired subjects undergoing both a phonemic and a semantic verbal fluency task. Although, as previously outlined, the two different fluency tasks may not rely on the same neural networks (e.g., Birn et al., 2010; Gourovitch et al., 2000; Perani et al., 2003), even though the LIFG seems to be involved in both tasks (see Costafreda et al., 2006, for a review). Therefore, a-tDCS over this region is expected to significantly improve word generation on both semantic and phonemic cues with respect to a sham control condition. A spatial detection task was also administered after stimulation to exclude that possible changes on verbal fluency were due to unspecific effects of a-tDCS over the level of general arousal or attention.

2.2 Experiment 1

2.2.1 Materials and methods

Participants

Ten neurologically unimpaired individuals (4 males, mean age 23.6 years, SD=3.2) took part in the experiment. All participants were native Italian speaking undergraduate students; they were naïve as to the experimental procedure, and the purpose of the study. All subjects were right-handed (as assessed by means of the Edinburgh Inventory Questionnaire, Oldfield, 1971) and with normal or corrected-to-normal vision. They had no history of chronic or acute neurologic, psychiatric, or medical disease; no family history of epilepsy; no current pregnancy; no cardiac pacemaker; no previous surgery involving implants to the head (cochlear implants, aneurysm clips, brain electrodes); and did not take acute or chronic medication. Written informed consent was obtained

from all participants. The experiment was approved by the local ethical committee of the University of Milano-Bicocca and subjects were treated in accordance with the Declaration of Helsinki.

tDCS

tDCS was delivered by a battery driven, constant current stimulator (Eldith, Neuroconn, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (7x5 cm: 35 cm^2). The anode was placed over the LIFG, while the cathode was placed over the right supraorbital region. This montage has been successfully used in previous studies (e.g., deVries et al., 2010; Iyer et al., 2005). The LIFG (left BA 44/45) was localised according to the 10-20 EEG system as the crossing point between T3-Fz and F7-Cz. This localization method has been used before in tDCS studies (e.g., Monti et al., 2008), and the reliability of the 10-20 system for cortical areas localization has been demonstrated by previous reports (Herwig et al., 2003). Real sessions stimulation protocol consisted in the delivery of 20 min of 2 mA direct current. Twenty minutes of stimulation at 2 mA are expected to induce long-lasting effects fully covering the overall duration (approximately 10 min) of the tasks following stimulation (Nitsche and Paulus, 2001). Current density (0.57 A/m^2) and charge density (685.7 C/m^2) were maintained below the safety limits (Poreisz et al., 2007). During sham condition, the electrodes were placed in the same position, but stimulation duration was set at 30s. At the onset of both real and sham stimulation procedures, the current was increased in a ramp-like fashion (Ambrus et al., 2012), eliciting a transient tingling sensation on the scalp that faded over seconds, consistent with previous reports (Ambrus et al., 2012). Similarly, at the end of the stimulation protocol, the current was slowly turned off out of the participants' field of view (Hummel et al., 2005). This procedure ensured that participants felt the initial itching sensation at the beginning of both stimulation

protocols, preventing subjects to clearly notice different sensations between sessions. The study was a single-blind experiment: subjects were not informed about the type of stimulation they received, while the experimenter knew it (see Fertonani et al., 2010, for a similar procedure).

Verbal fluency

Participants performed a verbal fluency task, both on phonemic and semantic cue (Novelli et al., 1986).

– Phonemic fluency: each subject was asked to orally generate as many words as he/she could, beginning with a specific letter (the letters 'P', 'F', 'L' and 'G') in 1 min. Participants were instructed that they could not provide proper nouns (such as Paul or Paris) or the same word twice, or use the root of a word more than once (e.g., bed, bedroom,...). The standardized letters for Italian are F, P, L (Novelli et al., 1986). According to the Corpus and Frequency Lexicon of Written Italian (COLFIS, see http://www.istc.cnr.it/material/database/colfis/index_eng.shtml), approximately the same number of words are available for the letter F (mean frequency[1] = 43.00) and P (mean frequency = 43.07). Similarly, approximately the same number of words is available for the letter G (mean frequency = 35.73) as the letter L (mean frequency = 34.47).

–Semantic (category) fluency: each subject was asked to produce as many words as possible belonging to a given category ('Fruits', 'Animals', 'Car brands and names', 'Musical instruments') in 1 min. Participants were instructed that they could not provide the same word twice, nor use two names referring to the same concept (i.e. 'dog', 'puppy', etc). The standardized categories for Italian are brands of cars, animals and

[1] The mean frequency for each letter has been computed by averaging the total frequency for all nouns, adjectives and verbs in the infinite form starting with that specific letter as reported in the COLFIS database.

fruits. Musical instruments were chosen in order to have a category matching brands of cars in terms of difficulty (see Hodges et al., 1995).

In each of the two experimental sessions, subjects were asked to perform both fluency tasks, using two with phonemic cue and two with semantic cue. Specifically, half participants were presented with the letters "G" and "F" in the first session and with the remaining letters "P" and "L" in the second one, while the other half was presented with these letters in the reversed order. The same procedure was used for the semantic fluency task: half of the participants were presented with the categories "Fruits" and "Car brands and names" in the first tDCS session and with the categories "Animals" and "Musical instruments" in the second tDCS session. In each session, the order of presentation of the two letters and categories was counterbalanced between participants. The order in which the phonemic and the semantic verbal fluency tasks were administered was also counterbalanced across subjects; for each subject, the order of the first session was reversed in the second one. Letters and categories were employed the same number of times in Sham and Real tDCS conditions.

Control task

Seven participants also performed a control task after verbal fluency, consisting in a spatial detection paradigm. Each trial started with a fixation point displayed in the middle of the screen flanked by two empty squares (measuring approx. 1°of visual angle), one to the left and one to the right of the fixation point and on the same horizontal axis, for 1s. A cross (target), then, appeared either in the left or in the right square. Participants had to indicate, as fast as possible, in which of the two squares the target appeared, by pressing with the right index or middle finger one of two keys, associated with "left" and "right" answers respectively. RTs and accuracy were

recorded for each trial. The control task consisted of 200 trials (1 min rest was given after 100 trials), and the procedure took approximately 5 min.

Procedure

Subjects were seated in front of a computer screen, in a normal-lightened and silent room. Before starting the experiment, participants were instructed about the tasks and the procedure. The 7 participants who performed the control experiment were also presented with a practice block. After the instructions, a cartoon movie (with no audio) was projected on the PC, and subjects were told to watch it. tDCS started concurrently with the beginning of the video. The same cartoon movie was presented to each subject and for the two experimental sessions, in order to reduce inter-subjects variability by exposing participants to the same visual experience. Verbal fluency was required *after* the end of stimulation. More specifically, 18 min from the beginning of the stimulation, the video was stopped and participants were told that in two minutes the experimental tasks would have started. The fluency tasks started within 1 minute from the end of tDCS and the four fluency tasks were completed in about 5 min. Then, the visual detection control task was administered. The control task took approximately 5 min.

2.2.2 Results

Verbal Fluency

Analyses were performed on the mean number of correct items in the phonemic and semantic fluency. Fig. 2.1 reports the mean number of words produced in the semantic fluency and in the phonemic fluency in the real and sham tDCS session, respectively.

A repeated measures ANOVA was carried out on the mean number of words produced with task (semantic vs. phonemic fluency) and stimulation condition (sham vs. real) as within-subjects variables. The effect of task was significant [$F(1,9)=11.18$, $p=.009$,

η^2=.55], being the mean number of words produced in the semantic fluency condition (19.33, SD=3.68) overall higher than the mean number of words produced in the phonemic fluency condition (14.98, SD=3.49). This is a well-known result. Similarly, the effect of stimulation condition was significant [F(1,9)=42.05, p<.001, η^2=.83]. The main effect of stimulation condition was due to real tDCS enhancing subjects' performance (mean number of produced words =18.93, SD=3.24) compared to the sham tDCS condition (mean=15.38, SD=2.89). The interaction task x stimulation condition was not significant [F(1,9)=3.68, p=.09, η^2=.29].

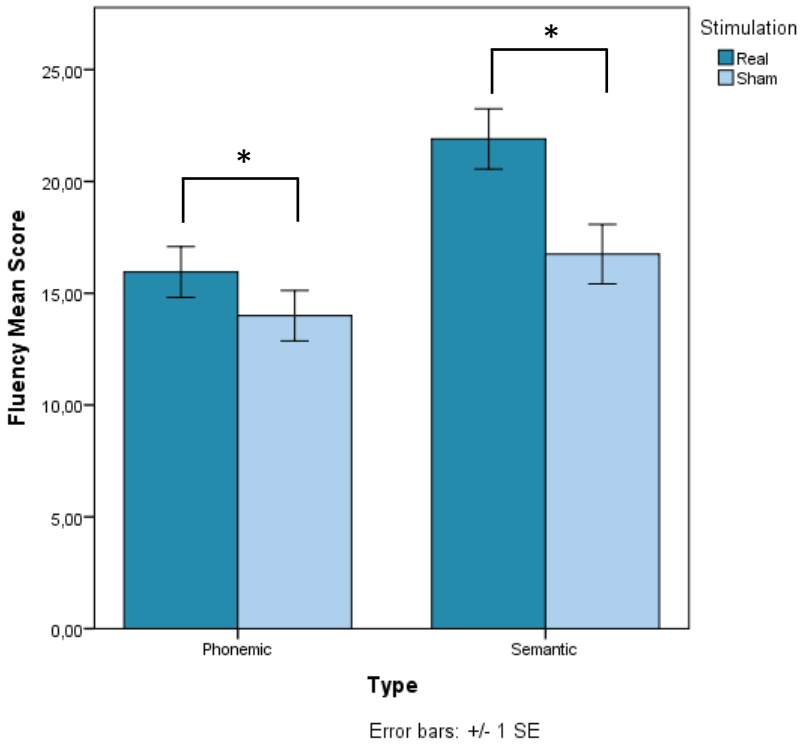


Fig. 2.1: Mean phonemic and semantic fluency scores of Experiment 1 for real and sham stimulation sessions.

Control experiment

Analyses on the mean RTs for correct responses in the control experiment showed that response latencies did not significantly differ in sham tDCS (mean RT=332.5ms, SD=15.0) vs. real tDCS (mean RT=340.5ms, SD=34.9; t(6)=.85, p=.43)(see Fig. 2.2).

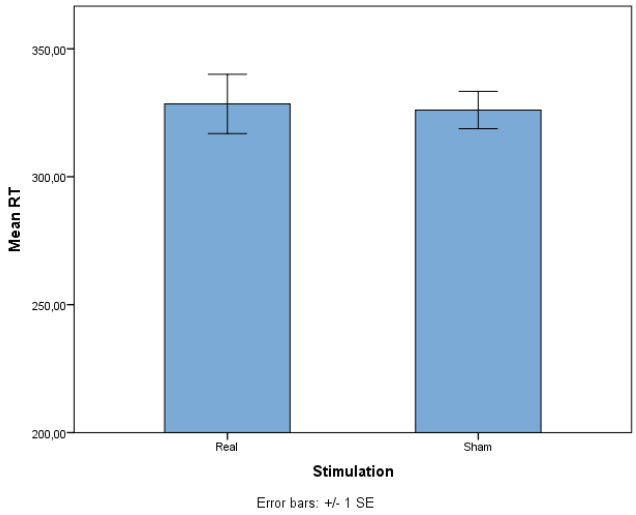


Fig. 2.2: Mean RTs of correct trials in Experiment 1 for the control task.

2.3 Experiment 2

Although there is evidence that participants cannot distinguish between real and sham stimulation when 1 mA tDCS is used (Gandiga et al., 2006), in the present experiment 2mA tDCS was applied. Therefore, one cannot exclude that at least some participant may have been able to distinguish between the two types of stimulation, affecting performance. In order to control for this possibility, a further group of neurologically unimpaired participants was tested, applying a-tDCS over the right inferior frontal gyrus (RIFG). If participants' verbal fluency in sham and real tDCS sessions of Experiment 1 was due to their capacity to distinguish between the two conditions, then also RIFG stimulation should affect fluency scores.

2.3.1 Materials and methods

Participants

Eight right-handed neurologically unimpaired individuals (3 males, mean age 23.8 years, SD=3.5) took part in this experiment. None of them was involved in the previous

experiment. The same criteria of exclusion were applied. Written informed consent was obtained from all participants.

Task and Procedure

Task, procedure, site localization and tDCS parameters were the same as in the previous experiment, except for the position of the electrodes: the anode was placed over the RIFG, while the cathode was placed over the left supraorbital region.

2.3.2 Results

The same analyses as in Experiment 1 were performed. The repeated measures ANOVA carried out on the mean number of words produced with task (semantic vs. phonemic fluency) and stimulation condition (sham vs. real) as within-subjects variables showed a main effect of task [$F(1,7)=37.66$, $p<.001$, $\eta^2=.84$], being the number of words produced in semantic fluency (mean =18.75, SD=4.15) higher than in phonemic fluency (mean =13.44, SD=3.61). Neither the effect of stimulation condition [$F(1,7)=.007$, $p=.94$, $\eta^2=.001$], nor the interaction task x stimulation condition [$F(1,7)=.35$, $p=.57$, $\eta^2=.05$], were significant (see Fig. 2.3).

Analyses on mean RTs for correct responses in the control spatial detection experiment demonstrated that response latencies did not significantly differ [$t(7)=.85$, $p=.42$] following sham tDCS (mean RT=318.6 ms, SD=55.8) vs. real tDCS (mean RT=323.5, SD=50.3).

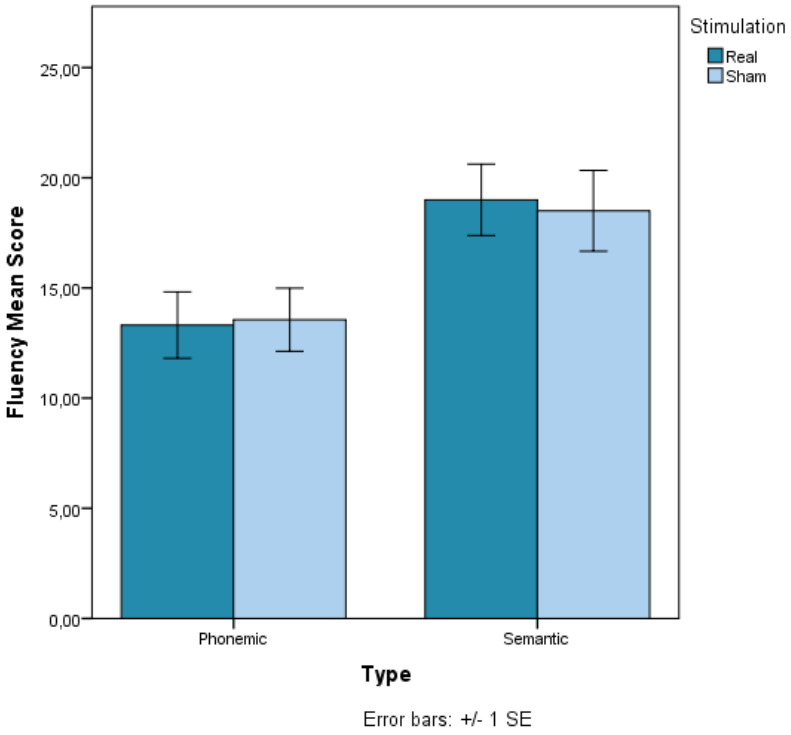


Figure 2.3: Mean fluency scores of Experiment 2 for real and sham stimulation sessions divided by fluency type.

2.4 Discussion

In the present Study, we have proved that a-tDCS over the LIFG significantly improved participants' performance in both semantic and phonemic fluency, compared to sham stimulation. Participants produced more words on semantic than on phonological cue, in line with previous evidence (Gollan et al., 2002; Grogan et al., 2009; Novelli et al., 1986), but a-tDCS performance modulation was comparable in the two tasks. The possibility that the results could depend in part on non-specific effects of tDCS over general arousal or attention was ruled out by administering a control experiment, in which performance was not modulated by a-tDCS. Moreover, although some participants may have discriminated between real and sham tDCS, this did not affect performance, as shown by the lack of difference in fluency between real and sham tDCS when the RIFG was stimulated.

Results from this first study support the role of the LIFG in verbal fluency and suggest that Broca's region is a critical candidate for stimulation in rehabilitation protocols aiming at improving language production in aphasic patients.

Verbal fluency tests have been largely used to assess language related and executive control processes in several neural disorders, such as traumatic brain injury (Henry and Crawford, 2004a), autism (e.g., Spek et al., 2009), Alzheimer's disease (Henry et al., 2004), Parkinson's disease (Henry and Crawford, 2004b), Huntington's disease (Henry et al., 2005), depression (Henry and Crawford, 2005), schizophrenia (Costafreda et al, 2011) and attention deficit/hyperactivity disorder (e.g., Hurks et al., 2004). a-tDCS may thus be of critical importance in these disorders. Crucially, a-tDCS over the LIFG can have a positive effect on other aspects of language processing, such as figurative language comprehension (e.g., Yang et al., 2010) or gesture-language interplay (Dick et al., 2009), in which the LIFG seems to play a critical role (Romero Lauro et al., 2008). It is worth noting that the facilitating effects induced by a-tDCS may not entirely depend on stimulation of the LIFG itself but also on spreading activation along the language network of which this region represents a central node (Grodzinsky and Santi, 2008). Indeed, tDCS has been found to affect functional connectivity (Meinzer et al., 2012).

Finally, subjects well tolerated the stimulation protocol, and they did not report adverse effects or asked to interrupt the experiment. This confirms the advantage of tDCS compared to other brain stimulation techniques, such as TMS that had already become an important tool for studying language (Devlin and Watkins, 2007). tDCS also produces fewer artefacts, such as acoustic noise and muscle twitching, and it is more suitable for double-blind, sham-controlled studies and clinical applications.

3 Study 2: Neurophysiological correlates of tDCS-driven enhancement of verbal fluency

3.1 Introduction

As shown in study 1, tDCS proved to be a useful tool in modulating healthy subjects verbal fluency. Why and how this technique is able to modulate performance on cognitive tasks like verbal fluency is still a matter of debate. Previously, a number of tDCS studies investigating performance modulation in different cognitive tasks both in healthy subjects (see Monti et al., 2012; Jacobson et al., 2012; Vallar & Bolognini; 2011 for recent reviews) and in neuropsychological patients (See Holland & Crinion, 2012 for a review) have been outlined. Even if behavioural tDCS-driven modulation has been extensively studied, indeed, the neural mechanisms underlying these changes are still far from being fully understood. As summarized in the introduction (pp. 21-23), on-line effects of stimulation are attributed to neuron membrane polarization (Bindman et al., 1964), while after effects are due to intra-cellular calcium concentration and LTP/LTD – like mechanisms (Nitsche et al., 2003a). To directly investigate how tDCS affects brain activity, some recent studies investigated, by means of TMS-EEG, the impact of tDCS on resting state cortical excitability (Pellicciari et al., 2013; Romero Lauro et al., under review). A First study assessed the effect of a-tDCS and c-tDCS on M1 excitability, measuring TMS evoked potentials (TEPs) before and after 13 min 1mA tDCS (Pellicciari et al., 2013). Results indicate that c-tDCS reduces, while a-tDCS increases, cortical excitability not only in the stimulated area but also in the contralateral one. Moreover, using HD-EEG recording equipment, Romero Lauro and colleagues highlighted a more complex pattern of increment in local mean field power (LMFP, Casarotto et al., 2013), an index of local cortical excitability, after 15 min of a-tDCS

over the right posterior parietal cortex (PPC). The increment was observed in left PPC, right PPC and left prefrontal cortex (PFC). It seems, thus, that tDCS effects spread, through cortical and subcortical pathways, to different brain regions not only affecting the area underneath the electrode. These first two studies, however, tested tDCS effects without combining stimulation with a cognitive task execution, thus preventing the investigation of how cortical excitability modulation may influence behavioural performance. Only a few studies investigated this relationship (Holland et al., 2011; Wirth et al., 2011; Meinzer et al., 2012, 2013). In particular, in an fMRI study, Holland and colleagues (2011) tested a-tDCS effects on brain metabolism after a naming task. Healthy subjects were asked to name pictures in primed or neutral condition during sham or a-tDCS. Independently from the naming condition, stimulation significantly, and selectively, reduced the BOLD signal in the left ventral frontal cortex. The authors speculate that presenting a behavioural task during stimulation might enhance task-specific membranes depolarization, resulting in a reduction of synaptic activity required for task execution. Similarly, Meinzer et al. (2012) found a decrement in BOLD signal in the LIFG after a-tDCS sessions compared to sham ones during a semantic fluency task. Moreover the authors performed a resting state connectivity analysis, which unveiled an increased connectivity between language-related areas, such as the LIFG, the LMFG and left superior frontal gyrus, left PPC, and LSTG.

These preliminary studies investigating the relationship between tDCS and brain metabolism suggest that on-line effects of tDCS may lead to a reduced task-related activity due to neurons membrane depolarization. After effects, instead, seems related to functional network increased connectivity. However, other studies report different results, i.e. an increased activity in the stimulated area both at resting state (measured by means of arterial spin labelling, Zheng et al., 2011) and during simple tasks execution (Antal et al., 2012; Stagg et al., 2009; Jang et al., 2009; Kwon & Jang 2011). A straight

evidence of this relationship deriving from methods that directly test cortical excitability is still lacking. Therefore, in this Study, a TMS-EEG integrated system has been used to investigate the effects of a-tDCS on cortical excitability of functional networks involved in verbal fluency. TMS-EEG, indeed, allows assessing cortical responses to magnetic pulses by recording TEPs, which are a reliable measure of cortical excitability and effective connectivity between areas involved in a particular task execution (for a review see Miniussi & Thut, 2010). The same experimental protocol used in Study 1 was coupled with TMS-EEG recordings before and after tDCS. a-tDCS-induced changes were assessed by eliciting TEPs from an area involved in verbal fluency, functionally connected to the LIFG (the LPMC, BA 6, see Meinzer et al., 2012; Costafreda et al., 2006) and from an area that is not involved in verbal fluency (the LSPL, BA 7). The aim was to verify whether a-tDCS during a cognitive performance modulates cortical excitability, and if these changes are specific to the functional network involved in that given task.

3.2 Materials and methods

Participants

Nine neurologically unimpaired individuals (4 Males, mean age 31.5 years, SD=4.69, range 26-38; all subjects had 18 years of formal education) took part in the experiment. All participants were native Italian graduate students; they were naïve as to the experimental procedure, and the purpose of the study. All subjects were right-handed (mean EHI=0.95; SD= 0.08; range= 0.79 - 1) and with normal or corrected-to-normal vision. As in Study 1 they had no history of chronic or acute neurologic, psychiatric, or medical disease; no family history of epilepsy; no current pregnancy; no cardiac pacemaker; no previous surgery involving implants to the head (cochlear implants, aneurysm clips, brain electrodes); and did not take acute or chronic medication. Written

informed consent was obtained from all participants. Each subject underwent three different experimental session, labelled from here on as “real frontal”, “real parietal” and “sham” sessions (see Fig. 3.1). The local ethical committee of the University of Milano-Bicocca approved the experiment and subjects were treated in accordance with the Declaration of Helsinki.

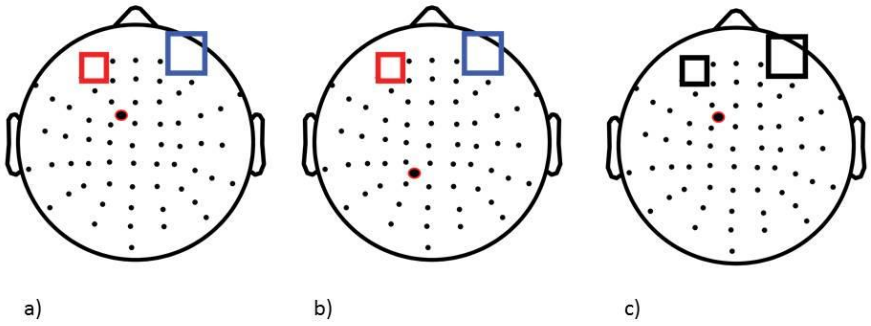


Fig. 3.1: Stimulation protocols of a) Real frontal: a-tDCS over the LIFG and TMS over BA6 b) Real parietal: a-tDCS over the LIFG and TMS over BA7 and c) Sham sessions: no tDCS and TMS over BA6. The red dot represents TMS hotspot, the red square the anode and the blue square the cathode. Black squares represent inert electrodes in sham tDCS montage.

tDCS

As in study 1, tDCS was delivered by a battery driven, constant current stimulator (Eldith, Neuroconn, Ilmenau, Germany) through a pair of electrodes fixed to the head by a conductive paste (Ten20, Kappamedical, USA). The anode (16 cm^2) was placed over the LIFG, while the cathode (25 cm^2) was placed over the right supraorbital region. Differently sized electrodes were used to increase the focality of stimulation (Nitsche et al., 2008). The LIFG was localized on the individual structural MRI of the subject through the integrated neuro-navigation system of the TMS EEG instrument (Eximia

Nexstim, Helsinki, Finland). The electrodes montage was slightly modified as compared to Study 1 in order to be applied concurrently with EEG recordings. Indeed, tDCS electrodes were placed under the EEG cap after the first TMS-EEG recording and removed before the second one. During real frontal and real parietal sessions, stimulation intensity was set at .75 mA resulting in a current density of .47 A/m^2 and charge density of 562 C/m2 for the anode and a density of .3 A/m^2 and charge density of 360 C/m^2 for the cathode; the duration of stimulation was 20 min. For Sham stimulation, the electrodes were placed in the same positions as real tDCS, but the duration was set at 30s. A fade in / fade out period (30s) was programmed at the beginning and at the end of both real and sham stimulation.

TMS – EEG

TMS protocol

In each session two different TMS recordings were performed, before and after a-tDCS. TMS was delivered by means of an Eximia TMS stimulator (Nextim, Helsinki, Finland) using a focal bi-pulse, figure of eight 70-mm coil. TMS targets were localized in each subject using a Navigated Brain Stimulation system (Nextim, Helsinki, Finland) that uses infrared-based frameless stereotaxy (Polaris Spectra) to map the position of the coil and the subject's head within the reference space of the individual's high resolution MRI space. In sham and real frontal sessions the coil was positioned near F1 and FC1 electrodes, targeting the LPMC (BA 6, MNI coordinates: x -16, y 4, z 68; Fig. 3.2. Other imaging studies report similar coordinates for BA6: Kircher et al., 2011; Costafreda et al., 2006; Meinzer et al., 2013). This area was chosen as TMS hotspot according to previous studies in which a greater activation of BA6 was reported for verbal fluency with respect to word repetition (Meinzer et al., 2012). The TMS hotspot (for sham and real frontal sessions) was selected in a pilot session as the site in BA6

where stimulation induced TEPs without muscular artefacts. Few subjects presented muscular artefacts that prevented reliable TEPs recording. For these subjects the coil was moved around the hotspot until no muscular artefacts were present.

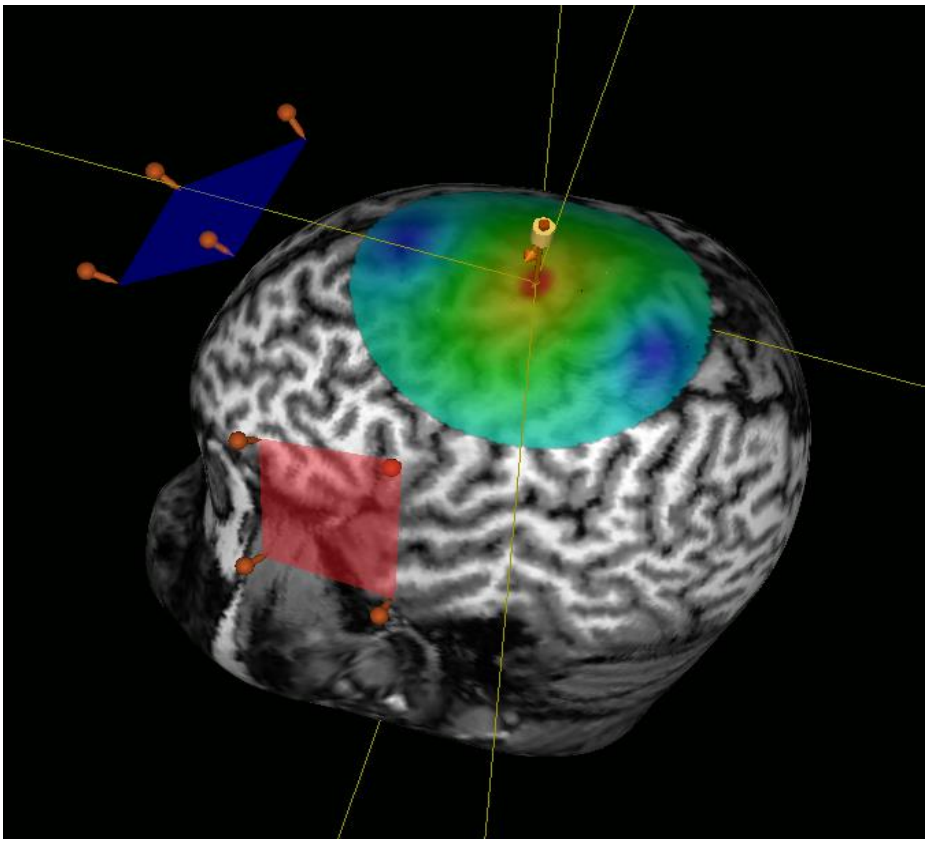


Fig. 3.2: BA6 TMS target with estimated electrical field. The red square represents the tDCS anode, the blue square the cathode.

In real parietal sessions, the TMS target was set over the left superior parietal lobule (BA 7, MNI coordinates: x -34, y -74, z 50; Fig. 3.3), an area not involved in the functional network for verbal fluency.

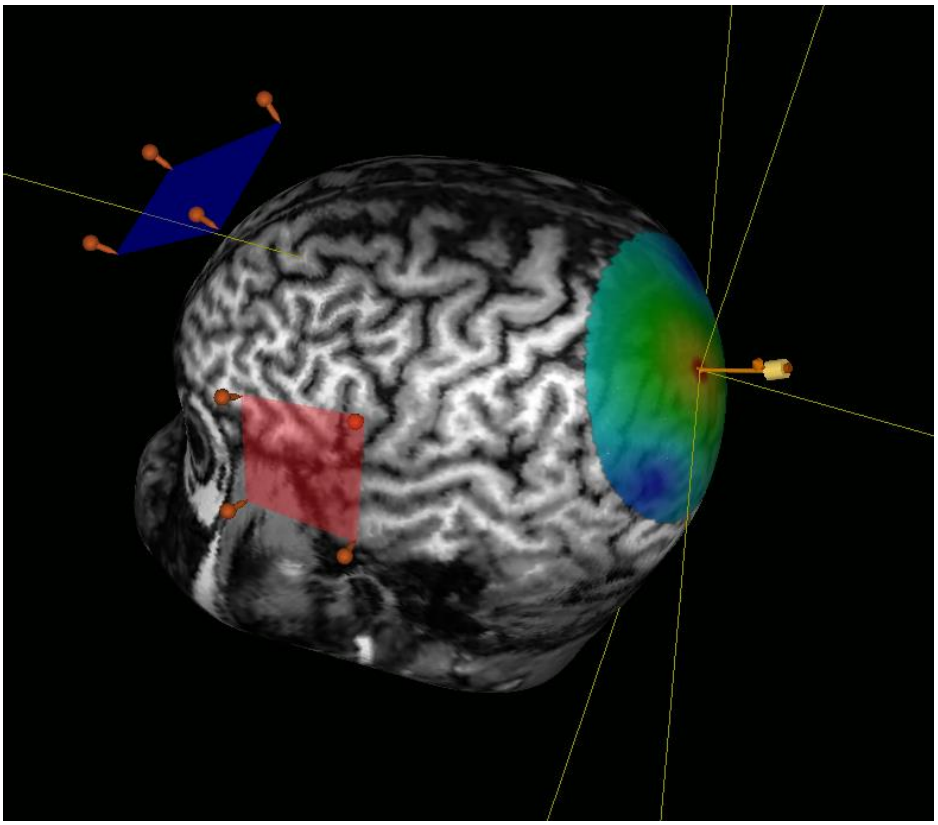


Fig. 3.3: BA7 TMS target with estimated electrical field. The red square represents the tDCS anode, the blue square the cathode.

TMS intensity was delivered at 63% of the maximum stimulator output (SD 6.25; range 50-70%), eliciting a mean electrical field at the TMS hotspot of 98 V/m (SD 12.02; range 75-120 V/m), as estimated by the navigated brain stimulation system. Critically, Wilcoxon non-parametric tests showed no difference in these two parameters between pre and post recordings within the three experimental sessions and between sessions (all ps>.34). Noise masking was obtained playing an audio file (composed by TMS click frequency components) through earplugs worn by participants, in order to avoid auditory evoked potentials triggered by TMS click (Massimini et al., 2005; Rosanova et al., 2009).

EEG recording and analysis

The TMS EEG system recorded a 60-channel EEG through a TMS compatible amplifier (Nextim; Helsinki, Finland). This makes use of a sample-and-hold system: EEG is interrupted and kept constant in a time window ranging from 100 μs pre- to 2ms post-TMS pulse in order to avoid amplifier saturation (Virtanen et al., 1999). Ground was recorded from two electrodes positioned over the frontal sinuses, while two additional electrodes, placed in the upper left corner of the left and the bottom right corner of the right eyes, recorded eye movements. EEG recording electrodes were average referenced, impedance was kept below 5 kΩ and data were acquired at a rate of 1450 Hz. Pre-processing was performed with SSP Biomedical Data Analysis Package, Version 1.7e (SiSyPhus Software, 2013) running in Matlab R2012a (Mathworks, Natick, MA, USA), a software specially designed to handle Eximia Nexstim TMS triggered EEG recordings. After data down-sampling at 725 Hz, a semi-automatic trial rejection was performed, excluding noisy trials and trials where eye movements could not be filtered out with a manual PCA. The continuous signal was then split in single trials using a time-window of 1600ms (800ms pre- and post TMS pulse) and data were band pass filtered between 2 and 80Hz, with a notch filter at 50Hz. Each trial was then re-referenced to the baseline signal (between -300 and -50ms pre TMS pulse). Global mean field power (GMFP; Massimini et al., 2005; Casarotto et al., 2013) and LMFP (Casarotto et al., 2013) were computed. While GMFP was computed for all 60 electrodes, LMFP was computed for seven different electrode clusters, defined on the basis of their anatomical position. More specifically, the first one included the two electrodes directly interested by the a-tDCS stimulated site, namely the LIFG (Cluster 1, electrodes F5-F7). Cluster 2 included the electrodes above the frontal TMS hotspot (BA6), therefore under the TMS coil (electrodes F1-FC1). Clusters 3, 4 and 5 were considered as control frontal clusters: they included electrodes near the TMS coil but

not over the stimulated area (Cluster 3, electrodes Fz-FCz), electrodes mirroring Cluster 2 (Cluster 4, electrodes F2-FC2) and 1 (Cluster 5, electrodes F6-F8). Finally, two parietal clusters were analysed: Cluster 6, including the electrodes over the parietal TMS hotspot (CP1-P1) and its contralateral homologue (Cluster 7, electrodes CP2-P2)(See Fig. 3.4). Channels presenting an excessively noisy recording were interpolated by means of a spherical spline interpolation (Perrin et al., 1989). TMS-related residual muscular or magnetic artefacts were then removed using an independent component analysis (ICA, Korhonen et al., 2011; Johnson et al., 2012) when necessary. GMFP and LMFP were computed for the whole considered TEP duration (0-150ms) and for three time windows, identified in order to separately analyse early and late TEPs components: 0-30ms; 30-65ms and 65-150ms. These temporal windows were selected on the basis of the time course of the average TEP across all subjects. To evaluate a-tDCS induced modulation of cortical excitability, the increase of cortical excitability was computed as the percentage of post-tDCS GMFP and LMFP excitability compared to the pre-tDCS excitability.

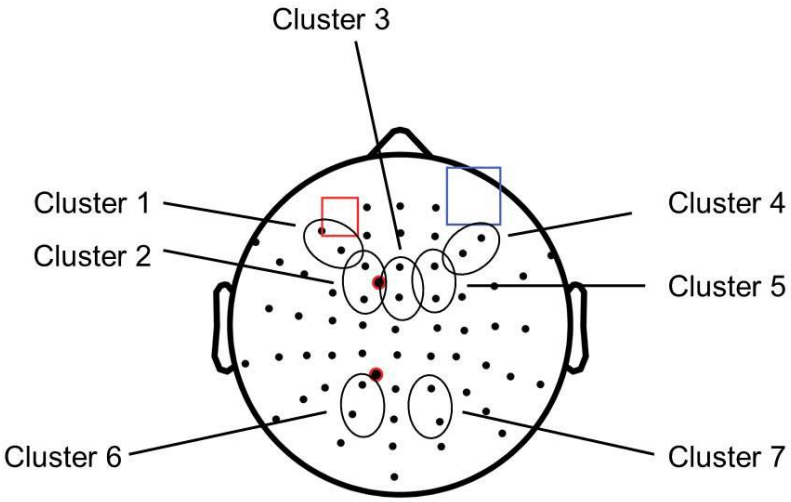


Fig. 3.4: LMFP electrodes clusters.

Verbal fluency

Verbal Fluency on phonemic and semantic cue was administered as in Study 1. The task was minimally modified. In particular, phonemic fluency was cued by letters 'P', 'F', 'L', 'G', 'C' and 'D'. Semantic (categorical) fluency was instead cued by three living and three non-living categories: 'Fruits', 'Vegetables', 'Animals', 'Tools', 'Clothing' and 'Vehicles'.

In each session participants had to perform the fluency task with 2 semantic and 2 phonemic cues. Letters were presented in fixed pairs ('P' and 'G', 'D' and 'L', 'F' and 'C') according to the relative frequency of names beginning with each pair of letters, as derived from the Corpus and Frequency Lexicon of Written Italian (COLFIS, see http://www.istc.cnr.it/material/database/colfis/index_eng.shtml). Category pairs were 'Clothing' and 'Vegetables', 'Animals' and 'Tools', and 'Vehicles' and 'Fruits'. As for letters, they were matched according to a pilot study performed on 10 healthy subjects in order to have (i) a similar number of words produced per each category pair (see Table 3.1) and (ii) a living and a non-living category in each session. Letters and categories pairs were balanced across sessions and stimulation condition, in order to have subjects performing the fluency task with different letters and categories in each experimental session.

	Animals	**Fruits**	**Vegetables**	**Tools**	**Clothing**	**Vehicles**
Mean fluency	24.37	18.12	16.5	10	18.75	15.37
SD	5.55	2.69	3.96	3.62	3.77	3.07

Table 3.1: Mean semantic fluency scores as assessed in the pilot study.

Procedure

At the beginning of each session the EEG impedance on each electrode was reduced to be < 5 kΩ. The optimal stimulation site was localized (i.e. the best coil orientation and inclination on the hotspot that did not elicit magnetic or muscular artefact in the EEG traces) and the baseline TMS EEG session was recorded. Immediately after the end of the baseline recording, the tDCS electrodes were applied and stimulation started. After 14 min of stimulation, the fluency tasks were administered (two on phonemic and two on semantic cue). As soon as tDCS ended, impedances of the EEG channels disturbed by the application of tDCS patches were adjusted to be < 5 kΩ (approx. 3min) and the post-tDCS TMS EEG recording started.

Analysis

Behavioural measures

Performance on the fluency task was analysed by means of a mixed effect model on mean number of words produced with session (3 levels: real frontal, real parietal, sham) and type of fluency (2 levels: semantic vs. phonemic) as fix factors, and subject intercept as random factor. Moreover the a-tDCS induced modulation on fluency performance was calculated for each subject as the percentage between real stimulation sessions (frontal and parietal, separately) and sham ones as follows:

$$\text{index of } x \text{ improvement} = (x\text{Real}/x\text{Sham})*100$$

Where *x* is the phonemic, semantic and global fluency performance.

TEPs

A mixed effect model was run on GMFP and LMFP modulation in each time window (T1: 0-30ms; T2: 30-65ms; T3: 65-150ms) with session (3 levels: Real frontal, Real parietal, Sham) as fix factor, and subject intercept as random factor. In analogy with

verbal fluency, a-tDCS induced modulation on cortical excitability was calculated for each subject as the percentage between real stimulation sessions (frontal and parietal, separately) and sham ones as follows

$$\text{index of } x \text{ increment} = (x\text{Real}/x\text{Sham})*100$$

Where *x* is the GMFP and LMFP for each time window.

3.3 Results

Bonferroni correction was applied to all post-hoc analyses.

The mixed model run on mean words produced in verbal fluency highlighted a significant main effect of session [F(2,40)= 6.17; p=.005], due to the lower number of items produced in sham sessions (mean= 29.89) as compared to real frontal (mean= 37.22, p=.007) and real parietal ones (mean= 36.11, p=.026), while there was no difference between the two real a-tDSC sessions (p=1; Fig. 3.5). The main effect of fluency type [F(1,40)= 4.74; p=.035] was also significant: subjects produced less words on phonemic (32.4) than on semantic cue (36.4).

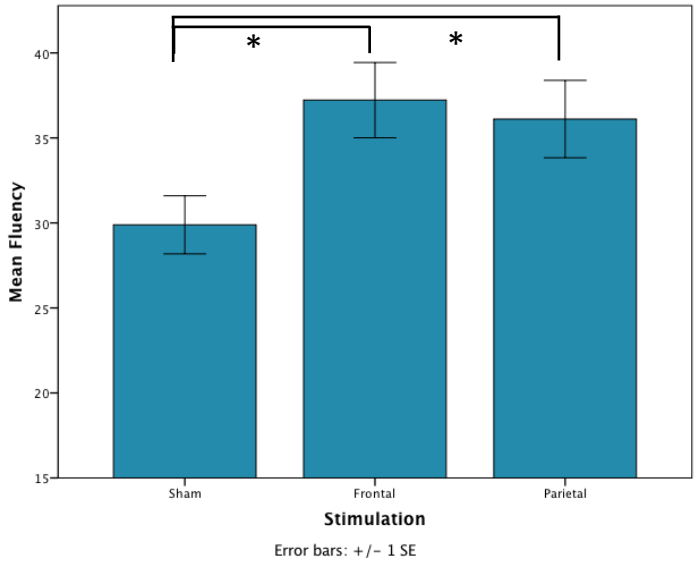


Fig. 3.5: Mean fluency scores in the three experimental sessions.

The mixed models run on the different time windows of the GMFP showed no effect of stimulation in any time window (T1: F(2,16):.95, p=.41; T2: F(2,16):1.21, p=.32; T3: F(2,16):1.25, p=.31).

The same model was run on each LMFP cluster. Results are reported in Table 3.2. a-TDCS significantly modulated cortical excitability in Cluster 2 for T3 time window (65-150ms [F(2,16)=5.21, p=.018], being LMFP increased after real frontal sessions (117.8%) compared to both sham (87.46%, p=.04) and real parietal ones (87.06%, p=.037; see Fig. 3.6).

	Time window	F(2,16)	p
Cluster 1	T1	.42	.66
	T2	2.04	.16
	T3	1.20	.33
Cluster 2	T1	.23	.79
	T2	.39	.68
	T3	**5.21**	**.018**
Cluster 3	T1	.16	.85
	T2	1.19	.33
	T3	3.05	.08
Cluster 4	T1	.24	.79
	T2	1.48	.26
	T3	.89	.43
Cluster 5	T1	1.40	.27
	T2	2.99	.08
	T3	.18	.83
Cluster 6	T1	.55	.58
	T2	1	.39
	T3	1.32	.29
Cluster 7	T1	1.32	.29
	T2	1.58	.23
	T3	.64	.54

Table 3.2: Results of the mixed models run on LMFP for the different time windows and clusters.

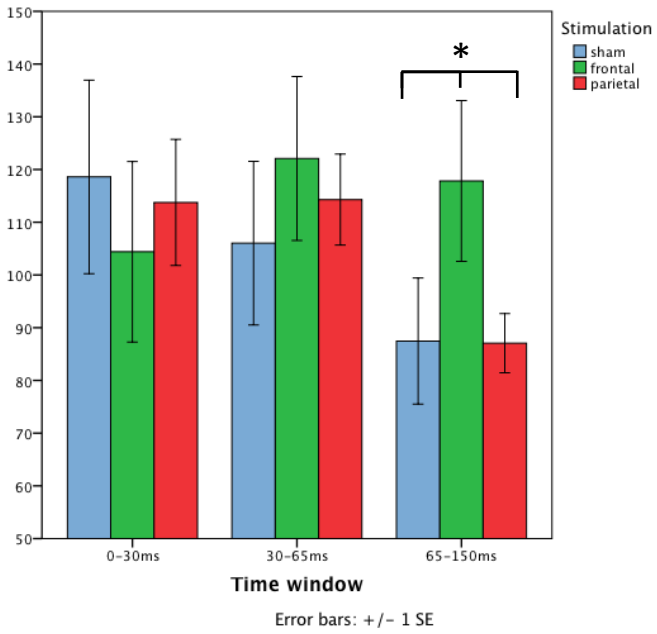


Fig. 3.6: LMFP for the considered time windows in Cluster 2.

Frontal sessions			Parietal sessions		
General Fluency index	Phonemic Fluency index	Semantic Fluency index	General Fluency index	Phonemic Fluency index	Semantic Fluency index
126,14	**130,01**	**125,73**	**121,25**	**128,63**	**120,50**
23,6	38,3	26,8	15,4	26,5	40,9

	Frontal sessions			Parietal sessions		
	T1 index	T2 index	T3 index	T1 index	T2 index	T3 index
Cluster 1	**108,60**	**110,42**	**160,76**	**146,12**	**171,36**	**157,32**
	58,22	63,61	86,18	119,06	130,03	83,94
Cluster 2	**95,16**	**141,24**	**138,38**	**112,18**	**129,69**	**108,94**
	46,31	84,63	35,14	53,09	67,89	36,32
Cluster 3	**106,37**	**150,55**	**121,74**	**115,16**	**139,33**	**96,04**
	50,72	86,45	41,92	67,70	122,26	35,16
Cluster 4	**150,32**	**174,09**	**96,62**	**110,01**	**148,56**	**95,71**
	174,62	139,72	25,41	81,01	203,46	39,62
Cluster 5	**164,90**	**251,91**	**119,44**	**151,96**	**235,04**	**115,62**
	116,44	272,54	43,47	74,51	240,65	56,10
Cluster 6	**130,02**	**160,53**	**169,31**	**128,96**	**172,26**	**141,53**
	74,93	126,18	115,28	45,46	172,78	69,02
Cluster 7	**182,67**	**218,31**	**124,83**	**282,57**	**124,79**	**115,95**
	158,03	270,12	52,79	362,48	78,14	45,06
GMFP	**112,29**	**129,75**	**118,94**	**122,39**	**129,99**	**112,17**
	29,43	53,52	24,41	33,60	71,13	44,81

Table 3.3: Mean improvement indexes (in bold) and SD (in light) for the behavioural and neurophysiological measures.

Mean improvement values and SD for each index in real frontal and real parietal sessions are reported in Table 3.3.

Correlation coefficients between the behavioural improvement indexes (general fluency, phonemic fluency and semantic fluency) and the neurophysiological modulation indexes (T1, T2, T3 both for GMFP and LMFP) are reported in Table 3.4 and 3.5. In Cluster 1, for T1 a-TDCS modulation index positively correlated with both general fluency improvement index (r= .833, p=.005) and phonemic fluency improvement index (r= 817, p= .007), with greater improvements in the behavioural indexes related to a greater increment in cortical excitability for real frontal sessions only (see Fig. 3.7 and 3.8). No other correlation reached significance.

		T1	T2	T3
Cluster 1	General fluency index	**.833 (p=.005)**	.067 (p=.86)	-.25 (p=.52)
	Phonemic fluency index	**.817 (p=.007)**	.000 (p=.1)	-.367 (p=.33)
	Semantic fluency index	.567 (p=.11)	-.083 (p=.83)	0.83 (p=.83)
Cluster 2	General fluency index	.183 (p=.64)	-.217 (p=.58)	-.283 (p=.46)
	Phonemic fluency index	.35 (p=..36)	-.067 (p=.86)	-.533 (p=.14)
	Semantic fluency index	.083 (p=.83)	-.25 (p=.52)	.20 (p=.61)
Cluster 3	General fluency index	-.15 (p=.7)	-.233 (p=.55)	-.55 (p=.12)
	Phonemic fluency index	.333 (p=.38)	-.017 (p=.97)	-.65 (p=.06)
	Semantic fluency index	-.483 (p=.19)	-.40 (p=.29)	-.083 (p=.83)
Cluster 4	General fluency index	-.083 (p=.83)	.15 (p=.7)	-067 (p=..86)
	Phonemic fluency index	.267 (p=.49)	.12 (p=.76)	-.20 (p=.61)
	Semantic fluency index	-.43 (p=.24)	-.50 (p=.17)	.42 (p=.26)
Cluster 5	General fluency index	-.083 (p=.83)	-.367 (p=.33)	.067 (p=.86)
	Phonemic fluency index	.00 (p=1)	-.167 (p=.64)	-.183 (p=.64)
	Semantic fluency index	-.267 (p=.49)	-.517 (p=.15)	.333 (p=.38)
Cluster 6	General fluency index	.20 (p=.6)	-.20 (p=.6)	-.05 (p=.9)
	Phonemic fluency index	.22 (p=.58)	-.15 (p=.7)	-.13 (p=.73)
	Semantic fluency index	-.12 (p=.76)	-.27 (p=.49)	-.10 (p=.8)
Cluster 7	General fluency index	.18 (p=.64)	.47 (p=.2)	.00 (p=.1)
	Phonemic fluency index	.13 (p=.73)	.65 (p=.06)	.17 (p=..67)
	Semantic fluency index	.10 (p=.8)	-.067 (p=.86)	-.067 (p=.8)

Table 3.4: Spearman correlation between behavioural improvement and cortical excitability enhancement indexed for frontal sessions for each cluster and time-window.

		T1	T2	T3
Cluster 1	General fluency index	.317 (p=.41)	-.233 (p=.55)	-.183 (p=.64)
	Phonemic fluency index	.033 (p=.93)	.183 (p=.64)	-.55 (p=.12)
	Semantic fluency index	.30 (p=.43)	-.133 (p=.73)	.167 (p=.67)
Cluster 2	General fluency index	.567 (p=.11)	-.083 (p=.83)	-.017 (p=.97)
	Phonemic fluency index	.083 (p=.83)	.383 (p=.31)	-.433 (p=.24)
	Semantic fluency index	.267 (p=.49)	-.083 (p=.83)	.25 (p=.52)
Cluster 3	General fluency index	-.10 (p=.8)	-.10 (p=.8)	-.217 (p=.58)
	Phonemic fluency index	.417 (p=.26)	.533 (p=.14)	-.517 (p=.15)
	Semantic fluency index	-.333 (p=.38)	-.25 (p=.52)	.20 (p=.61)
Cluster 4	General fluency index	.167 (p=.67)	-.333 (p=.38)	-.233 (p=.55)
	Phonemic fluency index	.133 (p=.73)	.55 (p=.12)	-.533 (p=.14)
	Semantic fluency index	.10 (p=.8)	-.40 (p=.27)	.22 (p=.58)
Cluster 5	General fluency index	-.35 (p=.36)	-.57 (p=.11)	-.117 (p=.76)
	Phonemic fluency index	.25 (p=.52)	.15 (p=.7)	-167 (p=.67)
	Semantic fluency index	-.233 (p=.55)	-.45 (p=.22)	.10 (p=.8)
Cluster 6	General fluency index	-.067 (p=.86)	-.40 (p=.29)	.25 (p=.52)
	Phonemic fluency index	-.267 (p=.49)	.067 (p=.86)	-.35 (p=.36)
	Semantic fluency index	.20 (p=.61)	-.167 (p=.67)	.483 (p=.19)
Cluster 7	General fluency index	.15 (p=.7)	.117 (p=.76)	.033 (p=.93)
	Phonemic fluency index	-.017 (p=.97)	.383 (p=.31)	.017 (p=.97)
	Semantic fluency index	.00 (p=1)	.017 (p=.97)	.067 (p=.86)

Table 3.5: Spearman correlation between behavioural improvement and cortical excitability enhancement indexed for parietal sessions for each cluster and time-window.

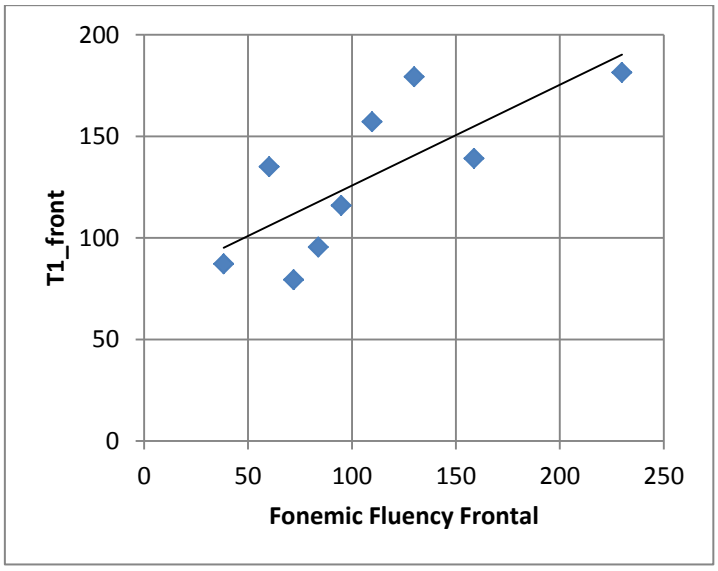


Fig. 3.7: Correlation between improvement index for phonemic fluency in frontal sessions and T1 increment in cortical excitability for Cluster 1.

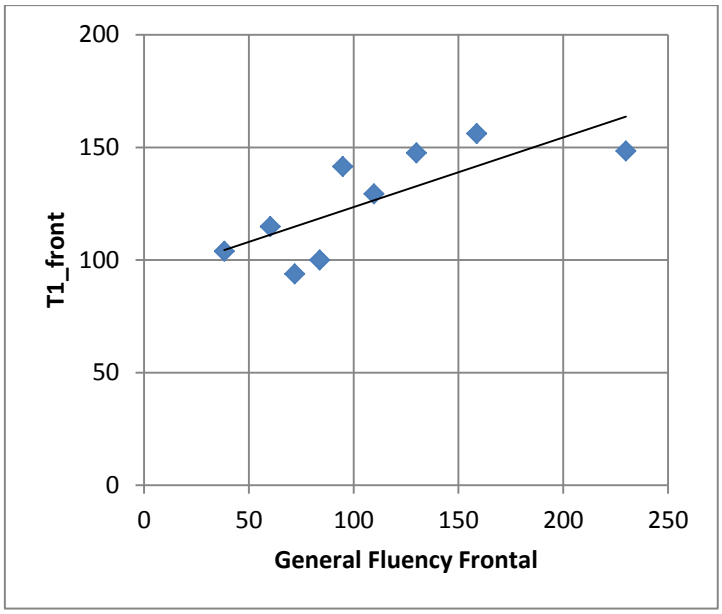


Fig. 3.8: Correlation between improvement index for general fluency in frontal sessions and T1 increase of cortical excitability for Cluster 1.

3.4 Discussion

Recently, fMRI studies highlighted that a-tDCS reduced cortical metabolism in task-relevant areas when a-tDCS was delivered during the execution of a language task (Holland et al., 2011; Meinzer et al., 2012, 2013). However, it has been also reported that a-tDCS induces greater activity in the cortical and subcortical areas under the electrodes, both during resting states (measured by means of arterial spin labeling, Zheng et al., 2011, and connectivity, Keeser et al., 2011; Penya Gomez et al., 2012) and during task execution (Antal et al., 2012; Stagg et al., 2009; Jang et al., 2009; Kwon & Jang 2011), thus leaving open other possible interpretations for the decrease in the BOLD signal due to a-tDCS, such as fMRI detecting an enhanced late undershoot of metabolic response (Logothetis & Wandell, 2004; Buxton et al. 1998). Moreover, the BOLD signal does not measure cortical excitability per se (Logothetis & Wandell, 2004), which is the aspect of neural functional activity that seems to be modulated by tDCS. In this study, the aim was to directly measure how a-tDCS modulates task

performance and cortical excitability by using a TMS-EEG system. TMS-EEG recordings were acquired before and after real and sham a-tDCS over the LIFG while subjects completed a verbal fluency task. TEPs were recorded stimulating BA6, a region involved in verbal fluency (see Meinzer et al., 2012) and BA7, not involved in this task. The present results indicate that verbal fluency was modulated by a-tDCS, thus replicating Study 1. At a neurophysiological level, while global excitability was not affected by a-tDCS, LMFP increased over BA6 in a late time-window, compared to sham and parietal sessions, while no difference was found between sham and parietal stimulation conditions. Moreover, the increase in cortical excitability detected under the electrodes close to the anode (Cluster 1) in an early time-window significantly correlated with the behavioural improvement in general and phonemic fluency only for real frontal sessions.

The significant increase in LMFP at BA6, when this measure was recorded after stimulation of this area, points to a specific effect of a-tDCS in enhancing cortical excitability during verbal fluency. Crucially, this enhancement is detectable in an area relevant for the task (BA6), but not in an unrelated area (BA7). The comparison between these two areas is critical since both were targeted by TMS to record TEPs, but at BA7 there were no differences in LMFP increase in parietal sessions as compared to sham ones. This increase in cortical excitability over BA6 has been found for a late component of LMFP, namely from 65ms to 150ms post TMS onset. This effect has been associated to the excitability of the functional network, which includes the target area, rather than excitability of the underlying cortical area per se (Ilmoniemi & Kicic, 2010; Pellicciari et al., 2013; Veniero et al., 2013). The present results might then reflect an enhanced functional connection between the LIFG and BA6, as found by Meinzer et al. (2012), ending in an improved verbal fluency.

As far as the relation between a-tDCS modulation on verbal fluency and increased cortical excitability is concerned, a positive correlation was found between early components of LMFP over the LIFG (the a-tDCS target area) and general performance and phonemic fluency improvement, but only when TEPs were recorded stimulating BA6. This result may reflect a direct relationship between a-tDCS neurophysiological enhancement of the targeted region and the behavioural outcome. Early TEPs components have indeed been linked to excitability of regions underlying the electrodes (Ilmoniemi & Kicic, 2010, Pellicciari et al., 2013), thus directely linking LIFG excitability increase to task performance improvement. The variability among subjects in the early TEP component, 0-30ms, in Cluster 1 may explain why no difference was found in this time window in sham and frontal sessions concerning LMFP increase. Nonetheless, this measure seems to highly correlate with the fluency improvement, suggesting that the behavioural modulation may be due to the increased excitability in the LIFG. Semantic fluency index did not correlate with cortical excitability increment, probably reflecting the difference in neural correlates between phonemic and semantic fluency (e.g. Birn et al., 2010).

In conclusion, these data are the first direct evidence suggesting that, if delivered during a task execution, a-tDCS increases cortical excitability in task-related regions. Moreover, the increased cortical excitability is related to behavioural improvement, supporting the hypothesis that a-tDCS modulates performance by enhancing cortical excitability in directly stimulated areas, as well as in those functionally connected.

4 Study 3: tDCS and the semantic interference effect. New evidence of LIFG and STG role in picture naming.

4.1 Introduction

tDCS modulates language performance, both at a behavioural and physiological level (as demonstrated in Study 1 and 2). A further and interesting issue is, thus, to understand whether more fine-grained aspects of language processing can be investigated by means of this technique. The low spatial resolution of tDCS, indeed, does not allow, as for TMS, to stimulate restricted sites. Focus must then be shifted to task design, in order to isolate specific sub-steps of the cognitive function under investigation and test whether stimulation affects performance or not. In this and in the next study I will focus on picture naming, namely on lexical and phonological selection mechanisms.

As previously described, naming a picture is a complex task involving a number of different processes. In particular, lexical retrieval, the process of selecting a lemma among competitors (lemma is referred to a holistic lexical representation, not associated with phonological or orthographic properties of the word but rather to its grammatical and syntactical information, see Levelt et al., 1998) is semantically based: manipulating the semantic context in which it is performed, affects naming latencies (SI effect; e.g., Schriefers, et al., 1990; Belke, et al., 2005; Costa et al., 2005; Moss et al., 2005; Schnur and Martin, 2012; Vitkovitch and Cooper, 2012). When participants are asked to repeatedly name a series of pictures shown in semantically related or unrelated sets (the so-called "blocked naming paradigm"), naming RTs are longer for pictures presented in semantically homogeneous lists than in semantically unrelated ones (Damian et al., 2001; Belke et al., 2005; Schnur et al., 2006; Abdel Rahman and Melinger, 2011, Ganushchak and Schiller, 2008). Similarly, aphasic patients produce more naming

errors when pictures are presented in semantically related than unrelated contexts (McCarthy and Kartsounis, 2000; Wilshire and McCarthy, 2002; Schnur et al., 2009).

Even if this effect is well known and documented, it is still unclear why it occurs, at which stage of lexical retrieval (e.g., at a pre-lexical, lexical, or post-lexical stage of processing), and which anatomical structures are involved. Some studies proposed that the SI effect might depend on either excitatory or inhibitory processes (see Schnur et al., 2006), both related to word production models (e.g., Roelofs, 1992, 1997; Levelt, 1999), according to which conceptual nodes are linked depending on their semantic relatedness. According to these models, concepts are hierarchically organized, from a more general attribute (category, e.g., "Animals") to more specific features (specific word, e.g., "Horse"). Within this framework, the excitatory explanation of the SI effect (Belke et al., 2005; see also Forde and Humphreys, 1997) implies that naming objects in a homogeneous semantic context produces an over-activation state (Forde and Humphreys, 1997) of the items in the same semantic category, increasing the competition between the target and its category-coordinates. For example, naming subsequent animal pictures increases the activation in the semantic node representing the "animal" category and in the lexical concepts representing its exemplars, resulting in an increased competition among the latter. Alternatively, the SI effect may depend on an increased inhibition, namely on the temporary spread of down activation between the representation of a just-named item and its related semantic coordinates. According to this hypothesis, in a normal, fluent production, lemmas should be activated and rapidly de-activated in order to generate several lexical outputs and to allow processing of subsequent words (Dell, 1986). Therefore after its selection, the target lemma might be briefly inhibited, ending in a spread of this inhibition to adjacent semantic nodes and

then generating longer naming latencies if naming of a semantically related target is required.

While these inhibitory and excitatory accounts identify the cause of the interference in mechanisms intrinsic to the mental lexicon representation the cause of the SI, others (mainly on the basis of aphasic patients' data) have proposed that the interference is due to the sub-optimal functioning in highly demanding situations of a general "executive selection" mechanism (see Robinson et al., 1998; Wilshire and McCarthy, 2002). This mechanism, thought to be part of the complex executive system, is supposed to be involved in both linguistic and non-linguistic selection processes in highly demanding contexts (Kan and Thompson-Schill, 2004a, 2004b; Moss et al., 2005). According to this hypothesis, frontal patients can exhibit naming difficulties in semantically related contexts due to a deficit in this selection mechanism, rather than to a problem involving lexical-semantic components of object naming.

Several neuroimaging and neuropsychological studies indicate the left temporal lobe as the neural substrate of SI. This area, indeed, plays an important role in semantically driven lexical retrieval (e.g., Mummery et al., 1996; Friedman et al., 1998; Moore and Price, 1999; Bell et al., 2001; de Zubicaray et al., 2001; Glosser and Donofrio, 2001; Antonucci et al., 2008), while converging evidence suggests that the involvement of the LIFG in lexical-semantic selection (Devlin et al., 2003; Moss et al., 2005; Hirshorn and Thompson-Schill, 2006; Schnur et al., 2006, 2009; Oztekin et al., 2009) possibly reflects demanding selection processes and/or detection of response conflicts.

In order to shed light on the cortical areas and functional mechanisms involved in the SI effect, a-tDCS was applied over the LSTG and the LIFG during a semantic blocked paradigm. In study 1 and 2, it has been demonstrated that a-tDCS applied over the LIFG improves both phonemic and semantic fluency. In a combined tDCS and EEG study,

Wirth et al. (2011) showed that a-tDCS applied over the LDLPFC (left dorsolateral prefrontal cortex) reduced the SI in a semantic blocked naming paradigm, likely due to an increase of prefrontal inhibitory functions.

If the SI effect in a semantic blocked naming paradigm depends on an exaggerated excitation of the semantic network, then a-tDCS over the LSTG, by enhancing the activation and hence the competition between category exemplars (and possibly interfering with subsequent inhibition of named items, see Dell, 1986), should increase SI. Moreover, if the SI effect depends on harder selection mechanisms tapping on executive functions, then enhancing activation of prefrontal regions by applying a-tDCS over the LIFG should reduce the SI effect.

4.2 Experiment 1

4.2.1 Materials and Methods

Participants

Twelve healthy subjects (2 males, mean age= 22.4 years, SD= 2.94; mean education= 14.7 years, SD=2.1) took part in the first experiment. Twenty-eight different healthy participants (6 males, mean age= 21.9 years, SD==2.4; mean education= 14.6 years, SD= 1.7) were tested in a pilot study, preceding the tDCS experiment, to ensure that the selected paradigm and stimuli were producing a consistent SI effect. All participants were right-handed Italian undergraduate students, naïve as to the experimental procedure and the purpose of the study. Handedness was assessed by means of the Edinburgh Inventory Questionnaire (Oldfield, 1971). All participants had normal or corrected-to-normal vision. The same criteria of exclusion as in the previous study were followed, as well as ethical procedures.

The Semantic blocked naming task

The same task was administered in the pilot and in the tDCS experiment. Stimuli were 36 pictures taken from the Viggiano et al. (2004)'s inventory, a standardised set of ecological pictures for experimental and clinical research on object processing. A further object, namely "train", was added to the category "vehicles" given its high familiarity, matched for within-category visual similarity (see Table 4.1 for familiarity and visual complexity values taken from Viggiano et al. (2004) and frequency index from the COLFIS). The selected pictures belonged to six different semantic categories (six pictures for each category): animals, clothing, furniture, kitchen utensils, fruits and vehicles. Twelve sets were created (see Table 4.2): half were "homogenous" sets in which items belonged to the same semantic category (e.g., animals: elephant, lion, dog, cat, mouse, zebra), half were "mixed" including an item (different for each mixed set) of each of the six different categories (e.g., Fork, Hat, Mouse, Lemon, Armchair, Train). The 12 sets were balanced for familiarity [$F(11,58)= 1.37$, $p=.21$], frequency [$F(11,60)= 1.05$, $p=.41$], and word length [number of syllables: $F(11,60)=1.32$, $p=.24$; number of letters: $F(11,60)= 1.80$, $p=.07$]. The sets differed for visual complexity [$F(11,58)= 2.92$, $p=.004$], due to the vehicles homogeneous set containing significantly more complex pictures compared to other homogeneous sets (clothing, $p=.02$, kitchen utensils, $p<.01$, and fruits, $p=.046$) and to one mixed set (referred as "Mixed set 2" in Appendix B, $p=.04$) (Bonferroni correction applied).

Category	Item (Italian/English)	Familiarity (SD)	Visual complexity (SD)	Frequency
Clothing	Calza/Sock	4.32 (0.89)	1.77 (0.77)	32
	Cappello/Hat	3.05 (1.03)	2.29 (0.91)	112
	Cravatta/Tie	3.68 (0.97)	3.13 (0.92)	48
	Pantaloni/Trousers	4.30 (0.94)	2.21 (0.84)	127
	Scarpa/Shoe	4.37 (0.85)	2.84 (1.01)	195
	Stivale/Boot	3.56 (0.91)	2.20 (0.75)	44
Animals	Topo/Mouse	3.12 (1.15)	3.24 (1.06)	69
	Cane/Dog	4.20 (0.84)	3.41 (1.05)	328
	Gatto/Cat	4.21 (0.80)	3.40 (0.82)	169
	Leone/Lion	2.99 (1.07)	3.53 (0.87)	78
	Elefante/Elephant	2.17 (1.00)	2.55 (0.94)	60
	Zebra/Zebra	2.07 (1.07)	3.76 (0.96)	1
Kitchen tools	Coltello/Knife	3.84 (1.29)	1.59 (0.76)	117
	Cucchiaio/Spoon	4.55 (0.86)	1.59 (0.68)	197
	Forchetta/Fork	4.41 (0.94)	2.08 (0.85)	25
	Pentolino/Pot	4.20 (0.77)	2.05 (0.85)	54
	Tazza/Cup	4.36 (0.65)	2.40 (0.78)	57
	Bicchiere/Glass	4.18 (0.82)	1.85 (0.80)	162
Fruits	Ananas/Pineapple	3.29 (1.06)	3.29 (1.02)	15
	Banana/Banana	4.01 (0.99)	1.75 (0.77)	24
	Fragola/ Strawberry	4.39 (0.76)	3.30 (0.96)	30
	Limone/Lemon	4.31 (0.80)	1.71 (0.91)	103
	Mela/Apple	4.29 (0.91)	1.87 (0.94)	66
	Uva/Grapes	4.49(0.74)	3.12 (0.88)	26
Furniture	Divano/Sofa	4.65 (0.61)	2.11 (0.83)	95
	Letto/Bed	4.32 (1.04)	3.24 (0.80)	511
	Libreria/Bookcase	3.52 (1.04)	3.73 (0.84)	90
	Poltrona/Armchair	4.25 (0.86)	2.79 (0.81)	168
	Tavolo/Table	4.03 (1.08)	1.92 (0.73)	390
	Sedia/Chair	4.40 (0.77)	2.04 (0.81)	122
Vehicles	Treno/Train			230
	Automobile/Car	4.21 (0.87)	4.01 (0.89)	806
	Bicicletta/Bicycle	4.30 (0.86)	4.15 (0.74)	104
	Aeroplano/Airplan	2.56 (1.09)	3.95 (0.94)	10
	Elicottero/Helicopter	3.38 (1.06)	4.65 (0.56)	105
	Trattore/Tractor	3.39 (1.15)	3.95 (0.93)	5

Table 4.1: Familiarity, Visual complexity and Frequency values of the 36 pictures used in the semantic blocked naming task. Visual complexity and Familiarity values are taken from Viggiano et al. (2004). Frequency values are taken from the Corpus and Frequency Lexicon of Written Italian (COLFIS).

a) Homogeneous sets:

Clothing	Sock	Hat	Tie	Boot	Trousers	Shoe
Animals	Mouse	Dog	Cat	Lion	Elephant	Zebra
Kitchen utensils	Knife	Fork	Spoon	Cup	Glass	Pot
Fruits	Pineapple	Banana	Strawberry	Lemon	Apple	Grapes
Furniture	Couch	Bed	Bookcase	Armchair	Table	Chair
Vehicles	Train	Car	Bicycle	Airplane	Helicopter	Tractor

b) Mixed sets:

Mix 1	Cat	Tractor	Sock	Pot	Banana	Bookcase
Mix 2	Fork	Train	Hat	Mouse	Lemon	Armchair
Mix 3	Strawberry	Car	Trousers	Lion	Knife	Table
Mix 4	Bicycle	Pineapple	Tie	Elephant	Cup	Bed
Mix 5	Boot	Helicopter	Grapes	Glass	Dog	Couch
Mix 6	Chair	Airplane	Apple	Spoon	Shoe	Zebra

Table 4.2: Homogeneous (a) and Mixed (b) sets used in the semantic blocked naming task.

Before the experiment, pictures were presented in a random order, to allow familiarization with the stimuli and their names. More specifically, in this session, pictures (average size = 12x12 degrees of visual angle) were displayed one at a time in the centre of the computer screen and were visible until participants named them aloud; the corresponding name was also shown in capital letters under each picture to avoid individual differences and ambiguity in naming. After this first presentation, participants were informed that immediately after tDCS (see below) they would have to name the same pictures seen in the practice session as accurately and as fast as possible. In the experimental session, each trial started with a fixation cross (1x1 deg of visual angle) in the centre of a computer screen for 500ms, followed by a blank screen (200ms), and by the target picture (same size as in the practice session but without label), visible for 1100ms (same presentation time as in Belke et al., 2005, Experiment 1). After picture offset, a blank screen appeared until participants produced the name of the picture and pressed a key to start with the following trial (Fig. 4.1 shows the timeline of an experimental trial).

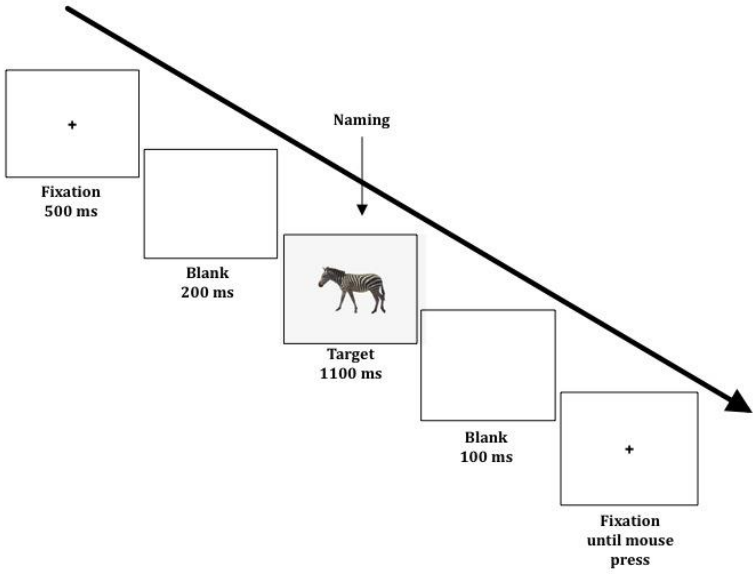


Fig. 4.1: timeline of a trial in the semantic blocked naming paradigm.

Each of the 6 items composing a set was consecutively presented 4 times (cycles), resulting in a block of 24 presentations for each set, for a total of 288 trials (see Schnur et al., 2006). Consecutive repetition of the same item was avoided. The order of presentation of homogeneous and mixed blocks and the order of pictures inside each cycle were randomly varied for each participant. After each block, the sentence ‘‘Get Ready...’’ was shown on the screen, allowing participants to briefly rest before the beginning of the next block. The experiment took approximately 15 min.

The pilot study confirmed the presence of a SI effect. A repeated-measures ANOVA run on mean RTs of correct trials with category (6 levels: animals, clothing, furniture, kitchen utensils, fruits and vehicles) and set (homogeneous vs. mixed) as within-subjects variables, revealed a significant main effect of set [$F(1,27)= 15.90$, $p<.001$], being naming latencies longer in homogeneous as compared to mixed sets (634ms vs. 621 ms). Category also affected naming latencies [$F(5,135)=10.99$, $p<.001$]: items from the category animals (605ms) were produced significantly faster than kitchen utensils (649ms, $p<.001$), furniture (646ms, $p<.001$), and vehicles (623ms, $p=.03$); naming fruits

(617ms) was significantly faster than naming kitchen utensils (p=.014) and furniture (p<.001); finally, naming vehicles was faster than naming furniture (p=.004) (Bonferroni correction applied). This result mirrors previous findings showing an advantage in naming living items, as compared to non-living ones, in healthy individuals (e.g. Laws and Neve, 1999; but see Coppens and Frisinger, 2005, for opposite results).

Control task

As in Study 1, to rule out the possibility that a-tDCS generally affected general arousal, a visual control task was administered. The timeline of this task is shown in Fig. 4.2. In brief, each trial started with a fixation point in the centre of the screen (500ms), followed by a blank screen (500ms); then twelve identical pictures in a ring configuration (10x10 deg of visual angle) around the fixation point (200ms) appeared. Eleven objects were parallel to the horizontal midline, whereas one (the target) was rotated 30° either clockwise or counter-clockwise around its horizontal axis. Participants had to indicate as fast as possible whether the target appeared in the left or right hemifield, by pressing a left or right key (with their right index and medium finger). There were overall 48 trials, 24 for each hemifield (left or right). The target appeared in any of the 12 positions an equal number of times. Before starting the experiment, participants were given instructions and were presented with a few experimental trials in order to familiarise with the task. The control task was performed immediately after the end of the semantic blocked naming paradigm, and took approximately 2 min to be completed.

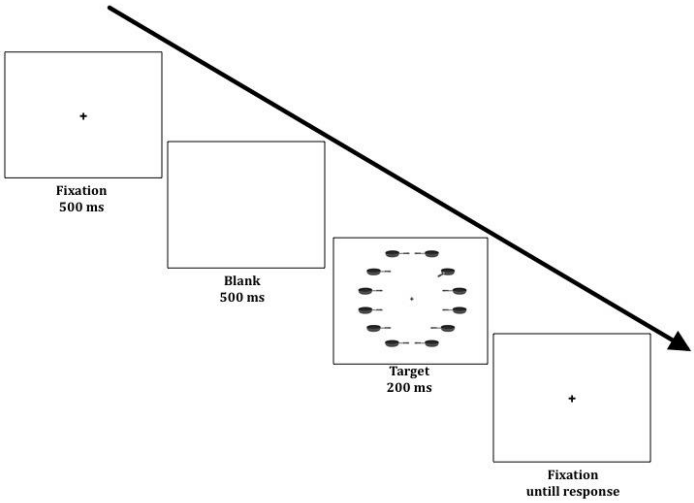


Fig. 4.2: Timeline of a control task trial.

tDCS

As in Study 1, tDCS was delivered by a battery driven, constant current stimulator (Eldith, Neuroconn, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (7x5 cm: 35 cm^2) kept firm by elastic bands. The anode was placed over the LSTG, while the cathode was placed over the right supraorbital region, as in previous studies (e.g., Floel et al., 2008). The LSTG was identified on the basis of a previous work reporting Talairach coordinates for Wernicke's area (x=-50; Y= -46; Z=1; Andoh et al., 2006). To localize the stimulation target on the subject's scalp, a SofTaxic Evolution Navigator system (E.M.S., Bologna, Italy) was used, which works on the basis of digitised skull landmarks (nasion, inion and two preauricular points) from which 40 uniformly distributed points can be mapped out on the scalp (3D Fastrak Polhemus digitiser) and related to cerebral anatomy. Since individual MRIs were not available, an MRI-constructed stereotaxic template (accuracy ~1 cm, Talairach space) was estimated by the neuronavigation system, and Talairach coordinates of cortical sites

underlying the anode were then localized on the basis of this reconstruction. This method has been already successfully used in previous studies (e.g., Urgesi et al., 2004).

A real and a sham stimulation session took place at the distance of one week from each other. In real sessions, stimulation intensity was set at 2 mA and the duration of stimulation was 20 min. Current density (0.57 A/m^2) and charge density (685.7 C/m^2) were maintained below the safety limits (Poreisz et al., 2007). In sham sessions, the same electrodes montage as for LSTG tDCS was used, but stimulation lasted for 30s only. The same fade/in fade/out shamming procedure of Study 1 was adopted, and order of sessions was balanced across subjects. The study was conducted as a single-blind experiment.

Procedure

Subjects were seated in front of a computer screen (at a distance of 57 cm), in a normal-lightened and silent room. E-prime software (Psychology Software Tools, Pittsburgh, PA) was used for the experimental procedure. A microphone triggered a voice key for RTs collection to the nearest millisecond. Before starting the experiment, participants were instructed about the tasks and the stimulation. A cartoon movie was presented along with the stimulation protocol. This ensured that participants were exposed to the same visual experience during the stimulation period, thus reducing inter-subjects variability. After 18 min from the beginning of tDCS, subjects were told that in 2 min they would have to perform experimental tasks.

4.2.2 Results

All the analyses were performed using the statistical software SPSS for Windows version 18.0.

Semantic blocked naming task

Trials in which the participant produced a wrong name, hesitated, or changed response were excluded from the analysis, as well as trials with voice key malfunction (see Schnur et al., 2006). Also trials with RTs slower than 300ms or faster than 1100ms (1100ms corresponding to time of presentation of the stimulus) were removed from the analysis. This criterion was also applied in the pilot study (see above). In sum, 2.95% of trials in real stimulation session and 4.95% in sham ones were excluded from the analysis. A repeated measures ANOVA was run on RTs, with category (6 levels: animals, clothing, furniture, kitchen utensils, fruits and vehicles), set (2 levels: homogeneous vs. mixed) and stimulation (2 Levels: real vs. sham) as independent variables. Fig. 4.3 shows mean RTs for correct responses for homogeneous and mixed sets after real and sham tDCS (collapsed across category type).

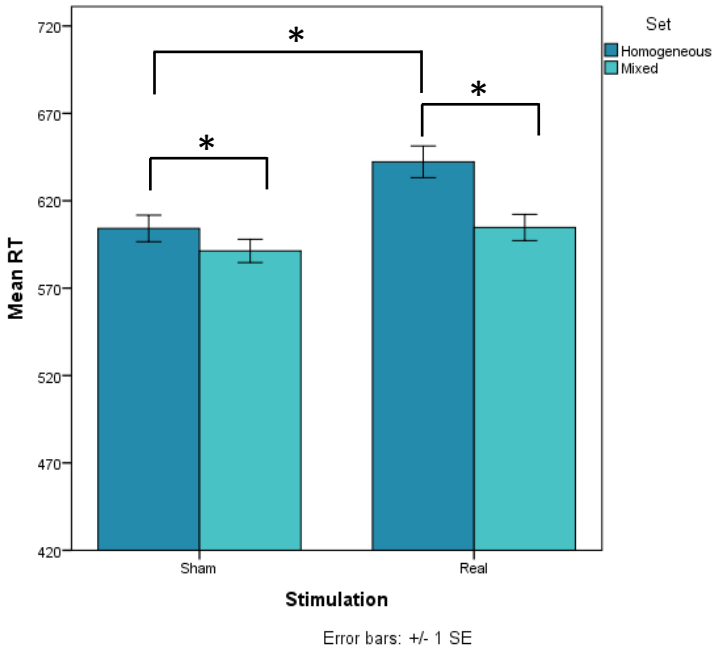


Fig. 4.3: Mean RTs for the blocked naming paradigm in Experiment 1 divided by stimulation condition and set.

The main effect of category [F(5,55)= 9.23, p<.001], set [F(1,11)= 51.31, p<.001], and stimulation [F(1,11)= 7.18, p=.021] were significant. The stimulation x set interaction was also significant [F(1,11)= 17.37, p=.002] as well as the stimulation x category interaction [F(5,55)=2.64, p=.033], while no other interactions reached significance (set x category: p=.60; stimulation x set x category: p=.37).

Post-hoc tests (with Bonferroni correction) showed that the significant main effect of category was due to RTs being faster for the category animal (588ms) as compared to kitchen tools (624ms, p=.037) and furniture (636ms, p<.001); RTs for fruits (596ms) being faster compared to furniture (p=.023); and RTs for vehicles being faster than for furniture (p=.014), mainly replicating the pattern found in the behavioural pilot study. The main effect of set was due to longer RTs for semantically homogeneous sets (623ms) compared to mixed ones (598ms), confirming the occurrence of the SI effect (mean SI= 25ms). The main effect of stimulation, instead, was due to a general increase of RTs after a-tDCS (624ms) compared to sham condition (598ms). Crucially, the effect of a-tDCS differed between sets, with longer RTs after real than sham a-tDCS in the homogeneous sets (642ms vs. 604ms; p=.007), whereas in mixed sets RTs did not differ for real (605ms) and sham (591ms) sessions (t(11)=1.60, p=.14). Accordingly, although naming latencies were slower for homogenous lists than for mixed ones in both sham (t(11)=2.65, p=.023), and real (t(11)=8.71, p<.001), a-tDCS sessions, the magnitude of the SI effect was higher after real (mean SI= 38ms) than after sham (mean SI= 13ms) a-tDCS, (t(11)=4.17, p=.002; see Fig. 4.4).

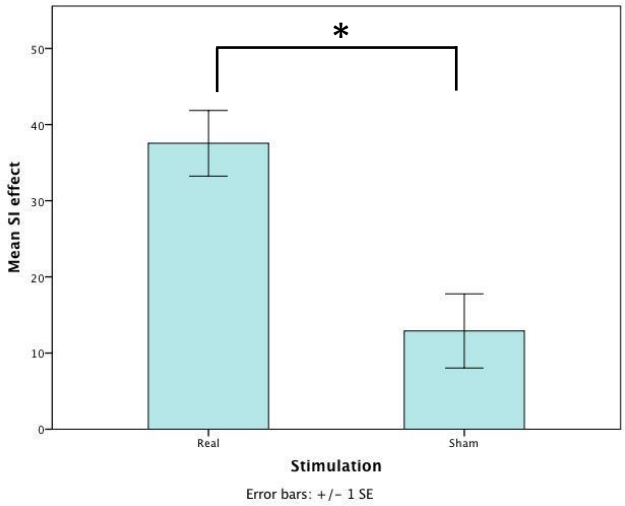


Fig. 4.4: Mean SI effect in Experiment 1 divided by stimulation condition.

To rule out any possible confounding effect due to the inclusion of the category "vehicles", the same analysis was run excluding this category. As in the previous analysis, all the main effects were significant: category [$F(4, 44)= 11.04$, $p<.001$], set [$F(1,11)= 56.87$, $p<.001$] and stimulation [$F(1,11)= 8.66$, $p=.013$]. Accordingly, the stimulation x category interaction resulted significant [$F(4,44)=2.92$, $p=.032$], as well as the stimulation x set interaction [$F(1,11)= 14.55$, $p=.003$]. No other interactions reached significance (set x category, $p=.46$; stimulation x set x category, $p=.33$). The magnitude of the SI effect was greater after real than after sham a-tDCS ($t(11)= 3.82$, $p=.003$), due to naming latencies in homogeneous lists being significantly slower after real than after sham a-tDCS ($p=.006$).

Control task

Participants' mean accuracy in the control task was 87% (SD = 17%) for real and 83% (SD= 18%) for sham a-tDCS. Mean RTs for correct responses were 321ms (SD = 96ms) for real and 367ms (SD=150ms) for sham tDCS. A repeated-measures ANOVA was carried out with stimulation (real vs. sham) as within-subjects variable on mean accuracy and on mean RTs for correct trials. No significant difference was reported

between real and sham a-tDCS, for either accuracy [F(1,11)=3.29, p=.10] or RTs, [F(1,11)= 2.48, p=.14].

4.3 Experiment 2

4.3.1 Materials and Methods

Participants

Twelve healthy participants took part in Experiment 2 (3 males, mean age= 21.8 years, SD= 2.1, mean education 15.3 years, SD=1.4). None of them was involved in Experiment 1. Inclusion criteria were the same as in Experiment 1.

tDCS and experimental procedure

Participants were asked to complete the semantic blocked naming task and the control visual detection task, as in Experiment 1. The tDCS protocol for real and sham sessions was the same as in Experiment 1; the cathode was placed over the right supraorbital region, whereas the anode was placed over the LIFG (left BA 44/45). The LIFG was localised according to the 10–20 EEG system as the crossing point between T3-Fz and F7-Cz, as in Study 1.

4.3.2 Results

Semantic blocked naming task

The same analyses carried out in Experiment 1 were used for Experiment 2. The percentage of incorrect responses (excluded from the analysis) was 3.5% in the real stimulation session and 3.7% of responses in the sham session. Fig. 4.5 shows mean RTs for correct responses for homogeneous and mixed sets after real and sham tDCS (collapsed across category type).

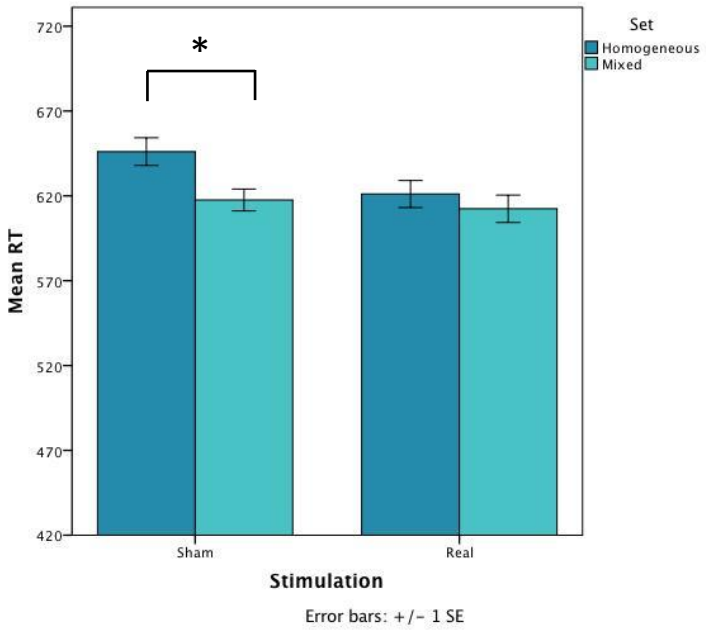


Fig. 4.5: Mean RTs for the blocked naming paradigm in Experiment 2 divided by stimulation condition and set.

The repeated-measures ANOVA carried out on mean RTs of correct trials, with category (animals, clothing, furniture, kitchen utensils, fruits and vehicles), set (homogeneous vs. mixed) and stimulation (real vs. sham) as within-subjects variables revealed a significant main effect of category [$F(5,55)= 17.15$, $p<.001$], and of set, [$F(1,11)= 12.80$, $p=.004$]. The main effect of stimulation, instead, was not significant, [$F(1,11)=1.09$, $p=.32$], but the interaction stimulation x set was [$F(1,11)= 10.56$, $p=.008$]. Moreover, the category x set interaction reached significance [$F(5,55)=2.94$, $p=.020$]. The interactions stimulation x category ($p=.21$) and stimulation x set x category ($p=.31$) were not significant. A post-hoc analysis showed that the significant main effect of category was due to RTs being faster for animals (590ms) compared to kitchen utensils (648ms, $p=.008$), furniture (652ms, $p=.001$) and vehicles (630ms, $p=.001$); faster for fruits (604ms) compared to kitchen utensils ($p=.013$), furniture ($p=.001$), and vehicles ($p=.005$); and slower for furniture compared to clothing (620ms, $p=.009$). The main effect of set depended on RTs for homogeneous sets (634ms) being

overall slower compared to RTs for mixed sets (615ms), confirming the occurrence of the SI effect (mean SI=19ms). The significant set x category interaction suggested that the SI effect was overall more evident for non-living categories than for living ones, furniture (p=.023), vehicles (p=.007), clothing (p=.076), kitchen tools (p=.14), animals (p=.57) and fruit (p=.29).

The difference in RTs between homogeneous and mixed sets was analysed for sham and real stimulation sessions separately, in order to clarify the significant stimulation x set interaction. RTs were significantly faster in mixed sets compared to homogenous sets in the sham sessions (p=.001), but not in the real ones (p=.14). Similarly, the magnitude of the SI effect was significantly greater in the sham (SI=29ms) than in the real stimulation condition (SI=9ms), (t(11)=3.25, p=.008; see Fig. 4.6). a-tDCS reduced (although not to a significant extent) RTs in homogenous sets (621ms for real vs. 646ms for sham tDCS; t(11)=1.66, p=.13) whereas response latencies in mixed sets were comparable in the two tDCS sessions (612ms for real vs. 618ms for sham tDCS; t(11)=.36, p=.73).

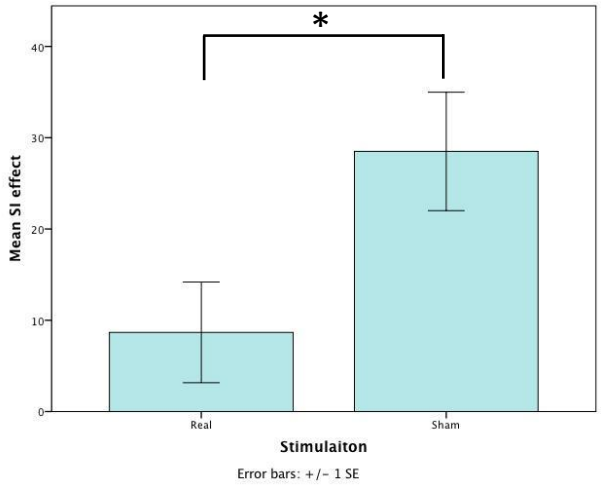


Fig. 4.6: Mean SI effect in Experiment2 divided by stimulation condition

As in Experiment 1, the same analysis was performed without including the category vehicles. This second analysis led to the same pattern of results: the main effects of set [F(1,11)=7.18, p=.021] and category [F(4,44)= 19.94, p<.001] were significant; similarly the interaction stimulation x set was significant [F(1,11)=8.43, p=.014]. No other main effects or interactions reached significance (all ps >.05). The stimulation x set significant interaction depended on response latencies being significantly faster for mixed lists (619ms) than for homogeneous ones (642ms) in sham stimulation condition (p=.01), demonstrating the occurrence of a SI effect. In real stimulation RTs did not differ between homogeneous (619ms) and mixed (613ms) lists, (p=.21), with real tDCS reducing naming latencies in homogeneous lists (but p=.18).

Control task

Mean accuracy in the Control task was 89% (SD = 8%) for real and 89% (SD= 10%) for sham tDCS. Mean RTs for correct trials were 249ms (SD =63) for real and 264ms (SD=56) for sham tDCS. A repeated-measures ANOVA on mean accuracy with stimulation (real vs. sham) as within-subjects variable revealed no significant difference between the two sessions [F(1,11)= .13, p=.73]. The same analysis performed on mean RTs for correct responses also showed no effect of a-tDCS [F(1,11)=1.75, p=.21].

4.4 Discussion

Data from the present study show that both the LSTG and the LIFG are causally involved in the SI effect: a-tDCS over these two areas modulated subjects' performance in a semantic blocked naming paradigm. In line with previous studies, participants were overall slower in naming pictures presented in a semantically related context compared to an unrelated one (Belke et al., 2005; Schnur et al., 2006, 2009). Crucially, this effect

was differently affected by a-tDCS. In particular, a-tDCS applied over the LSTG selectively increased RTs in semantically related lists, and, accordingly, the SI effect. In contrast, enhancing excitability of the LIFG resulted in a significant reduction of the SI effect: a-tDCS over LIFG reduced naming RTs in semantically homogeneous but not in mixed sets. Performance in a visual control attention task was not modulated by stimulation, discarding a possible unspecific effect of tDCS or a general modulation of arousal or attention. The different modulation on naming in the two experiments further supports a selective effect of a-tDCS on naming.

An increased SI effect following anodal stimulation of the LSTG is in line with word production models assuming that the SI effect arises due to several exemplars of the same semantic category being simultaneously co-activated and thus competing for lexical access (e.g., Levelt et al., 1998). a-tDCS applied over the posterior LSTG enhanced the competition among stimuli in semantically related clusters. Similarly, Maess et al. (2002) using the same paradigm in an event-related MEG study, showed a different activation of the left temporal cortex for the same-category compared to the mixed-category context. fMRI evidence also indicates that activation of the left temporal cortex is sensitive to the semantic blocking manipulation (Schnur et al., 2009). Using a different behavioural (picture-word interference, PWI) paradigm, in combination with fMRI, de Zubicaray et al. (2001) found differential activity associated to the SI effect in the LSTG. These results extend these previous findings, causally linking the level of activation of the left temporal cortex and the SI effect.

The present data also support a critical role of the LIFG in competition resolution in word production. Indeed, it has been suggested that this area supports processes that operate over semantic representations, rather than operating on the representations themselves (see Poldrack et al., 1999; Moss et al., 2005). More specifically, the LIFG

has been regarded as the neural locus of a general selection mechanism involved at different representational (i.e., phonological, semantic, and syntactic) levels (Novick et al., 2005) or as the neural site of an executive mechanism, which acts to inhibit verbal representations (Hamilton and Martin, 2005, 2007). It is not possible to directly disentangle among these different interpretations. Nevertheless, both agree about the role of the LIFG in a selection/control mechanism that would act during lexical retrieval. Upon these premises, one may expect that a-tDCS over the LIFG can speed up responses also in mixed contexts, by solving competition even among heterogeneous lexical items. However, the successful modulation of task performance via a-tDCS depends on task complexity, as indicated by previous studies failing to show a significant change in performance below a certain level of task complexity (e.g., Antal et al., 2004). Even assuming that a certain level of lexical competition is present in mixed sets, the task is not demanding enough to be significantly affected by tDCS.

Schnur et al. (2009) found, in different groups of aphasic patients with LIFG or LSTG lesions, that although all patients experienced difficulties in word production, the ability to resolve competition during language production depended on the integrity of the LIFG but was not related to LSTG (see also Schnur et al., 2006). Additional evidence from neuropsychological studies on brain-damaged patients also supports the relationship between the SI effect and LIFG lesions (e.g., McCarthy and Kartsounis, 2000; Wilshire and McCarthy, 2002; Biegler et al., 2008). Similarly, in healthy subjects, it has been shown that interfering with LIFG activity by means of TMS increased RTs in a semantic decision task (Devlin et al., 2003; Kohler et al., 2004). However, increased naming latencies in these studies may also depend on TMS interfering with other processes in which the LIFG may be involved, such as phonological encoding and syllabification, as demonstrated by TMS chronometric evidence (Schuhmann et al.,

2009, 2012). Overt naming, indeed, relies on a network of brain regions, with LSTG, LIFG and LMTG being involved at different time points (Schuhmann et al., 2009, 2012).

Finally, it is not possible to conclude whether the SI effect arises as a product of an "overactivation" or an "overinhibition" (i.e., refractory access) of the lexical selection system (Dell, 1986; see discussion in Schnur et al., 2006; Biegler et al., 2008). In both cases, indeed, the expected a-tDCS modulations are the same: if enhancing excitability of the left temporal cortex increases competition among items belonging to the same category, it might also enhance intra-category items inhibition. On this regard, one can object that a-tDCS over the LSTG should also "pre-activate" the target lexical entry, so that the difference in activation level between target and distracters should be unaffected by tDCS. However, SI likely depends on a "one-to-many" rather than on a "one to-one" competition (see Abdel Rahman & Melinger, 2009a, b), according to which SI is determined by the activation status of whole cohorts of inter-related lexical items that mutually co-activate each other and that together compete with the target entry for selection. Since the "activating" effect of a-tDCS should be comparable for all items of homogeneous lists, following tDCS the pre-activated target entry has to compete with the sum of the enhanced activations of the distracters. Accordingly, the amount of interference increases compared to a non-stimulation condition: in fact, if in a "one-to-one" competition the difference in activation between target and distracter would remain the same after stimulation, in a "one-to-many" competition the amount of interference provided by the other pre-activated distracters is higher because the effect of stimulation on distracters is additive.

It may be worth noting that the magnitude of the SI effect in the baseline (sham) condition of Experiment 1 (13ms) seems smaller than that reported in Experiment 2

(29ms; but note that the same SI magnitude of 13ms was also reported in the pilot behavioural study). Since stimuli and procedure used in the two experiments were identical, and since sham stimulation does not induce any effect at the cortical level, this apparent difference in baseline performance is attributable to inter-subjects' variability. Furthermore, the SI effects reported in the present experiments are in line with previous evidence. Using the blocked naming paradigm, SI effects of 20-30ms have been reported (for instance, SI=26ms in Maess et al. 2002; 29ms in Damian et al., 2001; 33ms in Schnur et al., 2006; 20ms in Experiment 1 of Navarrete et al., 2012), as well as SI effects smaller than 15ms (15ms in Ganushchak and Schiller, 2008; 13ms in Abdel Rahman and Melinger, 2011; 11ms in Damian et al., 2001, in PWI paradigms). In fact, the magnitude of the SI effect may depend on many factors, including semantic distance within and between categories (e.g., Navarrete et al., 2012; Vigliocco et al., 2002). Critically, the present conclusions are not based on a direct comparison between the two experiments (as it would be the case of a between-subjects design), but the effect of a-tDCS over the LIFG and LSTG was analysed in a within-subjects design: this makes the present findings statistically stronger and better accounting for inter-individual variability.

In conclusion, the present study confirms the existence of a distributed cortical network involved in lexical retrieval. In building the SI effect the LIFG seems crucial to resolve the conflict between lexical representations, while the LSTG seems to be the cortical underpinning of the lexical-semantic representational system (or at least to act as a convergence zone where higher-level supramodal semantic representations are stored, cf. Kiefer and Pulvermüller, 2011). Finally, these findings add to the literature on brain-damaged subjects suggesting that a-tDCS can be selectively used to reduce SI in aphasic patients: indeed, although SI is a normally occurring phenomenon, its magnitude is

usually heightened by brain damage to language areas (e.g., Hashimoto and Thompson, 2010; Thompson et al., 2012).

5 Study 4: LIFG and LSTG in phonological facilitation

5.1 Introduction

As Study 3 suggests, tDCS can be used to directly test the role of different brain areas in specific aspects of object naming, such as the resolution of the SI effect. This effect seems to take place at the lexical selection level of picture naming, and tDCS distinguished between LIFG and LSTG contribution at this stage. Object naming, however, is not only affected by the semantic context, but can also be modulated by phonological information concurrently presented with the target. The PF effect, indeed, refers to faster naming latencies when the target object is matched with the presentation (in the auditory or written modality) of a phonologically related word as compared to the occurrence of a phonologically unrelated one (e.g., Lupker, 1982, Rayner and Springer, 1986, Starreveld, 2000, Starreveld and La Heij, 1995 and Starreveld and La Heij, 1996; Abel et al., 2009; De Zubicaray et al., 2002, De Zubicaray and McMahon, 2009; Damian and Bowers, 2009; Schriefers et al., 1990). Several accounts of this effect posit that facilitation is induced thanks to the co-occurrent activation of overlapping phonological features of the target and the distracter words (see introduction in De Zubicaray and McMahon, 2009). This effect seems to contrast with the previously investigated SI effect, where a semantically related context triggers higher RTs than an unrelated one. However, the two effects rely on different mechanisms, possibly operating at separate stages of object naming (Dell'Acqua et al., 2007; Ayora et al., 2011). There is converging evidence, indeed, suggesting that the PF effect acts at the phonological encoding level (De Zubicaray and McMahon, 2009; De Zubicaray et al., 2002; Meyer, 1996, Roelofs, 1992; Meyer and Schriefers, 1991, Schriefers et al., 1990), i.e. after lexical selection, when the phonemes of the target word are combined into syllables and prosodic information is added (Indefrey, 2011). While the SI arises when

the target word still has to be selected, in PF lexical selection has already taken place, and PF may result as a faster phonological encoding when both target and distracter share similar features, thus summing their activations. Nevertheless, interactive models of word production (e.g. Dell, 1986; Dell and O'Seaghdha, 1994) do not exclude feedbacks from the word-form level to the lexical-conceptual level, thus not totally avoiding the possibility that the PF effect might also influence lexical selection (De Zubicaray and McMahon, 2009).

PF has been shown in PWI paradigms with distracters presented both in the written (Lupker, 1982; De Zubicaray et al., 2002) and auditory modality (Schriefers et al., 1990; Damian & Martin, 1999; Starreveld, 2000; Abel et al, 2006; De Zubicaray and McMahon, 2009). Crucially, facilitation disappears at given stimulus onset asynchronies (SOAs), different for each presentation modality. Namely, written distracters produce PF for SOAs ranging from -200ms to 200ms (De Zubicaray et a., 2002; Damian and Martin, 1999; Starreveld and La Heij, 1996), while auditory facilitators trigger greater PF from -100ms to 200ms SOAs (Schriefers et al., 1990; Damian and Martin, 1999; De Zubicaray and McMahon, 2009). There is still a debate about different aspects of the PF effect, with an increasing number of studies investigating the background mechanisms upon which it may rely (De Zubicaray and McMahon, 2009). The main dispute between serial or cascading activation models seems rather settled. A number of experimental evidence both at a behavioural and neuroimaging level (Damian and Bowers, 2003; 2009; De Zubicaray and McMahon, 2009) indicates that cascading phonological co-activation of all the lexical competing items is necessary in order to explain why PF happens. The main controversial issue, instead, is how the activation of competitors is suppressed once cascading activation has co-activated word-forms of distracters. Two possible mechanisms have been

hypothesized: a decay-based mechanism, according to which the selected item returns in time to its baseline level, or inhibition-based mechanism, suggesting that after its selection the target suppresses its own active state and that of its competitors, ending in a down-regulation of their responsiveness (e.g., Berg & Schade, 1992; Vitkovitch, et al., 2001).

Studies investigating the neural correlates of the PF effect point to an involvement of the LSTG associated to PF in picture naming, with a decreased BOLD signal in this region, corresponding to phonologically related distracters as compared to unrelated ones (De Zubicaray et al., 2001; Abel et al., 2006; De Zubicaray and McMahon, 2009), and naming in no interference condition (De Zubicaray and McMahon, 2009). The LIFG seems also to be involved in this task, showing greater activation when distracters are present (De Zubicaray et al., 2006; De Zubicaray and McMahon, 2009). Similarly, patients suffering from logopenic and agrammatic forms of primary progressive aphasia (PPA), a cortical degeneration that leads to a progressive loss of language, show abnormal PF effects in a PWI paradigm as compared to normal controls (Mack et al., 2013). However, it is not clear whether the detected BOLD signal changes really refer to the PF effect and which mechanism allows distracters suppression.

To investigate these issues, a PWI paradigm was administered after a-tDCS over the LSTG and the LIFG, in two separate experiments. The PWI consisted in a picture naming of objects coupled with the presentation of an auditory distracter (a phonologically related word, facilitator, or an unrelated one, distracter), at two different SOAs (150ms and 300ms). It was expected, in non-stimulation session, to replicate data available in the literature, namely an effect of facilitators only at 150ms SOAs (Schriefers et al., 1990; Damian and Bowers, 2009). In the case of a-tDCS delivered over the LSTG, a modulation of the PF effect was expected, measured as the RTs

difference between distracters and facilitators. If this effect relies on spread of activation, a-tDCS should enhance the PF. As in Study 3, indeed, an additive effect of activation might take place, thus over-activating the target phonemes and facilitating their selection. If the PF effect benefits, instead, of an additive lateral inhibition mechanism, a decreased PF should be recorded, since more inhibition may help in ignoring the phonological unrelated distracters. a-tDCS over the LIFG, instead, should not affect the PF, but a general selection mechanism, similarly affecting both facilitators and distracters.

5.2 Experiment 1

5.2.1 Materials and methods

Participants

Ten neurologically unimpaired individuals (1 Male, mean age 21.3 years, SD= 2.4; Range 18 – 25 years) took part in the experiment. All participants were native Italian speakers, undergraduate students (Mean years of education =13.9; SD= 1.4, Range = 13 – 16 years); they were naïve as to the experimental procedure, and the purpose of the study. All subjects were right-handed (mean EHI= 90.1; SD= 9.5; Range= 79 - 100), with normal or corrected-to-normal vision. They had no history of chronic or acute neurologic, psychiatric, or medical disease; no family history of epilepsy; no current pregnancy; no cardiac pacemaker; no previous surgery involving implants to the head (cochlear implants, aneurysm clips, brain electrodes) and did not take acute or chronic medication. Written informed consent was obtained from all participants. The experiment was approved by the local ethical committee of the University of Milano-Bicocca and subjects were treated in accordance with the Declaration of Helsinki.

Stimuli

Stimuli were 200 picture-word pairs. One hundred black and white pictures were chosen from the same database used for Study 3 (Viggiano et al., 2004) and were divided in two experimental sets. Each set included 25 pictures of living exemplars (animals, fruits, vegetables) and 25 pictures of objects (tools, vehicles, clothing, furniture). Pictures of the two sets were matched for visual complexity and familiarity (see Table 5.1), as well as for length in letters and syllables and name frequency (from the COLFIS). Each picture appeared in two picture-word pairs, once coupled with a phonologically related (facilitator) and once with an unrelated (distracter) word. Facilitators shared with the coupled picture name the first 2/3 phonemes, number of letters and syllables, stress position and had similar frequency. Distracters, instead, were matched with the coupled picture name only for number of syllables and letters, and frequency (see Table 5.2). Initial and final phonemes and stress position differed between picture name and distracter (see Table 5.3 and 5.4). Facilitators and distracters were read and recorded as individual ".wav" audio files. Each item set was administered in two different experimental sessions, with order of sets balanced across subjects.

	Familiarity	**Visual Complexity**	**Length (letters)**	**Length (syllables)**	**Frequency**
t(98)	.10	.40	.43	.88	.05
p	.92	.69	.67	.38	.96

Table 5.1: differences between lists for target pictures characteristics.

List 1	**F (2,147)**	**p**	**List 2**	**F (2,147)**	**p**
Frequency	.42	.66	Frequency	.23	.80
Length (letters)	.48	.62	Length (letters)	.30	.74
Length (syllables)	.02	.98	Length (syllables)	.02	.98

Table 5.2: Differences in the two experimental sets between target, facilitators and distracters in Frequency and length (letters/syllables).

Picture	Pronounciation	Frequency	Facilitator	Pronounciation	Frequency	Distracter	Pronounciation	Frequency
Arancia/Orange	a'rantʃa	36	Arazzo/Tapestry	a'rattso	16	Bibita/Beverage	'bibita	14
Asino/Donkey	'azino	27	Asola/Buttonhole	'azola	4	Camino/Fire place	ka'mino	29
Aspirapolvere/ Vacuumer	aspira'polvere	2	Astrodinamica/ Astrodynamics	astrodi'namica	2	Zuccherificio/Sugar factory	tsukkeri'fitʃo	1
Bicicletta/Bicycle	bitʃi'kletta	104	Biblioteca/Library	bibljo'tɛka	102	Fotografo/ Photographer	fo'tɔgrafo	117
Calzino/Sock	kal'tsino	12	Caldaia/Boiler	kal'daja	14	Viscere/Bowels	'viʃʃere	13
Cammello/Camel	kam'mɛllo	15	Campeggio/Camping	kam'peddʒo	13	Baratro/Chasm	'baratro	13
Candela/Candle	kan'dela	61	Cancello/Gate	kan'tʃello	87	Stomaco/Stomach	'stɔmako	78
Cane/Dog	'kane	328	Cassa/Case	'kassa	226	Aula/Classroom	'aula	225
Caramella/Candy	kara'mɛlla	23	Campanile/ Bell tower	kampa'nile	19	Mammifero/Mammal	mam'mifero	19
Carciofo/Artichoke	kar'tʃɔfo	22	Cartina/Map	kar'tina	21	Bombola/Tank	'bombola	21
Cavallo/Horse	ka'vallo	251	Calore/Heat	ka'lore	128	Polvere/Dust	'polvere	139
Cravatta/Tie	kra'vatta	48	Cratere/Crater	kra'tɛre	6	Pollice/Thumb	'pɔlliʧe	36
Delfino/Dolphin	del'fino	28	Delirio/Delirium	de'lirjo	33	Gomito/Elbow	'gomito	32
Divano/Couch	di'vano	95	Dimora/Dwelling	di'mɔra	62	Missile/Rocket	'missile	70
Finocchio/Fennel	fi'nɔkkjo	9	Fischietto/Whistle	fi'skjetto	15	Chiocciola/Snail	'kjɔttʃola	11
Forbice/Scissors	'fɔrbitʃe	22	Forfora/Dandruff	'forfora	9	Vitello/Calf	vi'tɛllo	17
Formaggio/Cheese	for'maddʒo	79	Foresta/Forest	fo'rɛsta	121	Cellula/Cell	'tʃɛllula	98
Fungo/Mushroom	'fuŋgo	38	Fusto/Stem	'fusto	13	Atrio/Lobby	'atrjo	22
Giraffa/Giraffe	ʤi'raffa	3	Gitano/Gipsy	ʤi'tano	4	Bandolo/Clew end	'bandolo	3
Gufo/Owl	'gufo	9	Gusto/Taste	'guʃʃo	17	Alpe/Alp	'alpe	12
Lampadario/ Chandelier	lampa'darjo	7	Lamantino/Manatee	laman'tino	1	Batuffolo/Wad	ba'tuffolo	1
Lattuga/Lettuce	lat'tuga	9	Lavagna/Blackboard	la'vaŋɲa	13	Balsamo/Balm	'balsamo	12
Lumaca/Snail	lu'maka	11	Lunotto/Rear window	lu'nɔtto	3	Cappero/Caper	'kappero	9
Mappamondo/Globe	mappa'mondo	4	Maggiorenne/Adult	maddʒo'rɛnne	4	Carambola/Carom	ka'rambola	3
Mattarello/Rolling-pin	matta'rello	2	Madreperla/Nacre	madre'pɛrla	4	Ecchimosi/Bruise	ek'kimozi	4
Melanzana/Egg-plant	melan'dzana	13	Memoriale/Memorial	memo'rjale	24	Pantofola/Slipper	pan'tɔfola	14
Moto/Motorcycle	'mɔto	187	Mossa/Move	'mɔssa	108	Alba/Dawn	'alba	144
Orologio/Watch	oro'lɔdʒo	143	Orizzonte/Horizon	orid'dzonte	97	Veicolo/Vehicle	ve'ikolo	121

Orso/Bear	'orso	69	Orma/Footprint	'orma	25	Uscio/Door	'uʃʃo	21
Pecora/Sheep	'pɛkora	56	Pentola/Pot	'pɛntola	54	Fontana/Fountain	fon'tana	40
Pennello/Brush	pen'nɛllo	29	Pendenza/Slope	pen'dɛntsa	17	Ciotola/Bowl	'ʧɔtola	24
Peperone/Pepper	pepe'rone	27	Pescatore/F isherman	peska'tore	82	Giocattolo/Toy	ʤo'kattolo	69
Pera/Pear	'pera	43	Pelo/Hair	'pelo	86	Osso/Bone	'ɔsso	102
Pettine/Comb	'pɛttine	20	Petalo/Petal	'pɛtalo	28	Salmone/Salmon	sal'mone	21
Pinza/Pincers	'pintsa	13	Pino/Pine tree	'pino	35	Anca/Hip	'aŋka	11
Pistola/Gun	pi'stɔla	250	Pilota/Pilot	pi'lɔta	226	Codice/Code	'kɔdiʧe	245
Poltrona/Armchair	pol'trona	168	Portiere/Janitor	por'tjɛre	133	Organo/Organ	'ɔrgano	164
Pomodoro/Tomato	pomo'dɔro	88	Portafoglio/Wallet	porta'fɔʎʎo	60	Deposito/ Warehouse	de'pɔzito	87
Pulcino/Chick	pul'ʧino	8	Pulsione/Drive	pul'sione	11	Alluce/Big toe	'alluʧe	8
Rinoceronte/ Rhinoceros	rinoʧe'ronte	7	Ristoratore/Restaurant owner	ristora'tore	9	Dirigibile/Airship	diri'ʤibile	10
Rosa/Rose	'rɔza	197	Rocce/Rocks	'rɔttʃe	102	Asta/Pole	'asta	105
Sedia/Chair	'sɛdja	122	Serbo/Serbian	'sɛrbo	106	Album/Album	'album	113
Serpente/Snake	ser'pɛnte	53	Sermone/Sermon	ser'mɔne	97	Fulmine/Lightning	'fulmine	57
Spazzolino/Toothbrush	spattso'lino	5	Spaccatura/Rift	spakka'tura	18	Allodola/Skylark	al'lɔdola	7
Tazzina/Cup	tat'tsina	13	Tartufo/Truffle	tar'tufo	18	Cintola/Waist	'ʧintola	9
Televisore/Television-set	televi'zore	49	Temperamento/ Temper	tempera'mento	30	Arcivescovo/ Archbishop	arʧi'veskovo	42
Torta/Cake	'tɔrta	67	Torcia/Flashlight	'tɔrʧa	21	Esca/Bait	'eska	27
Ventilatore/Fan	ventila'tore	10	Veterinario/ Veterinary	veteri'narjo	21	Pianerottolo/Landing	pjane'rɔttolo	13
Volpe/Fox	'volpe	23	Volgo/Folks	'volgo	10	Ascia/Axe	'aʃʃa	21
Zebra/Zebra	'dzɛbra	1	Zenit/Zenit	'dzɛnit	2	Urbe/City	'urbe	5

Table. 5.3: Target, Facilitators and distracters included in List 1, with pronunciation and frequency of each item.

Picture	Pronounciation	Frequency	Facilitator	Pronounciation	Frequency	Distracter	Pronounciation	Frequency
Albicocca/Apricot	albi'kɔkka	15	Algerino/Algerian	aldʒe'rino	10	Citofono/ Interphone	ʧi'tɔfono	10
Ananas/Pineapple	'ananas	15	Anatra/Duck	'anatra	46	Castigo/ Punishment	ka'stigo	13
Banana/Banana	ba'nana	24	Bagnino/Lifeguard	ba'ɲɲino	18	Chimico/Chemical	'kimiko	20
Bicchiere/Glass	bik'kjɛre	162	Biglietto/Ticket	biʎ'ʎetto	190	Moneta/Coin	mo'neta	170
Binocolo/ Binoculars	bi'nɔkolo	18	Bicipite/Biceps	bi'ʧipite	5	Acquedotto/ Aqueduct	akkwe'dotto	17
Cacciavite/ Screwdriver	kattʃa'vite	5	Caciarone/Talkative	katʃa'rone	1	Quaresima/Lent	kwa'rezima	4
Canarino/Canary	kana'rino	10	Caffettiera/Coffeepot	kaffet'tjɛra	5	Matricola/Fresher	ma'trikola	11
Canguro/ Kangaroo	kan'guro	12	Cancrena/Gangrene	kan'krɛna	14	Polline/Pollen	'pɔlline	12
Cappello/Hat	kap'pɛllo	112	Capriccio/Whim	ka'prittʃo	56	Zucchero/Sugar	'tsukkero	120
Carota/Carrot	ka'rɔta	41	Carbone/Coal	kar'bone	42	Orbita/Orbit	'ɔrbita	38
Chitarra/Guitar	ki'tarra	46	Chirurgo/Surgeon	ki'rurgo	51	Bambola/Doll	'bambola	46
Ciliegia/Cherry	ʧi'ljɛdʒa	14	Cinture/Belt	ʧin'ture	58	Sciopero/Strike	ʃ'ʃɔpero	100
Cipolla/Onion	ʧi'polla	76	Cinese/Chinese	ʧi'neze	51	Sintesi/Synthesis	'sintezi	81
Coltello/Knife	kol'tɛllo	117	Collina/Hill	kol'lina	126	Favola/Fairy tale	'favola	121
Coniglio/Rabbit	ko'niʎʎo	30	Coperta/Blanket	ko'pɛrta	74	Disputa/Quarrel	'disputa	29
Cuscino/Pillow	kuʃ'ʃino	57	Custode/Guardian	ku'stɔde	64	Serietà/Seriousness	serje'ta	51
Elefante/Elephant	ele'fante	60	Elettori/Voter	elet'tori	138	Ossigeno/Oxigen	os'sidʒeno	65
Falce/Sickle	falʧe	8	Falda/Layer	'falda	15	Ragù/Ragout	ra'gu	3
Farfalla/Butterfly	far'falla	55	Fardello/Burden	far'dɛllo	11	Profugo/Refugee	'prɔfugo	56
Forchetta/Fork	for'ketta	25	Fortino/Blockhouse	for'tino	13	Mandorla/Almond	'mandorla	27
Gallina/Hen	gal'lina	32	Galere/Jail	ga'lɛre	81	Prognosi/Prognosis	'prɔɲɲozi	34
Lampadina/Bulb	lampa'dina	24	Lamentela/Complaint	lamen'tɛla	23	Pneumatico/Tire	pneu'matiko	32
Lavatrice/Washing machine	lava'triʧe	11	Labirinto/Maze	labi'rinto	27	Astronomo/ Astronomer	a'strɔnomo	11
Leone/Lion	le'one	78	Leggenda/Legend	leg'gɛnda	107	Profilo/Profile	pro'filo	107
Libreria/ Bookcase	libre'ria	90	Liberale/Liberal	libe'rale	66	Deposito/Deposit	de'pɔzito	87
Limone/Lemon	li'mone	103	Licenza/Permit	li'ʧɛntsa	85	Circolo/Circle	'ʧirkolo	89
Maiale/Pig	ma'jale	40	Malato/Sick	ma'lato	123	Chimica/Chemistry	'kimika	39
Martello/ Hammer	mar'tɛllo	26	Marmitta/Silencer	mar'mitta	19	Palpebra/Eyelid	'palpebra	25

Mela/Apple	'mela	66	Meno/Minus	'meno	11	Agio/Cosiness	'adʒo	57
Mucca/Cow	'mukka	12	Muso/Muzzle	'muzo	6	Sofa/Couch	so'fa	11
Pantaloni/ Trousers	panta'loni	127	Panorama/Landscape	pano'rama	77	Filosofo/ Philosopher	fi'lɔzofo	123
Pappagallo/Parrot	pappa'gallo	12	Papilloma/Papilloma	papil'lɔma	4	Accumulo/Backlog	ak'kumulo	10
Patata/Potato	pa'tata	99	Parere/Advice	pa'rere	164	Complice/Accomplice	'kɔmplitʃe	98
Penna/Pen	pe'nna	80	Pepe/Pepper	'pepe	102	Virtù/Virtue	vir'tu	80
Piccione/Pigeon	pit'tʃone	19	Piccozza/Mattlock	pik'kɔttsa	2	Zattera/Raft	'dzattera	15
Pinguino/ Penguin	pin'gwino	5	Pinzetta/Tweezers	pin'tsetta	2	Ciondolo/Pendant	'tʃondolo	6
Piselli/Peas	pi'sɛllo	14	Pilastro/Pillar	pi'lastro	18	Lealtà/Loyalty	leal'ta	24
Ragno/Spider	'raŋŋo	27	Rame/Copper	'rame	23	Tribù/Tribe	tri'bu	33
Scala/Stair	'skala	217	Scambio/Exchange	'skambjo	190	Treno/Train	'trɛno	230
Scarpa/Shoe	'skarpa	195	Scatto/Sprint	'skatto	79	Taglio/Cut	'taʎʎo	174
Scopa/Broom	'skopa	12	Scoglio/Reef	'skɔʎʎo	30	Metrò/Subway	met'ro	23
Spazzola/Hair-brush	'spattsola	18	Spasimo/Spasm	'spazimo	7	Bollino/Sticker	bol'lino	18
Stivale/Boot	sti'vale	44	Stipendio/Salary	sti'pɛndjo	131	Monaco/Monk	'mɔnako	44
Sveglia/Alarm clock	'zveʎʎa	16	Svista/Blunder	'zvista	7	Ambra/Amber	'ambra	8
Tavolo/Table	'tavolo	390	Tattica/Tactics	'tattika	48	Carcere/Jail	'kartʃere	412
Topo/Mouse	'tɔpo	69	Torti/Wrongs	'tɔrti	85	Bontà/ Kindness	bon'ta	50
Trapano/Drill	'traˈpano	9	Tramite/Medium	'tramite	17	Zitella/Spinster	dzi'tɛlla	7
Trattore/Tractor	trat'tore	5	Tracolla/Shoulder belt	tra'kɔlla	3	Dondolo/ Rocking chair	'dondolo	7
Valigia/Suitcase	va'lidʒa	101	Vapore/Steam	va'pore	54	Farmaco/Drug	'farmako	143
Zucchina/Courgette	tsuk'kina	26	Zuppiera/Tureen	tsup'pjɛra	5	Briciola/Crumb	'britʃola	22

Table 5.4: Target, Facilitators and distracters included in List 2, with pronunciation and frequency of each item.

The picture-word interference task (PWI)

The same procedure was used for the pilot and the experimental session. Before the experiment, pictures were randomly presented for self-paced naming, so that participants could familiarize with the stimuli and their names. Following this practice, participants were informed that after tDCS they would have been required to name the same pictures presented in the training session as accurately and as fast as possible, ignoring the concurrent auditory stimuli. Each subject performed three naming blocks per session: a block in which each picture appeared without any interfering word (no interference condition); a second block in which each picture-word pair was presented at a SOA of 150ms (i.e. the auditorily presented word started 150ms after the picture); a third block in which each picture-word pair was presented at a SOA of 300ms. Hence, in each naming session, each picture appeared 5 times in different contexts: no interference, with a facilitator at 150ms or at 300ms, with a distracter at 150ms or at 300ms, for a total of 250 naming trials. Order of blocks was balanced across subjects. Each trial started with a fixation point of 500ms followed by a blank screen (500ms) and by the picture, lasting for 2000ms. After the picture was shown, the audio file started at the predetermined SOA, and, after naming, a fixation cross was presented (1000ms; as in Damian and Bowers, 2009. See Fig. 5.1 for a timeline of an experimental trial).

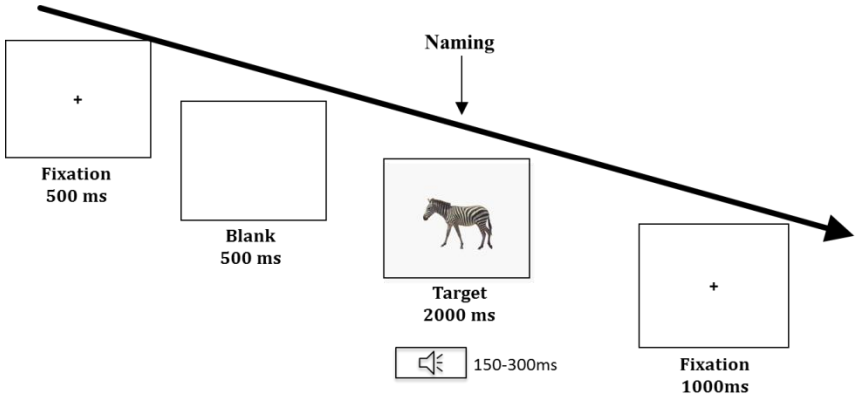


Fig.5.1: Experimental timeline for the PWI paradigm.

After each block, 1 min-interval was left in order to allow participants resting before the next block. The experiment took approximately 20 minutes.

The pilot study confirmed the presence of a PF effect. A repeated measures ANOVA on RTs of correct trials with SOA (2 levels: 150 and 300 ms), and type of interference (2 levels: facilitator vs. distracter) as within subject variables and list (2 levels: list 1 vs. 2) as between subject variable, highlighted a significant main effect of type of interference [$F(1,10)= 13. 4$; $p=.004$; $\eta^2=.57$], since facilitators triggered faster naming latencies (593ms) compared to distracters (624ms), and a significant interaction SOA x type of interference [$F(1,10)=9.18$; $p=.013$, $\eta^2=.48$]. Post hoc analyses (Bonferroni corrected), revealed slower RTs for distracters compared to facilitators at 150ms SOA (639ms vs. 583ms respectively, $p=.003$), while they did not differ at 300ms SOA (610ms vs. 604ms; $p=.43$). Critically, neither a main effect of list or any of its interactions was significant, confirming that both sets similarly elicited the aforementioned effects. Interestingly, as previously reported (Schriefers et al., 1990), PF effect measured as distracters RTs – facilitators RTs, at 150ms SOA significantly differed from PF effect at 300ms SOA [56ms vs. 6ms; $t(11)=3.14$; $p=.009$]. Generally, naming when both distracters and facilitators were presented at 150ms SOA was faster than naming in no

interference condition (677ms vs. 605ms; t(11)=3.16, p=.009), unlike previous reports (Schriefers et al., 1990; De Zubicaray and McMahon, 2009).

Control task

In order to exclude a general effect of tDCS on attention or arousal, an external cueing visual paradigm was administered after the PWI experiment, including 60 trials. At the beginning of each trial, a fixation cross was presented for 2000ms. Then, two rectangular frames appeared at the left and right of the fixation cross and, after a randomly jittering interval (200ms-700ms), one of the two squares blinked for 100ms (cue). After 100ms, a small square appeared in the centre of one of the two frames (target). According to the side of the cue and of the target, trials could be congruent (when cue and target appeared to the same side of the screen, 24 trials), or incongruent (when side of the cue and target were not the same, 24 trials). Subjects had to answer where they detected the target, ignoring the cue, as fast and as accurately as they could, by pressing, with the left or right index finger, one of two aligned keys on a qwerty Italian keyboard: "F" when the target appeared to the left and "J" when it appeared to the right of the fixation point. Catch trials in which no target appeared were included (12 trials; see Fig. 5.2 for a timeline of the control experiment). Subject who answered more than one third of the times to catch trials were excluded from the analysis. RTs and accuracy were collected.

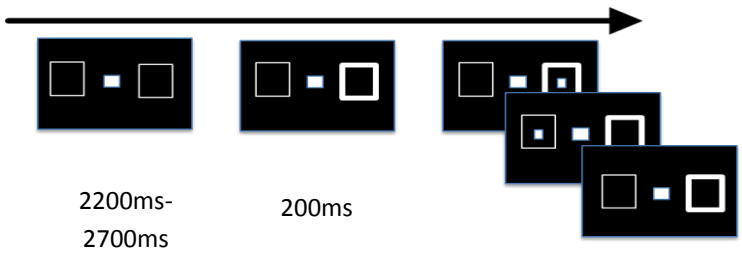


Fig. 5.2: Experimental timeline for the control task.

tDCS

As in the previous studies, tDCS was delivered by a battery driven, constant current stimulator (Eldith, Neuroconn, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes kept firm by elastic bands. The anode (25 cm^2) was placed over the LSTG, while the cathode (50 cm^2) was placed over the right supraorbital region. The LSTG was identified as the EEG 10 – 20 electrodes positioning site CP5 (Fiori et al., 2010; Sparing et al., 2008). Participants took part in two experimental sessions, with a break of at least 3 days in between. In real sessions, the stimulation protocol lasted for 20 min at 2mA intensity. Current and charge densities (0.8 A/m^2 and 960 C/m^2 for the anode and 0.4 A/m^2 and 480 C/m^2 for the cathode respectively) were maintained below the safety limits (Poreisz et al., 2007). In sham sessions, the same electrodes montage as real sessions was used, but stimulation duration was only 30s. A fade-in/out period of 30s was administered at the beginning and at the end of the stimulation procedure. Order of stimulation condition was balanced across subjects. The study was conducted as a single-blind experiment.

Procedure

As in Study 3, subjects performed the experiment in a silent and lightened room. E-prime 2 software (Psychology Software Tools, Pittsburgh, PA) was used for the experimental procedure. A microphone triggered a voice key for RTs collection to the nearest millisecond. Before the experimental procedure, participants were instructed about the tasks and the stimulation. While stimulating, a cartoon movie was presented so that participants could relax; meanwhile, it was possible to control their visual experience during stimulation. After 18 min from the beginning of tDCS, subjects were told that in 2 min they would have to perform the experimental tasks.

5.2.2 Results

PWI paradigm

All the analyses were performed using the statistical software SPSS for Windows version 20.0. Bonferroni correction was applied for all post-hoc comparisons.

Incorrect trials were excluded from the analysis. The same criteria used in Study 3 for trial rejection were applied. This resulted in the exclusion of 6.14% of the naming trials (6.12% in real and 6.16% in sham sessions).

A repeated measure ANOVA was run on RTs of correct trials, with stimulation (2 levels: real vs. sham), SOA (2 levels: 150 and 300ms), and type of interference (2 levels: facilitator vs. distracter) as within subject variables. The main effect of stimulation [$F(1,9)=3.46$; $p=.1$] was not significant while the main effect of type of interference was [$F(1,9)=12.3$; $p=.007$; $\eta^2=.58$], being RTs of facilitators (602ms) faster as compared to distracters' (622ms). The interaction SOA x type of interference was also significant [$F(1,9)=16.96$; $p=.003$, $\eta^2=.65$], replicating the results of the pilot study: naming latencies for facilitators (582ms) differed from those of distracters (620ms) at 150ms SOA ($p<.002$), while there was no difference at 300ms SOA (622ms vs. 623ms; $p=.84$). Moreover facilitators differed across SOAs ($p=.046$). The interaction of stimulation x type of interference reached significance [$F(1,9)=8.68$; $p=.016$, $\eta^2=.49$], since naming latencies for distracters in real sessions (600ms) were significantly faster than in sham sessions (643ms, $p=.039$)(See Fig. 5.3).

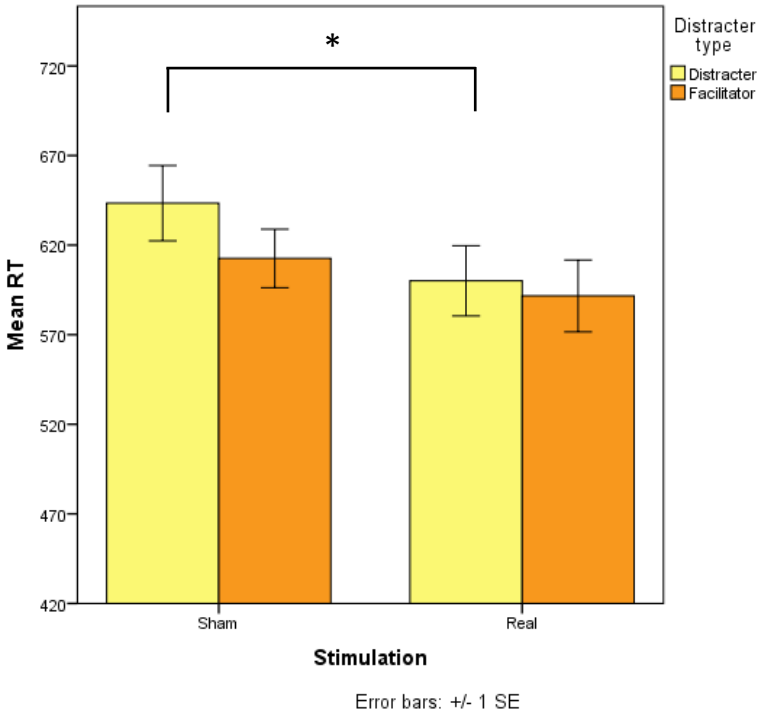


Fig. 5.3: RTs of correct trials in the PWI task in Experiment 1, divided by stimulation session and distracter type.

Planned comparisons (paired two tailed t-tests) were run to compare RTs in no interference condition and the magnitude of the PF effect between stimulation conditions at 150ms SOA. Since at 300ms no difference between facilitators and distracters was found, no analysis was run for the PF at 300ms SOA.

There was no difference in RTs for the "no interference" condition among stimulation sessions (sham: 716ms, real: 690ms; t(9)=.77; p=.46). The magnitude of the PF effect at 150ms SOA, instead, differed between stimulation conditions (sham: 54.9ms, real: 21.7ms; t(9)=.2.72; p=.02) (See Fig. 5.4). Finally, as for the pilot study, naming in no interference condition was slower than when distracters and facilitators were presented at 150ms SOA (716ms vs. 613ms; t(9)=2.55; p=.03).

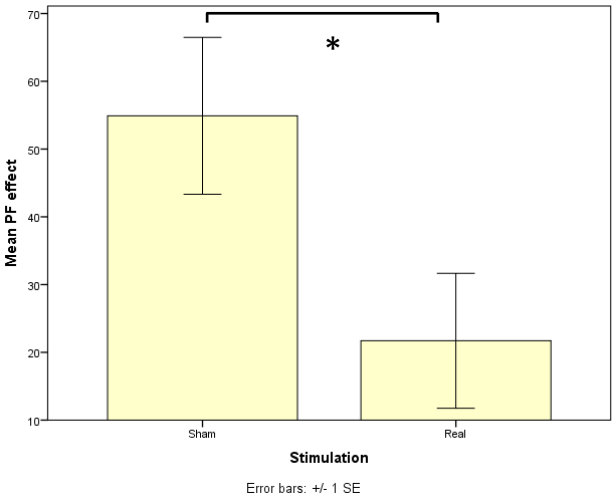


Fig. 5.4: Magnitude of the PF effect in Experiment 1 divided by stimulation session.

Control task

RTs for incorrect trials were excluded. 1.5% of trials were rejected (1.5% both in real and sham sessions). The identical proportion of errors in the two sessions did not allow an accuracy analysis. Three subjects were excluded after catch trials analysis.

A repeated measures ANOVA was run on RTs, with stimulation (2 levels: real vs. sham) and congruency (2 levels: congruent vs. incongruent) as within subject independent factors. The main effect of congruency was significant [$F(1,6)=8.78$; $p=.025$, $\eta^2=.59$], being RTs of incongruent trials slower (384ms) than RTs of congruent ones (357ms). Neither the effect of stimulation [$F(1,6)=.008$; $p=.93$] or the stimulation x congruency interaction [$F(1,6)=.45$; $p=.53$] were significant.

5.3 Experiment 2

5.3.1 Materials and methods

Participants

Twelve neurologically unimpaired individuals (3 Males, mean age 25 years, SD= 3.5; Range 20 – 30 years) took part in the experiment. As in Experiment 1, all participants were native Italian speakers, undergraduate students (Mean years of education = 15.5;

SD= 2.2, Range = 13 – 18 years); they were naïve as to the experimental procedure, and the purpose of the study. All subjects were right-handed (mean EHI= 95; SD= 9.8; Range= 67 - 100), with normal or corrected-to-normal vision. The same recruitment criteria and procedures of Experiment 1 were used.

tDCS

The same stimulation protocol of Experiment 1 was administered. The only difference was the anode placed over the LIFG, identified as in Study 1 and 3 as the crossing point between Fz-T3 Cz-F7 electrodes sites in the EEG 10 – 20 electrodes positioning system (Herwig et al., 2003).

Procedure

The same stimuli and experimental procedure as in Experiment 1 were used in Experiment 2.

5.3.2 Results

PWI paradigm

Excluded trials were 5.25% of the total answers (4.1% for real and 6.4% for sham sessions). As in Experiment 1, a repeated measure ANOVA was run on RTs of correct trials, with stimulation (2 levels: real vs. sham), SOA (2 levels: 150 and 300 ms), and type of interference (2 levels: facilitator vs. distracter) as within subject variables. The main effect of stimulation [$F(1,11)=6.26$; $p=.029$, $\eta^2=.36$] was significant, being RTs in real sessions (666ms) higher than RTs in sham ones (630ms). The interaction SOA x type of interference was also significant [$F(1,11)=31.84$; $p<.001$, $\eta^2=.74$], since naming latencies for facilitators (619ms) differed from those of distracters (657ms) at 150ms SOA ($p<.001$). Interestingly, also the interaction of stimulation x SOA reached

significance [F(1,11)=5.05; p=.046; η^2=.31], being RTs for 150ms SOA in real sessions (668ms) significantly slower than in sham sessions (608ms, p=.012)(See Fig. 5.5).

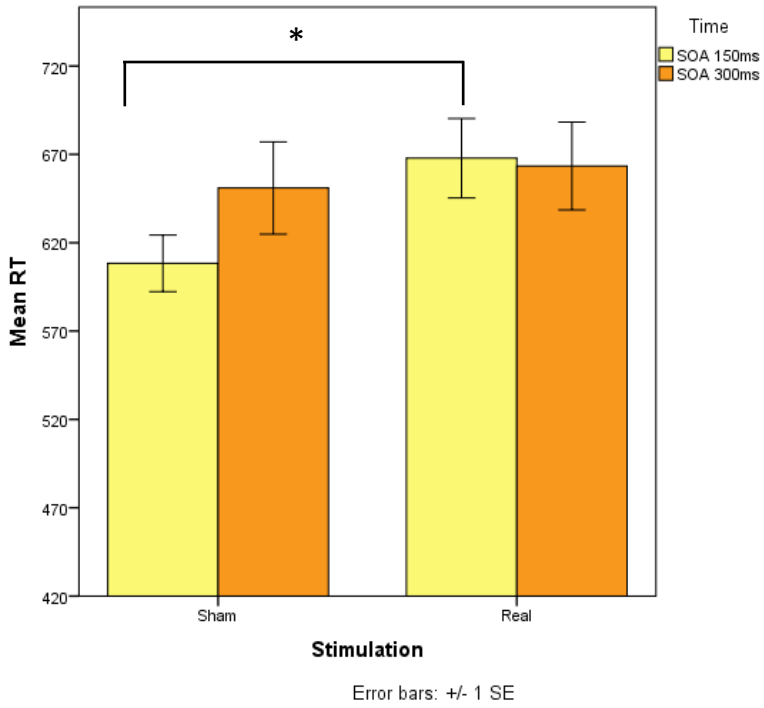


Fig. 5.5: RTs of correct trials in the PWI task in Experiment 2, divided by stimulation session and SOA.

Paired two tailed t-tests did not show any difference in RTs for the "no interference" condition between stimulation sessions (sham: 681ms, real: 679ms; t(11)=.16; p=.88). The magnitude of the PF effect at 150ms SOA did not differ between tDCS conditions (Sham: 38ms, Real: 37ms; t(11)=.07; p=.95). Finally, as for the pilot study and Experiment 1, RTs of no interference condition were slower compared to RTs of conditions in which facilitators or distracters were presented at 150ms SOA (681ms vs. 608ms; t(11)=3.26; p=.008).

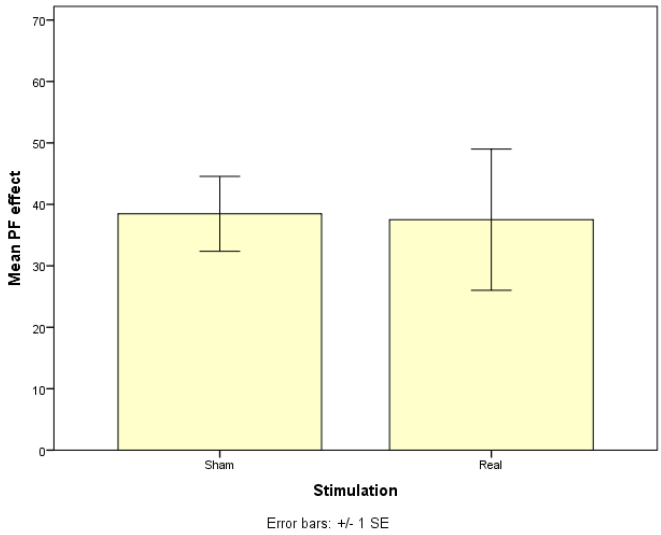


Fig. 5.6: Magnitude of the PF effect in Experiment 2 divided by stimulation session.

Control task

1.5% of trials were excluded (1.83% in real and 1.16% in sham sessions) because incorrect, preventing an analysis on accuracy. Also in this experiment three subjects were removed after analysing the catch trials.

The same repeated measures ANOVA used in Experiment 1 was run on RTs. As for Experiment 1, the main effect of congruency was significant [$F(1,8)=10.33$; $p=.012$, $\eta^2=.56$], being RTs for incongruent trials slower (357ms) than RTs for congruent ones (336ms). The effect of stimulation [$F(1,9)=.84$; $p=.39$] was not significant, as well as the stimulation x congruency interaction [$F(1,9)=.13$; $p=.73$].

5.4 Discussion

The role of the LSTG (Experiment 1) and LIFG (Experiment 2) in the PF effect was investigated in two PWI experiments by delivering a-tDCS immediately before task execution. The present data confirm a role of the LSTG in phonological encoding, since a-tDCS induced faster RTs in trials in which an auditorily presented distracter word was

provided concurrently with the target picture. Moreover, an analysis of PF magnitude showed that this was reduced by tDCS at a SOA at which the PF effect normally occurs (150ms SOA). As regarding PWI performance after a-tDCS over the LIFG, there was no difference depending on the specific interference (distracter of facilitator), or on the magnitude of the PF effect, being comparable both after real and sham stimulation. Nevertheless, stimulation over this area increased RTs when the interfering word was presented at 150ms SOA. One explanation could be that a-tDCS modulated attention focusing (De Zubicaray et al., 2006; Nozari and Thompson-Schill, 2013). The absence of modulation on performance in the control task and on naming latencies in the "no interference" condition further supports the specificity of the data.

Results of Experiment 1 support the finding that LSTG is a crucial area for the occurrence of PF (De Zubicaray et al., 2002; Abel et al., 2006; 2012; De Zubicaray and McMahon, 2009), and, more generally, for phonological encoding (Indefrey, 2011). Enhancing LSTG activation by means of a-tDCS reduced the PF effect in real sessions as compared to sham ones and, critically, this decrement was due to a faster naming when a distracter word was presented.

Some interactive models of word production (e.g. Harley 1993; Berg and Schade, 1992) include mutual inhibitory connections across and within stages of word production to account for conflict resolution. An enhancement of this mechanism, by means of a-tDCS, might have increased inhibition on distracters, thus improving participants' performance in phonologically unrelated conditions: word-form of distracters might have been much strongly inhibited, resulting in faster RTs in real as compared to sham sessions when phonologically unrelated words were presented. Notably, PF effect modulation is reported only at 150ms SOA, when distracters and facilitators usually modulate phonological encoding, accounting for the specificity of this finding. The

LSTG, thus, may be involved not only in lexical retrieval, as suggested in Study 3, but more generally in cascading activation processes involved in object naming (Indefrey and Levelt, 2004; De Zubicaray et al., 2002; De Zubicaray and McMahon, 2009). Moreover, the present data support the existence of an inhibitory-based mechanisms suppressing distracters activation. Finally, the performance with facilitators was not modulated. This negative result may depend on a ceiling effect. tDCS, indeed, has been found to be ineffective at low levels of task difficulty (as in Study 3, Experiment 2; Antal et al., 2004).

Results of Experiment 2 do not account for a specific role of LIFG in phonological encoding, rather they suggest a role of this area on control and attention focus in word production. It is well established that LIFG plays a crucial role at different stages of object naming, probably acting as a top-down regulator system (as in Study 3; De Zubicaray et al., 2006; Kan and Thompson-Schill, 2007; Nozari and Thompson-Schill, 2013). De Zubicaray et al. (2006; De Zubicaray and McMahon, 2009) reported increased BOLD signal of this region in object naming in conflict contexts. Two hypotheses can account for this result. One possibility is that enhancing the inhibitory mechanism driven by LIFG leads to a general increase in RTs, especially when distracters are presented at SOAs at which they usually trigger an interference effect. However, in Study 3 the performance improved in the interference condition when the LIFG was stimulated. Alternatively, a-tDCS can increase the focus of attention, affecting distracters processing at early SOAs. Recently, in a tDCS experiment, Nozari and Thompson-Schill (2013) tested the involvement of the LIFG in language production-related attention. a-tDCS over the LIFG improved performance on target items, but increased errors in non-target ones, showing a detrimental effect of a-tDCS in processing items out of the attentional focus. It is important to note that in the present

PWI paradigm, in sham sessions, distracters and facilitators at 150ms SOA always reduced naming latencies as compared to no interference condition. This is not in line with the literature (Schriefers et al., 1990; De Zubicaray et al., 2009), but can be due to the specific experimental procedure, since it is consistent in both Experiment 1 and 2 sham sessions as well as in the pilot study. Similarly to Nozari and Thompson-Schill's data, stimulating the LIFG may have increased the attentional focus on the presented picture, decreased distracters processing and thus removing their triggering effect at 150ms SOA. The limited number of errors does not allow us checking accuracy on target items, and the absence of a sound-cued naming condition prevents from testing this hypothesis.

In conclusion, the present study corroborates previous findings indicating the LSTG as a critical area in phonological encoding, while the LIFG does not seem directly involved in this task; however, the LIFG could control lexical selection by means of top down attentional mechanisms. Finally, it might be useful to test this protocol, with a-tDCS over the LSTG, in patients with phonological encoding disorders, such as in logopenic subtype of PPA.

6 Study 5: The left temporal pole in proper name recall

6.1 Introduction

As previously reported, learning the name of a new acquaintance is a challenging task. Experimental evidence indicates that learning a person's name is more difficult than learning other information, like his/her job (e.g., James, 2004; James & Fogler, 2007). Several explanations have been proposed to account for this greater difficulty in proper name learning. First, they generally lack meaning (Cohen, 1990), i.e. they do not convey any feature of the person they refer to. In general, unlike common names, proper names, do not have sense, while they possess reference; they may be considered 'pure referring expressions' (e.g. Kripke, 1980). Second, proper nouns contain a broader variety of phonological sequences than those found in other types of words (Brennen, 1993). Finally, they denote individual entities but do not essentially rely on (or at least only to a limited extent) sets of attributes, ending in a one-to-one relationship between name and concept, while common names refer to categories.

It is a common finding, as well as a common life experience, that learning proper names becomes increasingly difficult with age (Cohen & Faulkner, 1986). Several studies support this claim, although there is some contradictory data (see Maylor, 1997). James (2004), for example, found that older adults are more impaired in learning proper names than other biographical information in association with a new face. Similarly, more recently, James and Fogler (2007) found that young adults recalled more names than older or oldest adults. Besides learning, also proper name retrieval is one of the most common difficulties in healthy aging population (Evrard, 2002). Indeed, Evrard (2002), comparing naming of common objects and celebrities in participants of three different age groups, found that the tip of the tongue state (TOT), a familiarity feeling about an

item coupled with the inability to retrieve the corresponding name, was significantly more evident in aging population, and mainly concerned proper names, while common names did not differ in the experimental groups.

Concerning the neural correlates of proper names, a critical review has been made by Semenza (2011) who concluded that while clinical group studies support the idea that proper name processing takes place in the left temporal lobe, single case studies of selective proper name anomia or sparing, as well as neuroimaging studies, suggest the involvement of a larger neural network; this network has proved to involve the uncinate fasciculus and the prefrontal cortex, as recently demonstrated in patients with a left frontal or temporal glioma (Papagno et al. 2011).

Gainotti (2007) systematically reviewed all published single cases and group studies of patients with a prevalent damage to the anterior parts of the right or left temporal lobe and a selective disorder of famous people recognition. The author highlighted two distinct patterns of impairment: a loss of familiarity feeling and of person specific information retrieval, when the right temporal lobe was damaged; and a prevalent impairment in proper names retrieval when the anterior parts of the left temporal lobe were selectively damaged (Gainotti, 2007). This finding is in line with fMRI studies, which demonstrated bilateral temporal pole activations for famous people's recognition, explaining the right hemisphere activation as a recognition-related access to personal semantic knowledge (Damasio et al., 1996, 2004; Grabowski et al., 2001), while activation of the left temporal pole would specifically occur for proper names retrieval (Grabowski et al., 2001).

Starting from these premises, there has been increasing interest in interventions for optimizing proper name retrieval. However, these first attempts are far from being positive, and an effective paradigm has not yet been established. For example, Ross et

al. (2010) investigated whether a-tDCS over the temporal poles affected famous people and places naming. No significant improvement was obtained, but selecting the most difficult responses, i.e. answers that took more than 5 s to be produced, they showed an improvement in person recognition after right temporal pole stimulation compared to sham condition, while no difference was found after left anterior temporal stimulation. The results from this study are rather controversial, starting from the quite arbitrary selection of answers with longer RTs, to the resulting predominant role of the anterior part of the right temporal lobe, suggesting that, if ever, faster people recognition was taking place rather than faster name retrieval. Moreover, people without cognitive deficits would presumably perform almost at ceiling with a very low margin of improvement. Nevertheless, Ross et al. (2011) used the same paradigm with a group of healthy elderly participants, obtaining a better performance on famous people naming when the left anterior temporal lobe was stimulated, in contrast with their previous study. The authors explain their contradictory results as due to the decreased lateralization, which characterizes aging.

However, the results of these two tDCS studies are not conclusive, in particular it is not clear whether tDCS was directly modulating access to phonological information (the name itself) or to people recognition. As reported above, typically the main difficulty experienced by healthy people, especially in aging, is to access the phonological information, which is closely related to the left anterior temporal lobe (Gainotti, 2007). To this aim, a-tDCS was applied over the anterior part of the left temporal lobe, during a face-name association learning task and, afterwards, participants were tested for both recall and recognition. In order to avoid ceiling effects and the retrieval of semantic information during the recognition stage, in this study unfamiliar faces arbitrarily paired with names were used. The hypothesis was that a-tDCS over the left anterior temporal lobe should affect subsequent recall and recognition.

6.2 Experiment 1

6.2.1 Materials and methods

Participants

Twelve neurologically unimpaired individuals (four males, mean age= 27 years, SD=4 y, range 20-38; mean educational level = 17.6 years, SD= 2.5, range 13-22) participated in the study. All participants were right-handed, as assessed by means of the Edinburgh Inventory Questionnaire (Oldfield, 1971; mean= 89.4%, range 78.9-100, SD= 7.7), Italian native speakers, naive to the experimental procedure and the purpose of the study. All subjects had normal or corrected-to-normal vision. They had no history of chronic or acute neurologic, psychiatric, or medical disease; no family history of epilepsy; no current pregnancy; no cardiac pacemaker; no implants to the head (cochlear implants, aneurysm clips, brain electrodes) and did not take acute or chronic medication. Written informed consent was obtained from all participants. The experiment was approved by the local ethical committee of the University of Milano-Bicocca and subjects were treated in accordance with the Declaration of Helsinki and Oviedo.

Material

Thirty-two colour pictures of faces (taken from the AR face database, Martinez & Benavente, 1998) with a neutral expression were selected as stimuli, paired with a proper (first) name, in part used in a previous experiment (Cattaneo, et al., 2011a). These items were divided into two lists, each administered in one of the two experimental sessions (see below). In order to balance the pictures between lists, faces were preliminary rated on attractiveness and peculiarity. Ten Italian subjects (5 males, mean age: 23.8 years; mean educational level: 11.6 years) took part in the pilot rating experiment. Sixty pictures of faces, 30 males and 30 females, taken from the same

database, were rated on a Likert scale both for attractiveness, ranging from 1 (not attractive at all) to 7 (very attractive), and peculiarity (being 1 very common and 7 very uncommon). The mean value was then calculated for the two variables. Thirty-two pictures, 16 male and 16 female faces, with attractiveness and peculiarity values close to average (attractiveness=2.94, SD=0.83; peculiarity= 3.86, SD=0.94), were included in the experimental task (mean indices: attractiveness=3.17, SD=0.74; peculiarity=3.20, SD=0.54). The 32 items were divided into two lists of 16 items each (8 male and 8 female pictures) balanced for these two variables. T-test comparisons showed no significant differences for both attractiveness [t (15)=0.21; p=0.84] and peculiarity [t (15)= 0.26; p=0.8]. Concerning proper names, the items taken from Cattaneo et al. (2011) (n=17) plus 15 additional items were divided into two lists of 16 items each (8 male and 8 female names each). Proper names were controlled for number of letters and syllables. T-test comparisons showed no difference between the names of the two lists either for number of letters [t (15)=0.27; p=0.79] or syllables [t (15)=0.70; p=0.50].

tDCS parameters

tDCS was delivered by a battery driven, constant current stimulator (Eldith, Neuroconn, Ilmenau, Germany) through a pair of saline-soaked sponge electrodes (Anode 25 cm^2; Cathode 35 cm^2) kept firm by elastic bands. Following a previous study (Ross et al., 2010), the anode was placed over the left temporal pole, while the cathode was placed over the right supraorbital region. The stimulation site was localized by the 10-20 EEG electrode positioning system, corresponding to T3 location.

Each subject underwent two stimulation sessions, with an interval of one week between each other. Order of stimulation was balanced across subjects. Stimulation intensity was set at 2 mA. In the real session, the duration of stimulation was 20 min, while in the sham condition stimulation lasted for 30 s. In both cases the current was delivered after

a fade-in and was followed by a fade out periods of 30s each (Nitsche et al. 2003; Ambrus et al.,2010). Current density (Anode: 0.8 A/m^2; Cathode: 0.57 A/m^2) and charge density (Anode: 960 C/m^2; Cathode: 685.7 C/m^2) were maintained below the safety limits (Poreisz et al., 2007). The study was a single-blind experiment.

Experimental task

The experimental task consisted of two parts: an associative-learning phase and a test phase. During the learning phase, subjects were presented with face-name pairs. Participants were required to learn the association between names and faces, for later recall. In particular, faces and names were presented simultaneously, the picture size being 10.5x8 cm, and appearing in the centre of the computer screen, with the name below it, in upper case, font Courier New, point size 18. Each name-face pair was shown for 5 s, randomly recurring 4 times (total item presentations: 64, mean procedure duration: 5.3 min). The learning phase was performed during the last 6 min of the stimulation protocol. Immediately after tDCS (within approximately 2 min from the end of stimulation), participants were tested for recall. During recall, the same faces presented in the learning phase appeared on the screen without the corresponding name. Subjects were required to orally produce the associated name through a microphone. This procedure allowed recording both RTs and responses, and saving them as individual audio files. The time limit to answer was 5 s. After the presentation of a fixation point in the centre of the screen lasting for 500ms, the next trial appeared. If the answer was produced before the time limit, the experimenter manually triggered the next presentation by pressing a mouse key. The audio files were then listened off-line to evaluate accuracy, thus marking each trial as correct or incorrect. Errors were classified as intrusions, when the subject produced a name associated with a different face, or omissions, when the subject did not produce any answer in the 5s time limit

(participants produced only these two types of error). The procedure lasted approximately 2 min. After completion of this task, subjects performed a recognition task. In this case, faces were shown simultaneously with two names presented in the left and right bottom corners of the screen: one was the correct item, while the other name had been coupled with a different face of the set. Participants had to choose the correct response, by pressing one of two keys (keys 1 and 9 on a standard Italian QWERTY keyboard, for the name in the left or right corner of the screen, respectively). There was no time limit and the next presentation was triggered by the subjects' answer. The side of the correct responses was balanced across trials (see Fig. 6.1 for a timeline of the different experimental steps).

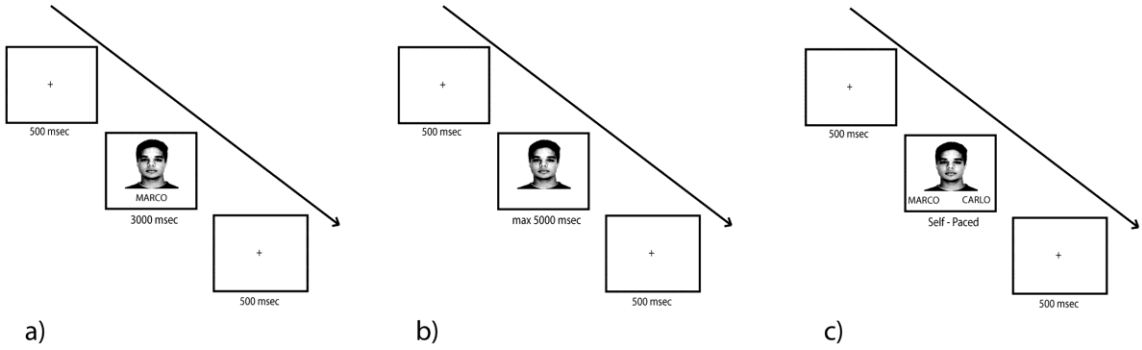


Fig. 6.1: Experimental timelines for a) the learning phase, b) the recall and c) the recognition tasks.

Procedure

Subjects were seated in front of a computer screen (at a distance of 57 cm), in a normal-lightened and silent room. E-prime 2 (Psychology Software Tools, Pittsburgh, PA, USA) was used for stimuli presentation and data collection. A microphone triggered a voice key to collect RTs to the nearest ms, while a second microphone recorded an audio file, with the participants' answer, for each trial. At the beginning of the experiment, participants were instructed about the procedure. Concurrently with the start of stimulation, a cartoon movie – the same for each participant and for the two

tDCS (sham and real) sessions – was projected on the computer screen. This was done to expose participants to the same experience during the stimulation period, thus reducing inter-subjects variability (for a similar procedure, see Study 1 and 3). After 12 min from the beginning of stimulation, the cartoon movie was stopped and subjects were told that in 2 min they would have been submitted to the face-name association recall, followed by the recognition task.

6.2.2 Results

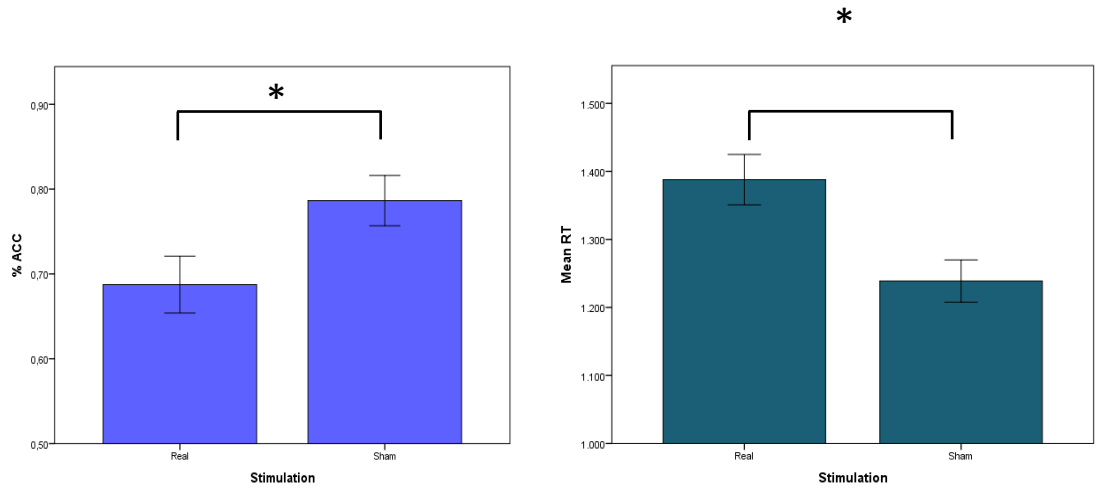
Data were analysed by means of a mixed effects model on RTs and accuracy. As fix factors, list (2 levels: list 1 vs. list 2), experimental session (2 levels: first vs. second) and stimulation (2 levels: real vs. sham) were included, while subjects and items intercepts entered the model as random factors.

The mean recall accuracy was 73.69% (range 53.12-90.62, SD = 14.5). The mixed effect model run on accuracy levels showed a significant main effect of stimulation [$F(1,338)=5.39$, $p=0.021$], being performance worse in real stimulation sessions (68.7%) as compared to sham (78.6%). No other main effects were significant, while the only significant interaction was stimulation x list [$F(1,8)=11.22$; $p=0.001$], being the detrimental effect of stimulation greater for list 1 rather than list 2 (-28% vs. -11% respectively, $p=0.003$). Random factors were not significant (see Fig. 6.2a).

Mean RTs were 1541ms for real sessions (range 1110-2029ms, SD=395) and 1381ms for sham ones (range 718-2191ms, SD=364). The mixed effect model run on RTs of correct trials showed a trend towards significance for the main effect of stimulation [$F(1,242.31)=3.447$, $p=0.065$] being mean RTs of real sessions slower than sham ones. No other main effect or interaction of fixed effects or random effects reached significance.

Concerning recognition, the mean accuracy was 93% (range 71.9%-100%, SD 8.4%). No main effect or interaction between the considered fixed factors was significant [stimulation: F(1,366.19)=0.014, p=0.91; session: F(1,337.44)=0.007, p=.93; list: F(1,367.79)=1.35; p=0.24]. Subject random factor was not significant while item was (Wald Z=2.53; p=0.011) [2].

The same model run on RTs of correct items highlighted a significant main effect of stimulation [F(1,336.7)=15, p<0.001], being RTs longer in real sessions (1388ms, range 1052-1839ms, SD=268) than in sham ones (1239ms, range 994-1558, SD= 179) (see Fig. 6.2b). The main effect of session was also significant [F(1,310.45)=23.56, p<0.001] with shorter latencies in the second sessions (1229ms) compared to the first ones (1396ms). Subject random factor was not significant while item was (Wald Z=2.59; p=0.01).



a) b)

Fig. 6.2: a) Mean accuracy for the recall task and b) mean RTs in the recognition task of Experiment 1 divided by stimulation condition.

To investigate participants' performance in detail, an error analysis was run on incorrect trials. A mixed model was performed on number of omissions and number of intrusions, separately. Since set and session had no effect on accuracy, only stimulation was

[2] The significant effect of item means that some item is more difficult than some other and the model has taken into account it while calculating fixed effects.

considered as a fix factor (2 levels: real vs. sham), while subject and item were included as random factors.

Intrusion analysis revealed a significant effect of stimulation [F(1,351.93)=4.1, p=0.044], with a higher intrusion rate in real sessions as compared to sham (14.6% and 8.3% respectively). The same model run on omissions, instead, showed no effect of stimulation [F(1, 354.74)=0.96, p=0.33], with similar rates of omissions in both tDCS conditions (13.1% vs. 16.6% in sham and real sessions, respectively). Random factors were not significant for both models (see Fig. 6.3).

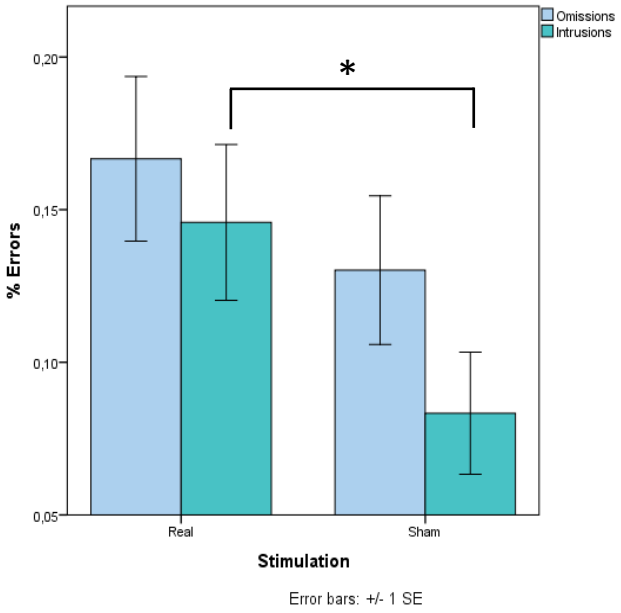


Fig. 6.3: Mean error rate for omissions and intrusions in Experiment 1 divided by stimulation condition.

6.2.3 Comment

a-tDCS applied over the left temporal lobe modulated face-name association, although not in the expected direction. Indeed, in the recall task, not only accuracy was lower in real sessions as compared to sham ones, but there were significantly more intrusions during anodal stimulation compared to sham, while no difference was found in the case of omissions. Possibly, stimulation increased interference among competitors (i.e., the

different names) when associating a specific name to a face. Slower RTs in the recognition task after real a-tDCS support this hypothesis: stimulation seems to increase the difficulty to discriminate between two options. Yet, a worse performance during real tDCS could depend from different reasons, as discomfort, anxiety or distractibility. To rule out these possibilities, a further experiment was run using the same material and procedure on a different group of participants inverting the stimulation polarity. The hypothesis was that whether the results from the first experiment were driven by side effects, c-tDCS should produce the same results, since tDCS elicits similar sensations for both anodal and cathodal applications (Ambrus et al., 2010).

6.3 Experiment 2

6.3.1 Materials and methods

Participants

Twelve neurologically unimpaired individuals took part in Experiment 2 (four males, mean age= 24.3 years, range 20-32 years, SD=3.6; mean educational level = 15.7, range 13-18 years, SD= 2.2). None of them participated in Experiment 1. Participants were right-handed (mean Edinburgh handedness index 96.5%, range 78.9-100, SD 8.2) Italian undergraduate students with normal or corrected-to-normal vision, and fulfilled the safety criteria for tDCS administration. Written informed consent was obtained from all participants.

Procedure

The experimental procedure was identical to Experiment 1. Stimulation parameters for real and sham tDCS were also the same, but the polarity was reversed: the cathode ($25cm^2$) was placed over the left temporal pole (T3 site in EEG 10-20 electrode

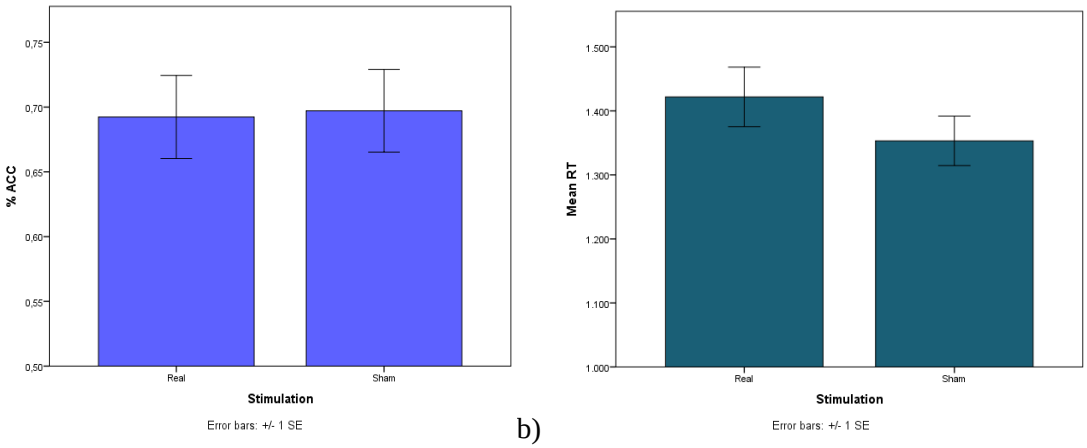
placement system), whereas the anode (35 cm^2) was placed over the right supra-orbital region.

6.3.2 Results

The same statistical models as in Experiment 1 were applied.

For the recall task, the mean accuracy was 71.61% (range 56.25-93.75, SD = 13.49). The mixed effects model run on accuracy showed a significant main effect of session [F(1,338)=5.96, p=0.015], with a better performance on the second session (74%) compared to the first one (63.02%). No other main effect or interaction was significant. Subject random factor did not reach significance while item did (Wald Z=2.43; p=0.015).

Mean RTs were 1530ms for real sessions (range 893-2035ms, SD=369) and 1453ms for sham ones (range 1031-2076ms, SD=292). The mixed model run on RTs of correct trials showed no significant main effect or interaction, or significant random effects (see Fig. 6.4).



a) b)

Fig. 6.4: a) Mean accuracy for the recall task and b) mean RTs in the recognition task of Experiment 2 divided by stimulation condition.

Concerning recognition, mean accuracy was 93.49% (range 81.25-100, SD 6.4). The mixed effects model showed a main effect of session [F(1,338)=5.44, p=0.02], being the

first performance (91.1%) lower than the second one (96.6%), as expected. No other main effect [stimulation: F(1,338)=0.99, p=0.32; list: F(1,31.21)=1.48; p=0.23] or interaction between the considered fix factors was significant. Subject random factor was not significant, while item was (Wald Z=2.62; p=0.009).

Mean RTs for correct trials were 1330ms (range 998 – 2133ms; SD= 309). The analysis did not highlight significant main effects or interaction. Subject random factor was not significant while item was (Wald Z=1.96; p=0.05).

Intrusion and omission analyses run with the same model as in Experiment 1 did not show any significant effect of stimulation for both error types [F(1,352.12)=0.14, p=0.71; F (1,349.05)=0.04, p=0.83 for intrusions and omissions, respectively], being the percentage of intrusions (11.5% vs. 10.4%) and omissions (19.9% vs. 20.7%) not different between real and sham sessions (Fig. 6.5). Random factors were not significant for intrusions, while in the case of omissions only item factor approached significance (Wald Z=1.94; p=0.05).

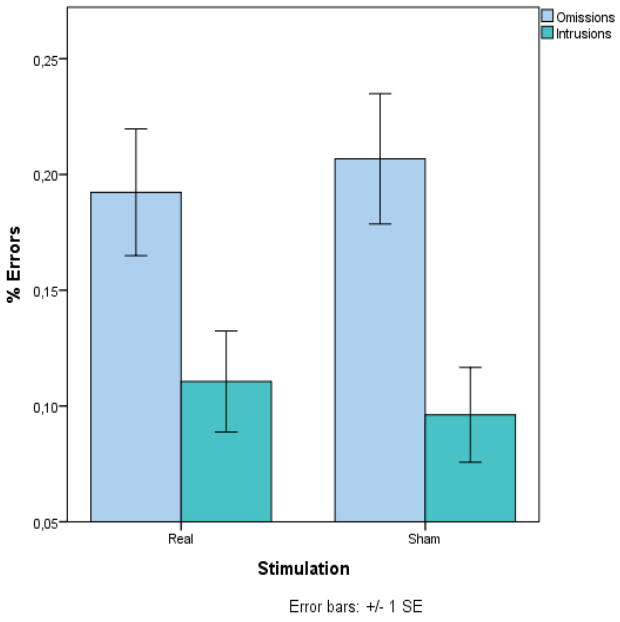


Fig. 6.5: Mean error rate for omissions and intrusions in Experiment 2 divided by stimulation condition.

6.3.3 Comment

No effect of cathodal stimulation on face-name association emerged, showing that c-tDCS had no detrimental effect on performance. Therefore, it is unlikely that side effects, such as discomfort or stimulation-driven expectation effects, could have influenced results from Experiment 1. As a consequence, a-tDCS can have increased interference in name selection, ending in a higher number of intrusions. However, it could still be argued that, being tDCS not strictly spatially defined, the application of the anode over T3 could have modulated frontal activity as well. The PFC is classically related to interference control and executive functions (for a review see for example Miller & Cohen, 2001), and tDCS could have disrupted this control. This possibility seems unlikely, since performance usually improves after anodal stimulation over the prefrontal cortex (see, for example, Iyer et al., 2005; Fertonani, et al., 2010; Study 1 and 2) reducing interference in monitoring tasks (Wirth et al., 2011; Study 3). However, to rule out this hypothesis, an additional control experiment was conducted, using a classic interference test, the color-word Stroop task (Stroop, 1935). The hypothesis was that if the increased interference among proper names were due to a reduction in prefrontal control, the same type of stimulation should produce a detrimental effect also in a colour-word Stroop task. Alternatively, if the effect is specific for proper names, namely a general increase of their activation, then a-tDCS over the left temporal pole should not change the Stroop performance.

6.4 Control experiment

6.4.1 Materials and methods

Twelve right-handed (mean EHI 93.9%, range 68.4-100, SD 10.5) Italian subjects performed the Stroop task (six males, mean age = 27.6 years, range 20-33 years, SD = 3.4, mean education = 17 years, range 13-22, SD = 2.4). The same stimulation

parameters and inclusion criteria of Experiment 1 were applied. Ninety trials were presented in three different blocks on a computer screen. The first 30 trials were words (names of three colours: red, green, and blue) that the subject had to read aloud. The word was written in black on a white background (Font Courier New, Size points 40), each colour name appearing 10 times in a random order. The second block consisted of 30 coloured squares, and the color (red, green or blue) had to be named, each colour appearing 10 times in a random order. The last 30 items were the same colour names of the first block, written in coloured letters, the colour being incongruent with the displayed name. The participant had to name the colour in which the word was written. Each stimulus appeared for 2 s (see Fig. 6.6 for the experimental timeline). RTs and accuracy were recorded. The task was performed immediately after the end of the stimulation protocol and lasted about 5 min.

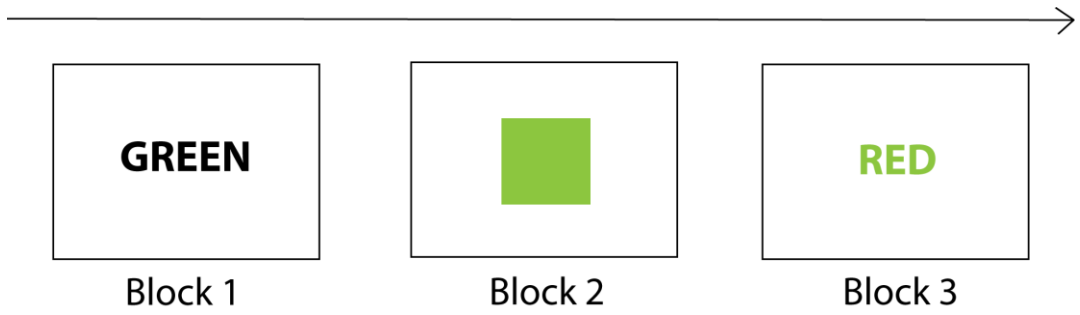


Fig. 6.6: Experimental timeline for the Stroop task.

6.4.2 Results

RTs for correct trials were analysed by means of a mixed effects model, including as fix factors: condition (2 levels: interference vs. non-interference) and stimulation (2 levels: real vs. sham), while subjects' intercept entered the model as a random factor.

No analysis was run on accuracy since the overall amount of incorrect answers was 0.9%.

Mean RTs were 543ms (range 390-746ms, SD=87.4). The analysis revealed a main effect of condition [F (1,33)=49.98; p<0.001], while neither stimulation [F(1,33)=1.82; p=0.19] or the interaction stimulation x condition (F(1,33=0.80; p=0.38) were significant. Random effect did not reach statistical significance (see Fig. 6.7).

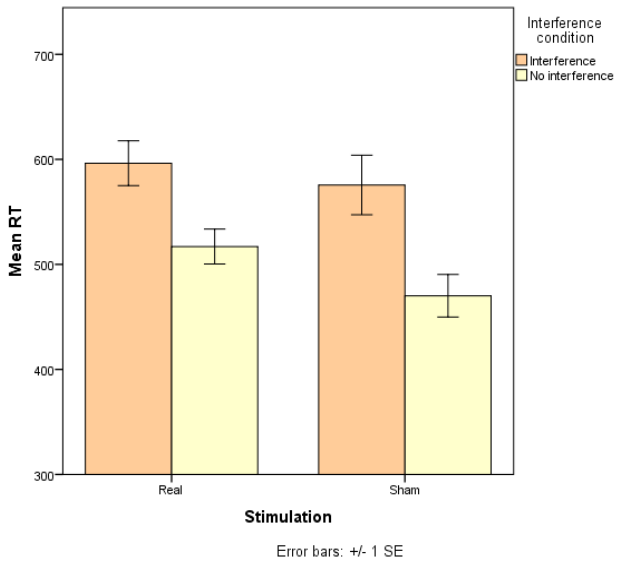


Fig. 6.7: Mean RTs in the Stroop task divided by interference and stimulation condition

6.5 General Discussion

In this study, a-tDCS applied over the left temporal pole impaired performance in a face-name association task, both on recall and recognition. More specifically, in the case of recall, in real as compared to sham sessions significantly more errors were produced, in particular intrusions, while the number of omissions did not differ in the two stimulation conditions; in addition, RTs were slower, although not significantly, in real stimulation than in sham. In the recognition task, slower RTs were recorded after real stimulation than after sham. Although these data partially support a role of the anterior part of the temporal lobe in name retrieval, the direction of the tDCS effect was

not the expected one. Stimulation side effects or dysexecutive mechanisms as possible explanations were ruled out: indeed, c-tDCS over the same area had no effect on performance, and the same tDCS paradigm did not produce any significant change on a different task tapping executive functions.

The circuit involved in the retrieval of proper names includes the anterior part of the left temporal lobe, possibly as a converging zone between person identification and name retrieval (Gainotti, 2007; Tranel, 2009, but see also Semenza, 2006 for a different position). Indeed, several neuropsychological patients with neurodegenerative (Papagno & Capitani, 1998), neoplastic (Giussani et al. 2009), traumatic (Miceli et al., 2000), and vascular (Lucchelli & De Renzi, 1992; Vertischel et al., 1996; Reinkemeier, et al., 1997; Saetti et al., 1999) brain lesions in the anterior part of the left temporal lobe show selective proper name retrieval deficits (for a review see Semenza 2006, 2009, but see Semenza, 2006 for controversial results). A recent meta-analysis on patients with temporal lobe damage has confirmed a deficit in proper name retrieval in the case of left temporal pole lesions (Gainotti et al., 2007). Accordingly, Papagno et al. (2011) demonstrated in a follow-up study that the surgical removal of the left uncinate fasciculus, the major white matter tract connecting the anterior temporal lobe with the orbito-frontal cortex, causes a deficit in proper names retrieval, which persists over time.

As reported in the introduction, two recent studies have tried to address the role of the temporal poles in proper names retrieval using tDCS both in young (Ross et al., 2010) and aging population (Ross et al., 2011). However, famous people names, which are likely to be known by participants, were used, and no effect was found. To obtain a significant result, the authors analysed only part of the stimuli, namely those requiring longer RTs, finding an improvement only after right stimulation. This result is quite

puzzling and suggests that not name retrieval, but possibly people identification, was enhanced in this condition. Therefore, this result has no potential interest for the difficulties in name retrieval experienced with aging. Indeed, Ross et al. (2011) themselves in a subsequent study suggest that retrieval more than identification could be the major deficit in healthy aging individuals, in line with the current literature (Evrard, 2002; James, 2004; Maylor, 1997). Accordingly, in the present study, it has been specifically examined face-name association, bypassing any possible effect of famous face recognition, and specifically investigating the access to the phonological form of proper names (Bruce & Young, 1986).

As mentioned in the introduction, James (2004) found that proper name learning was more difficult for older adults than learning their occupation. Interestingly, in that study the same label was used for proper names and jobs (for example Mr. Baker vs. a baker). The author argues that the greater difficulty in learning a proper name, and in retrieving it later, in association to the correct owner, is due to fewer connections in the semantic network for family names rather than for jobs, resulting in a feeble memory trace for the former (see also Semenza, 2009). Moreover, these difficulties are explained as a result of an inhibitory deficit in older participants (Hasher & Zacks, 1988; Zacks & Hasher, 1994), producing interference among the new learned material.

The present findings may depend on a similar interference effect: applying a-tDCS during the learning phase, when face-name pairs were repeatedly presented, might have over-activated name representations, leading to a greater interference during the following name selection. Similarly, in Study 3, using a blocked naming paradigm, a-tDCS applied over the LSTG significantly increased the SI effect, possibly because tDCS produced an over-lasting lexical activation of items in semantically related clusters, thus enhancing competition between target and distracters. Accordingly,

Schnur et al. (2006) showed in Broca's aphasics that errors arise from competition among increasingly activated items when homogenous sets of stimuli were used in a blocked-cyclic naming task.

The primary goal of tDCS in rehabilitation is to induce plastic changes in the neural activity to improve performance. However, plasticity does not always result in behavioural compensation, as found for example in congenitally deaf people (Bolognini et al., 2012), in phantom limb experiences (Flor, et al., 2006) or in aphasia recovery (Szaflarski, et al., 2013). Accordingly, a worse performance following a-tDCS is not totally uncommon (see for example Antal et al., 2004; Ferrucci et al., 2008; Jacobson, et al., 2012; Peters et al., 2013, Study 3 and 4), and it has been explained with an over-activation of non-target distracters.

However, despite the negative effect obtained by means of a-tDCS, this study confirms the role of the anterior part of the left temporal lobe in proper name retrieval. It is not clear, though, how to enhance it, in order to develop a useful protocol for rehabilitation. Certainly, tDCS should not be applied in the learning phase. Due to the widespread network responsible for proper names retrieval, a combined stimulation of temporal and frontal lobes may help in both activating proper names and inhibiting inter-item interference. Another possibility could be to apply a-tDCS after the learning phase, in order to avoid plasticity during repeated presentation. Further research should test these options.

7 General conclusions

Language has a primary role in everyone's life. There are few moments in which we are not processing or producing some verbal material in order to interact with other people and our environment. Therefore it is crucial to understand how this amount of information is processed. Word production, for example, apparently is an easy task, but evidence from people affected by cerebral diseases (stroke, neural degeneration, infections) shows at how many levels it can be impaired. There are, indeed, several different language processes, and the dysfunction of one (or most likely few) of them may end in the production of an altered output, as well as no production at all. The present study aimed at shedding light on some aspects of word production by means of a novel NiBS technique: tDCS.

In the last years, tDCS application in cognition has greatly increased (Nitsche and Paulus, 2011). This technique has the advantage, with respect to other NiBS techniques, to be easy to use, relatively cheap, safe and less invasive than ECS or TMS. Because of these features, tDCS has become an attractive tool for both research and, mainly, rehabilitation. It is of high interest then, to investigate whether tDCS could be used to study language processing and how its effects can modulate word production.

Accordingly, in Study 1 and 2, I focused on verbal fluency. This task is widely used in clinical studies (see Costafreda et al., 2006; Schwartz and Baldo, 2001), to assess the ability to produce and retrieve words using a given cue (initial letter or semantic category). In Study 1, I investigated whether a-tDCS could modulate performance on this task, by applying 20 min anodal or sham stimulation over the LIFG before verbal fluency. Participants, overall, produced more words after real than sham tDCS, confirming the role of this structure in verbal fluency. In Study 2 the mechanisms underlying this improvement in verbal fluency were investigated. To directly test the

relationship between behavioural and neurophysiological tDCS-driven modulation, the experimental protocol of Study 1 was combined with the investigation of cortical excitability recorded by means of a TMS-EEG system. a-tDCS modulation of cortical excitability was tested on an area (BA6) that is involved in the task and on an unrelated area (BA7) after both real and sham a-tDCS. a-tDCS was applied over the LIFG and a verbal fluency task was concurrently performed. TEPs from 60 electrodes measuring GMFP, and LMFP from 7 different electrodes clusters were measured. As in Study 1, verbal fluency increased in real a-tDCS compared to sham sessions. While there were no different increases in the three experimental sessions concerning global cortical excitability, local cortical excitability selectively increased over BA6 after real a-tDCS, compared to real tDCS sessions with TEPs elicited stimulating BA7, and sham sessions. The local cortical excitability increased in a late TEP component (65-150ms), reflecting an enhanced activity in the functional network involved in verbal fluency. Moreover, the increment of local excitability with real stimulation in the cluster of electrodes over the LIFG positively correlated with the improvement in verbal fluency performance. These are the first results showing, by means of a technique that directly tests cortical excitability and with a high temporal resolution, that there is an increased excitability in a functional network after a-tDCS delivered during a specific task performance; these results also suggest that the effect of tDCS on verbal fluency is due to an increase of cortical excitability in LIFG, i.e. the stimulated area.

In Study 3 and 4, I investigated the role of the LIFG and LSTG in SI and PF. SI effect refers to a greater difficulty in naming an object in a semantically related context with respect to a semantically unrelated one (Damian et al., 2001; Wilshire and McCarthy, 2002; Belke et al., 2005; Schnur et al., 2006; Abdel Rahman and Melinger, 2011, Ganushchak and Schiller, 2008); PF refers to a facilitation in picture naming in a

phonologically related context (Lupker, 1982; Schriefers et al., 1990; De Zubicaray et al., 2001; Abel et al., 2009; Damian and Bowers., 2009). LSTG activation apparently is related to object naming in both contexts: there is an increased BOLD signal in this area with SI (De Zubicaray et al., 2001) and decreased BOLD signal with PF (De Zubicaray et al., 2002). LIFG, instead, is involved in lexical selection in demanding contexts (Kan and Thompson-Schill, 2004a, 2004b; Moss et al., 2005), and in aphasic patients a damage in this area produce significant SI (Schnur et al., 2006; 2009). In Study 3 a semantic blocked naming paradigm was used: subjects were asked to name pictures in semantically related or unrelated contexts (Belke et al., 2005; Schnur et al., 2006, 2009), after a-tDCS delivered over LIFG or LSTG. While the SI effect increased after LSTG stimulation, it decreased after LIFG stimulation. The results concerning LSTG were interpreted as supporting the involvement of this area in lexical selection, which occurs by competition process. Increasing activation of this area, indeed, increased the spread of activation that causes the SI effect in blocked naming, thus ending in a more difficult selection of the target among distracters. a-tDCS applied over LIFG, instead, reduced the SI effect, probably enhancing the ability to select the correct target . With regard to PF, the same areas were stimulated before a PWI paradigm, a task in which the subject named a picture concurrently with the auditory presentation of a phonological facilitator or distracter. While LIFG stimulation did not modulate the PF effect, stimulating the LSTG ended in a smaller PF effect, indicating an improved selection of the target phonemes even when a distracter was presented. RTs after LIFG increased, in line with previous findings, suggesting a detrimental effect of a-tDCS over this area when multiple stimuli are presented (Nozari and Thompson-Schill, 2013). Overall, the results from Study 3 and 4 support the role of the LSTG in SI and PF effects, and of LIFG in demanding selection contexts.

In Study 5, I focused on proper names learning and retrieval. Evidence from neuropsychological studies points to the left temporal pole as the crucial area for proper names retrieval (Gainotti, 2007). Since a deficit of this ability is one of the most frequently reported side effects of aging (Evrard, 2002), the aim was to develop a stimulation protocol apt to improve performance. In this last study a face-name association task was administered, while delivering a-tDCS over the left temporal pole. The performance worsened after stimulation, with an increased number of intrusions in real sessions compared to sham ones, while omissions did not change. Procedural discomfort was excluded as a possible explanation, since inverting tDCS polarity did not modulate participants' performance. To rule out the possibility that a-tDCS effects were due to spreading to the LIFG, being this area involved in interference control, a Stroop task was administered after stimulation of the left temporal pole: no effects of tDCS were found, thus ruling out a possible spread of stimulation. Study 5 then, failed to develop a protocol to improve performance in proper names retrieval; nevertheless, it confirmed the role of left temporal pole in this process.

Altogether, the studies further support that tDCS can be used in investigating the neural correlates of word production, encouraging the design of technical and experimental solutions to overcome the drawbacks of this technique and exploit its potentials in research and clinical settings.

8 References

1. Abdel Rahman R, Melinger A (2009a) Semantic context effects in language production: A swinging lexical network proposal and a review. Language and Cognitive Processes 24:713-734.

2. Abdel Rahman R, Melinger A (2009b) Dismissing lexical competition does not make speaking any easier: A rejoinder to Mahon and Caramazza (2009). Language and Cognitive Processes 24:749-760.

3. Abdel Rahman R, Melinger A (2011) The dynamic microstructure of speech production: semantic interference built on the fly. Journal of experimental psychology 37:149-161.

4. Abel S, Dressel K, Bitzer R, Kummerer D, Mader I, Weiller C, Huber W (2009) The separation of processing stages in a lexical interference fMRI-paradigm. NeuroImage 44:1113-1124.

5. Ambrus GG, Paulus W, Antal A (2010) Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol 121:1908-1914.

6. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W (2012) The fade-in--short stimulation--fade out approach to sham tDCS--reliable at 1 mA for naive and experienced subjects, but not investigators. Brain stimulation 5:499-504.

7. Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Cachia A, Plaze M, Paillere-Martinot ML, Martinot JL (2006) Modulation of language areas with functional MR image-guided magnetic stimulation. NeuroImage 29:619-627.

8. Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB (2012) Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain stimulation 4:84-89.

9. Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann KP, Paulus W (2004) Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. Journal of cognitive neuroscience 16:521-527.

10. Antal A, Kovacs G, Chaieb L, Cziraki C, Paulus W, Greenlee MW (2012) Cathodal

stimulation of human MT+ leads to elevated fMRI signal: a tDCS-fMRI study. Restorative neurology and neuroscience 30:255-263.

11. Antonucci SM, Beeson PM, Labiner DM, Rapcsak SZ (2008) Lexical retrieval and semantic knowledge in patients with left inferior temporal lobe lesions. Aphasiology 22:281-304.

12. Ayora P, Peressotti F, Alario FX, Mulatti C, Pluchino P, Job R, Dell'acqua R (2011) What Phonological Facilitation Tells about Semantic Interference: A Dual-Task Study. Frontiers in psychology 2:57.

13. Baker JM, Rorden C, Fridriksson J (2010) Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke; a journal of cerebral circulation 41:1229-1236.

14. Baldo JV, Shimamura AP (1998) Letter and category fluency in patients with frontal lobe lesions. Neuropsychology 12:259-267.

15. Baldo JV, Schwartz S, Wilkins D, Dronkers NF (2006) Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. J Int Neuropsychol Soc 12:896-900.

16. Barwood CH, Murdoch BE, Whelan BM, Lloyd D, Riek S, JD OS, Coulthard A, Wong A (2010) Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. Eur J Neurol 18:935-943.

17. Been G, Ngo TT, Miller SM, Fitzgerald PB (2007) The use of tDCS and CVS as methods of non-invasive brain stimulation. Brain research reviews 56:346-361.

18. Belke E, Meyer AS, Damian MF (2005) Refractory effects in picture naming as assessed in a semantic blocking paradigm. The Quarterly journal of experimental psychology 58:667-692.

19. Bell EE, Chenery HJ, Ingram JC (2001) Semantic priming in Alzheimer's dementia: evidence for dissociation of automatic and attentional processes. Brain and language 76:130-144.

20. Berg T, Schade U (1992) The role of inhibition in a spreading-activation model of language production. I. The psycholinguistic perspective. Journal of Psycholinguistic Research 21:405-434.

21. Biegler KA, Crowther JE, Martin RC (2008) Consequences of an inhibition deficit for word production and comprehension: evidence from the semantic blocking paradigm. Cognitive neuropsychology 25:493-527.

22. Bikson M, Datta A, Rahman A, Scaturro J (2010) Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. Clin Neurophysiol 121:1976-1978.

23. Bikson M, Rahman A, Datta A (2012a) Computational models of transcranial direct current stimulation. Clin EEG Neurosci 43:176-183.

24. Bikson M, Rahman A, Datta A, Fregni F, Merabet L (2012b) High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. Neuromodulation 15:306-315.

25. Bindman LJ, Lippold OC, Redfearn JW (1964) The Action of Brief Polarizing Currents on the Cerebral Cortex of the Rat (1) During Current Flow and (2) in the Production of Long-Lasting after-Effects. The Journal of physiology 172:369-382.

26. Birn RM, Kenworthy L, Case L, Caravella R, Jones TB, Bandettini PA, Martin A (2010) Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. NeuroImage 49:1099-1107.

27. Bolognini N, Fregni F, Casati C, Olgiati E, Vallar G (2010a) Brain polarization of parietal cortex augments training-induced improvement of visual exploratory and attentional skills. Brain research 1349:76-89.

28. Bolognini N, Olgiati E, Rossetti A, Maravita A (2010b) Enhancing multisensory spatial orienting by brain polarization of the parietal cortex. The European journal of neuroscience 31:1800-1806.

29. Bolognini N, Cecchetto C, Geraci C, Maravita A, Pascual-Leone A, Papagno C (2012) Hearing shapes our perception of time: temporal discrimination of tactile stimuli in deaf people. Journal of cognitive neuroscience 24:276-286.

30. Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, Madan A, Barth K, George MS (2012) A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain 13:112-120.

31. Brennen T (1993) The difficulty with recalling people's names: the plausible phonology hypothesis. Memory (Hove, England) 1:409-431.

32. Bruce V, Young A (1986) Understanding face recognition. Br J Psychol 77 (Pt 3):305-327.

33. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, Giacopuzzi M, Barbieri S, Priori A (2012) Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Progress in neuro-psychopharmacology & biological psychiatry 35:96-101.

34. Buxton RB, Wong EC, Frank LR (1998) Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med 39:855-864.

35. Caramazza A, Costa A (2000) The semantic interference effect in the picture-word interference paradigm: does the response set matter? Cognition 75:B51-64.

36. Casarotto S, Canali P, Rosanova M, Pigorini A, Fecchio M, Mariotti M, Lucca A, Colombo C, Benedetti F, Massimini M (2013) Assessing the effects of electroconvulsive therapy on cortical excitability by means of transcranial magnetic stimulation and electroencephalography. Brain topography 26:326-337.

37. Cattaneo Z, Mattavelli G, Platania E, Papagno C (2011) The role of the prefrontal cortex in controlling gender-stereotypical associations: a TMS investigation. NeuroImage 56:1839-1846.

38. Cerruti C, Schlaug G (2009) Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. Journal of cognitive neuroscience 21:1980-1987.

39. Chouinard PA, Whitwell RL, Goodale MA (2009) The lateral-occipital and the inferior-frontal cortex play different roles during the naming of visually presented objects. Human brain mapping 30:3851-3864.

40. Cohen G, Faulkner D (1986) Memory for proper names: Age differences in retrieval. British Journal of Developmental Psychology 4:187-197.

41. Cohen G (1990) Recognition and retrieval of proper names: Age differences in the fan effect. European Journal of Cognitive Psychology 2:193-204.

42. Coppens P, Frisinger D (2005) Category-specific naming effect in non-brain-damaged

individuals. Brain and language 94:61-71.

43. Costa A, Alario FX, Caramazza A (2005) On the categorical nature of the semantic interference effect in the picture-word interference paradigm. Psychonomic bulletin & review 12:125-131.

44. Costafreda SG, Fu CH, Lee L, Everitt B, Brammer MJ, David AS (2006) A systematic review and quantitative appraisal of fMRI studies of verbal fluency: role of the left inferior frontal gyrus. Human brain mapping 27:799-810.

45. Costafreda SG, Fu CH, Picchioni M, Toulopoulou T, McDonald C, Kravariti E, Walshe M, Prata D, Murray RM, McGuire PK (2011) Pattern of neural responses to verbal fluency shows diagnostic specificity for schizophrenia and bipolar disorder. BMC psychiatry 11:18.

46. Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR (1996) A neural basis for lexical retrieval. Nature 380:499-505.

47. Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A (2004) Neural systems behind word and concept retrieval. Cognition 92:179-229.

48. Damian MF, Martin RC (1999) Semantic and phonological codes interact in single word production. Journal of experimental psychology 25:345-361.

49. Damian MF, Vigliocco G, Levelt WJ (2001) Effects of semantic context in the naming of pictures and words. Cognition 81:B77-86.

50. Damian MF, Bowers JS (2003) Locus of semantic interference in picture-word interference tasks. Psychonomic bulletin & review 10:111-117.

51. Damian MF, Bowers JS (2009) Assessing the role of orthography in speech perception and production: Evidence from picture–word interference tasks. European Journal of Cognitive Psychology 21:581-598.

52. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M (2009) Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain stimulation 2:201-207, 207 e201.

53. Datta A, Truong D, Minhas P, Parra LC, Bikson M (2013) Inter-Individual Variation during Transcranial Direct Current Stimulation and Normalization of Dose Using MRI-Derived Computational Models. Frontiers in psychiatry 3:91.

54. de Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Floel A (2010) Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. Journal of cognitive neuroscience 22:2427-2436.

55. de Zubicaray GI, Wilson SJ, McMahon KL, Muthiah S (2001) The semantic interference effect in the picture-word paradigm: an event-related fMRI study employing overt responses. Human brain mapping 14:218-227.

56. de Zubicaray GI, McMahon KL, Eastburn MM, Wilson SJ (2002) Orthographic/phonological facilitation of naming responses in the picture-word task: an event-related fMRI study using overt vocal responding. NeuroImage 16:1084-1093.

57. de Zubicaray G, McMahon K, Eastburn M, Pringle A (2006) Top-down influences on lexical selection during spoken word production: A 4T fMRI investigation of refractory effects in picture naming. Human brain mapping 27:864-873.

58. de Zubicaray GI, McMahon KL (2009) Auditory context effects in picture naming investigated with event-related fMRI. Cognitive, affective & behavioral neuroscience 9:260-269.

59. Dell GS (1986) A spreading-activation theory of retrieval in sentence production. Psychological review 93:283-321.

60. Dell GS, O'Seaghdha PG (1994) Inhibition in interactive activation models of linguistic selection and sequencing: Academic Press.

61. Dell GS (2013) Cascading and feedback in interactive models of production: a reflection of forward modeling? The Behavioral and brain sciences 36:351-352.

62. Dell'Acqua R, Job R, Peressotti F, Pascali A (2007) The picture-word interference effect is not a Stroop effect. Psychonomic bulletin & review 14:717-722.

63. Devlin JT, Matthews PM, Rushworth MF (2003) Semantic processing in the left inferior prefrontal cortex: a combined functional magnetic resonance imaging and transcranial magnetic stimulation study. Journal of cognitive neuroscience 15:71-84.

64. Devlin JT, Watkins KE (2007) Stimulating language: insights from TMS. Brain 130:610-622.

65. Dick AS, Goldin-Meadow S, Hasson U, Skipper JI, Small SL (2009) Co-speech gestures influence neural activity in brain regions associated with processing semantic

information. Human brain mapping 30:3509-3526.

66. Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 29:7271-7277.

67. Evrard M (2002) Ageing and lexical access to common and proper names in picture naming. Brain and language 81:174-179.

68. Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A (2008) Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. Journal of cognitive neuroscience 20:1687-1697.

69. Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacopuzzi M, Barbieri S, Priori A (2009) Transcranial direct current stimulation in severe, drug-resistant major depression. Journal of affective disorders 118:215-219.

70. Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C (2010) Naming facilitation induced by transcranial direct current stimulation. Behavioural brain research 208:311-318.

71. Finkbeiner M, Caramazza A (2006) Now you see it, now you don't: on turning semantic interference into facilitation in a Stroop-like task. Cortex; a journal devoted to the study of the nervous system and behavior 42:790-796.

72. Fiori V, Coccia M, Marinelli CV, Vecchi V, Bonifazi S, Ceravolo MG, Provinciali L, Tomaiuolo F, Marangolo P (2010) Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. Journal of cognitive neuroscience 23:2309-2323.

73. Floel A, Rosser N, Michka O, Knecht S, Breitenstein C (2008) Noninvasive brain stimulation improves language learning. Journal of cognitive neuroscience 20:1415-1422.

74. Flor H, Nikolajsen L, Staehelin Jensen T (2006) Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci 7:873-881.

75. Forde M, Glyn W. Humphreys E (1997) A semantic locus for refractory behaviour: Implications for access storage distinctions and the nature of semantic memory. Cognitive neuropsychology 14:367-402.

76. Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nature clinical practice 3:383-393.

77. Fridriksson J, Richardson JD, Baker JM, Rorden C (2011) Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke; a journal of cerebral circulation 42:819-821.

78. Friedman L, Kenny JT, Wise AL, Wu D, Stuve TA, Miller DA, Jesberger JA, Lewin JS (1998) Brain activation during silent word generation evaluated with functional MRI. Brain and language 64:231-256.

79. Gainotti G (2007) Different patterns of famous people recognition disorders in patients with right and left anterior temporal lesions: a systematic review. Neuropsychologia 45:1591-1607.

80. Gandiga PC, Hummel FC, Cohen LG (2006) Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 117:845-850.

81. Ganushchak LY, Schiller NO (2008) Brain error-monitoring activity is affected by semantic relatedness: an event-related brain potentials study. Journal of cognitive neuroscience 20:927-940.

82. Ganushchak LY, Christoffels IK, Schiller NO (2011) The use of electroencephalography in language production research: a review. Frontiers in psychology 2:208.

83. Gernsbacher MA, Kaschak MP (2003) Neuroimaging studies of language production and comprehension. Annual review of psychology 54:91-114.

84. Giussani C, Roux FE, Bello L, Lauwers-Cances V, Papagno C, Gaini SM, Puel M, Demonet JF (2009) Who is who: areas of the brain associated with recognizing and naming famous faces. J Neurosurg 110:289-299.

85. Glosser G, Donofrio N (2001) Differences between nouns and verbs after anterior temporal lobectomy. Neuropsychology 15:39-47.

86. Gollan TH, Montoya RI, Werner GA (2002) Semantic and letter fluency in Spanish-English bilinguals. Neuropsychology 16:562-576.

87. Gough PM, Nobre AC, Devlin JT (2005) Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. J Neurosci 25:8010-8016.

88. Gourovitch ML, Kirkby BS, Goldberg TE, Weinberger DR, Gold JM, Esposito G, Van Horn JD, Berman KF (2000) A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 14:353-360.

89. Grabowski TJ, Damasio H, Tranel D, Ponto LL, Hichwa RD, Damasio AR (2001) A role for left temporal pole in the retrieval of words for unique entities. Human brain mapping 13:199-212.

90. Grodzinsky Y, Santi A (2008) The battle for Broca's region. Trends in cognitive sciences 12:474-480.

91. Grogan A, Green DW, Ali N, Crinion JT, Price CJ (2009) Structural correlates of semantic and phonemic fluency ability in first and second languages. Cereb Cortex 19:2690-2698.

92. Hamilton AC, Martin RC (2005) Dissociations among tasks involving inhibition: a single-case study. Cognitive, affective & behavioral neuroscience 5:1-13.

93. Hamilton AC, Martin RC (2007) Proactive interference in a semantic short-term memory deficit: role of semantic and phonological relatedness. Cortex; a journal devoted to the study of the nervous system and behavior 43:112-123.

94. Hamilton RH, Chrysikou EG, Coslett B (2011) Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain and language 118:40-50.

95. Harley TA (1993) Phonological activation of semantic competitors during lexical access in speech production. Language and Cognitive Processes 8:291-309.

96. Hasher L, Zacks R (1988) Working memory, comprehension, and aging: A review Experimental Psychology: Learning, Memory and Cognition 12:288-294.

97. Hashimoto N, Thompson CK (2010) The use of the picture–word interference paradigm to examine naming abilities in aphasic individuals. Aphasiology 24:580-611.

98. Heim S, Eickhoff SB, Amunts K (2008) Specialisation in Broca's region for semantic, phonological, and syntactic fluency? NeuroImage 40:1362-1368.

99. Henry JD, Crawford JR (2004a) A meta-analytic review of verbal fluency performance in patients with traumatic brain injury. Neuropsychology 18:621-628.

100. Henry JD, Crawford JR (2004b) Verbal fluency deficits in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc 10:608-622.

101. Henry JD, Crawford JR, Phillips LH (2004) Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia 42:1212-1222.

102. Henry J, Crawford JR (2005) A meta-analytic review of verbal fluency deficits in depression. Journal of clinical and experimental neuropsychology 27:78-101.

103. Henry JD, Crawford JR, Phillips LH (2005) A meta-analytic review of verbal fluency deficits in Huntington's disease. Neuropsychology 19:243-252.

104. Herwig U, Satrapi P, Schonfeldt-Lecuona C (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain topography 16:95-99.

105. Hillis AE, Caramazza A (1991) Category-specific naming and comprehension impairment: a double dissociation. Brain 114 (Pt 5):2081-2094.

106. Hirshorn EA, Thompson-Schill SL (2006) Role of the left inferior frontal gyrus in covert word retrieval: neural correlates of switching during verbal fluency. Neuropsychologia 44:2547-2557.

107. Hodges JR, Graham N, Patterson K (1995) Charting the progression in semantic dementia: implications for the organisation of semantic memory. Memory (Hove, England) 3:463-495.

108. Holland R, Leff AP, Josephs O, Galea JM, Desikan M, Price CJ, Rothwell JC, Crinion J (2011) Speech facilitation by left inferior frontal cortex stimulation. Curr Biol 21:1403-1407.

109. Holland R, Crinion J (2012) Can tDCS enhance treatment of aphasia after stroke? Aphasiology 26:1169-1191.

110. Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG (2005) Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 128:490-499.

111. Hurks PP, Hendriksen JG, Vles JS, Kalff AC, Feron FJ, Kroes M, van Zeben TM, Steyaert J, Jolles J (2004) Verbal fluency over time as a measure of automatic and controlled processing in children with ADHD. Brain and cognition 55:535-544.

112. Ilmoniemi RJ, Kicic D (2010) Methodology for combined TMS and EEG. Brain

topography 22:233-248.

113. Indefrey P, Levelt WJ (2000) The neural correlates of language production. In: The New Cognitive Neurosciences (Gazzaniga, M., ed), pp 845-865 Cambridge, Mass.: MIT.

114. Indefrey P, Levelt WJ (2004) The spatial and temporal signatures of word production components. Cognition 92:101-144.

115. Indefrey P (2011) The spatial and temporal signatures of word production components: a critical update. Frontiers in psychology 2:255.

116. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM (2005) Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64:872-875.

117. Jacobson L, Koslowsky M, Lavidor M (2012) tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Experimental brain research Experimentelle Hirnforschung 216:1-10.

118. James LE (2004) Meeting Mr. Farmer versus meeting a farmer: specific effects of aging on learning proper names. Psychol Aging 19:515-522.

119. James LE, Fogler KA (2007) Meeting Mr Davis vs Mr Davin: effects of name frequency on learning proper names in young and older adults. Memory (Hove, England) 15:366-374.

120. Jang SH, Ahn SH, Byun WM, Kim CS, Lee MY, Kwon YH (2009) The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neuroscience letters 460:117-120.

121. Javadi AH, Cheng P, Walsh V (2012) Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. Brain stimulation 5:468-474.

122. Javadi AH, Walsh V (2012) Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain stimulation 5:231-241.

123. Johnson JS, Kundu B, Casali AG, Postle BR (2012) Task-dependent changes in cortical excitability and effective connectivity: a combined TMS-EEG study. Journal of neurophysiology 107:2383-2392.

124. Kan IP, Thompson-Schill SL (2004a) Effect of name agreement on prefrontal activity during overt and covert picture naming. Cognitive, affective & behavioral neuroscience 4:43-57.

125. Kan IP, Thompson-Schill SL (2004b) Selection from perceptual and conceptual representations. Cognitive, affective & behavioral neuroscience 4:466-482.

126. Kay J, Lesser R, Coltheart M (1996) Psycholinguistic assessments of language processing in aphasia (PALPA): An introduction. Aphasiology 10:159-180.

127. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Moller HJ, Reiser M, Padberg F (2011) Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci 31:15284-15293.

128. Kiefer M, Pulvermuller F (2011) Conceptual representations in mind and brain: theoretical developments, current evidence and future directions. Cortex; a journal devoted to the study of the nervous system and behavior 48:805-825.

129. Kircher T, Nagels A, Kirner-Veselinovic A, Krach S (2011) Neural correlates of rhyming vs. lexical and semantic fluency. Brain research 1391:71-80.

130. Köhler S, Buckner RL, Milner B (2004) Effects of Left Inferior Prefrontal Stimulation on Episodic Memory Formation: A Two-Stage fMRI—rTMS Study. Journal of cognitive neuroscience 16:178-188.

131. Korhonen RJ, Hernandez-Pavon JC, Metsomaa J, Maki H, Ilmoniemi RJ, Sarvas J (2011) Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. Medical & biological engineering & computing 49:397-407.

132. Kripke S (1980) Naming and Necessity. Oxford: Basil Blackwell.

133. Kuo HI, Bikson M, Datta A, Minhas P, Paulus W, Kuo MF, Nitsche MA (2012) Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. Brain stimulation 6:644-648.

134. Kwon YH, Jang SH (2011) The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. Neuroscience letters 492:105-108.

135. Lauro LJ, Reis J, Cohen LG, Cecchetto C, Papagno C (2010) A case for the involvement of phonological loop in sentence comprehension. Neuropsychologia 48:4003-4011.

136. Laws KR, Neve C (1999) A normal' category-specific advantage for naming living things. Neuropsychologia 37:1263-1269.

137. Levelt WJ, Praamstra P, Meyer AS, Helenius P, Salmelin R (1998) An MEG study of picture naming. Journal of cognitive neuroscience 10:553-567.

138. Levelt WJ (1999) Models of word production. Trends in cognitive sciences 3:223-232.

139. Liebetanz D, Nitsche MA, Tergau F, Paulus W (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125:2238-2247.

140. Liebetanz D, Koch R, Mayenfels S, Konig F, Paulus W, Nitsche MA (2009) Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol 120:1161-1167.

141. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G (2010) Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology 75:2176-2184.

142. Logothetis NK, Wandell BA (2004) Interpreting the BOLD signal. Annual review of physiology 66:735-769.

143. Lucchelli F, De Renzi E (1992) Proper name anomia. Cortex; a journal devoted to the study of the nervous system and behavior 28:221-230.

144. Lupker SJ (1982) The role of phonetic and orthographic similarity in picture-word interference. Canadian journal of psychology 36:349-367.

145. Mack JE, Cho-Reyes S, Kloet JD, Weintraub S, Mesulam MM, Thompson CK (2013) Phonological facilitation of object naming in agrammatic and logopenic primary progressive aphasia (PPA). Cognitive neuropsychology 30:172-193.

146. Maess B, Friederici AD, Damian M, Meyer AS, Levelt WJ (2002) Semantic category interference in overt picture naming: sharpening current density localization by PCA. Journal of cognitive neuroscience 14:455-462.

147. Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44:5-21.

148. Martinez A, Benavente R (1998) The AR face database. CVC Technical Report 24.

149. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science 309:2228-2232.

150. Maylor E (1997) Proper name retrieval in old age: Converging evidence against disproportionate impairment. Aging, Neuropsychology and Cognition 4:211-226.

151. McCarthy RA, Kartsounis LD (2000) Wobbly words: Refractory anomia with preserved semantics. Neurocase 6:487-497.

152. Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, Flaisch T, Floel A (2012) Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci 32:1859-1866.

153. Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Floel A (2013) Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci 33:12470-12478.

154. Meyer AS, Schriefers H (1991) Phonological facilitation in picture-word interference experiments: Effects of stimulus onset asynchrony and types of interfering stimuli. Journal of Experimental Psychology: Learning, Memory, and Cognition 17:1146.

155. Meyer AS (1996) Lexical access in phrase and sentence production: Results from picture–word interference experiments. Journal of Memory and Language 35:477-496.

156. Miceli G, Capasso R, Daniele A, Esposito T, Magarelli M, Tomaiuolo F (2000) Selective deficit for people's names following left temporal damage: an impairment of domain-specific conceptual knowledge. Cognitive neuropsychology 17:489-516.

157. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167-202.

158. Miniussi C, Cappa SF, Cohen LG, Floel A, Fregni F, Nitsche MA, Oliveri M, Pascual-Leone A, Paulus W, Priori A, Walsh V (2008) Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain stimulation 1:326-336.

159. Miniussi C, Thut G (2010) Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain topography 22:249-256.

160. Miranda PC, Lomarev M, Hallett M (2006) Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 117:1623-1629.

161. Miranda PC, Faria P, Hallett M (2009) What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? Clin Neurophysiol 120:1183-1187.

162. Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, Nitsche MA (2012) Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain stimulation 6:424-432.

163. Monti A, Cogiamanian F, Marceglia S, Ferrucci R, Mameli F, Mrakic-Sposta S, Vergari M, Zago S, Priori A (2008) Improved naming after transcranial direct current stimulation in aphasia. Journal of neurology, neurosurgery, and psychiatry 79:451-453.

164. Monti A, Ferrucci R, Fumagalli M, Mameli F, Cogiamanian F, Ardolino G, Priori A (2012) Transcranial direct current stimulation (tDCS) and language. Journal of neurology, neurosurgery, and psychiatry 84:832-842.

165. Moore CJ, Price CJ (1999) A functional neuroimaging study of the variables that generate category-specific object processing differences. Brain 122 (Pt 5):943-962.

166. Moss HE, Abdallah S, Fletcher P, Bright P, Pilgrim L, Acres K, Tyler LK (2005) Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. Cereb Cortex 15:1723-1735.

167. Mottaghy FM, Sparing R, Topper R (2006) Enhancing picture naming with transcranial magnetic stimulation. Behavioural neurology 17:177-186.

168. Mummery CJ, Patterson K, Hodges JR, Wise RJ (1996) Generating 'tiger' as an animal name or a word beginning with T: differences in brain activation. Proceedings 263:989-995.

169. Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, Theoret H, Fregni F, Maria-Tormos J, Kurland J, Doron KW, Pascual-Leone A (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain and language 93:95-105.

170. Naeser MA, Martin PI, Treglia E, Ho M, Kaplan E, Bashir S, Hamilton R, Coslett HB, Pascual-Leone A (2010) Research with rTMS in the treatment of aphasia. Restorative neurology and neuroscience 28:511-529.

171. Navarrete E, Del Prato P, Mahon BZ (2012) Factors determining semantic facilitation and interference in the cyclic naming paradigm. Frontiers in psychology 3:38.

172. Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology 527 Pt 3:633-639.

173. Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57:1899-1901.

174. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W (2003a) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. The Journal of physiology 553:293-301.

175. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W (2003b) Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 114:2220-2222; author reply 2222-2223.

176. Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W (2003c) Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 114:600-604.

177. Nitsche MA, Grundey J, Liebetanz D, Lang N, Tergau F, Paulus W (2004a) Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex 14:1240-1245.

178. Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke K, Frommann K, Lang N, Henning S, Paulus W, Tergau F (2004b) GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. The European journal of neuroscience 19:2720-2726.

179. Nitsche MA, Niehaus L, Hoffmann KT, Hengst S, Liebetanz D, Paulus W, Meyer BU (2004c) MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin Neurophysiol 115:2419-2423.

180. Nitsche MA, Doemkes S, Karakose T, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W (2007) Shaping the effects of transcranial direct current stimulation of the human motor cortex. Journal of neurophysiology 97:3109-3117.

181. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A (2008) Transcranial direct current stimulation: State of the art 2008. Brain stimulation 1:206-223.

182. Nitsche MA, Paulus W (2011) Transcranial direct current stimulation--update 2011. Restorative neurology and neuroscience 29:463-492.

183. Nixon P, Lazarova J, Hodinott-Hill I, Gough P, Passingham R (2004) The inferior frontal gyrus and phonological processing: an investigation using rTMS. Journal of cognitive neuroscience 16:289-300.

184. Novelli G, Papagno C, Capitani E, Laiacona M (1986) Tre test clinici di ricerca e produzione lessicale. Taratura su sogetti normali. Archivio di Psicologia, Neurologia e Psichiatria.

185. Novick JM, Trueswell JC, Thompson-Schill SL (2005) Cognitive control and parsing: reexamining the role of Broca's area in sentence comprehension. Cognitive, affective & behavioral neuroscience 5:263-281.

186. Nozari N, Thompson-Schill SL (2013) More attention when speaking: Does it help or does it hurt? Neuropsychologia 51:2770-2780.

187. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113.

188. Oztekin I, Curtis CE, McElree B (2009) The medial temporal lobe and the left inferior prefrontal cortex jointly support interference resolution in verbal working memory. Journal of cognitive neuroscience 21:1967-1979.

189. Papagno C, Capitani E (1998) Proper name anomia: a case with sparing of the first-letter knowledge. Neuropsychologia 36:669-679.

190. Papagno C, Miracapillo C, Casarotti A, Romero Lauro LJ, Castellano A, Falini A, Casaceli G, Fava E, Bello L (2011) What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. Brain 134:405-414.

191. Paulus W (2003) Transcranial direct current stimulation (tDCS). Supplements to Clinical neurophysiology 56:249-254.

192. Pellicciari MC, Brignani D, Miniussi C (2013) Excitability modulation of the motor system induced by transcranial direct current stimulation: A multimodal approach. NeuroImage 83:569-580.

193. Peña-Gómez C, Sala-Lonch R, Junqué C, Clemente IC, Vidal D, Bargalló N, Falcón C, Valls-Solé J, Pascual-Leone Á, Bartrés-Faz D (2012) Modulation of large-scale brain

networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain stimulation 5:252-263.

194. Perani D, Cappa SF, Tettamanti M, Rosa M, Scifo P, Miozzo A, Basso A, Fazio F (2003) A fMRI study of word retrieval in aphasia. Brain and language 85:357-368.

195. Perrin F, Pernier J, Bertrand O, Echallier JF (1989) Spherical splines for scalp potential and current density mapping. Electroencephalography and clinical neurophysiology 72:184-187.

196. Peters MA, Thompson B, Merabet LB, Wu AD, Shams L (2013) Anodal tDCS to V1 blocks visual perceptual learning consolidation. Neuropsychologia 51:1234-1239.

197. Pickering MJ, Garrod S (2013) An integrated theory of language production and comprehension. The Behavioral and brain sciences 36:329-347.

198. Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JD (1999) Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 10:15-35.

199. Poreisz C, Boros K, Antal A, Paulus W (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain research bulletin 72:208-214.

200. Price CJ (2010) The anatomy of language: a review of 100 fMRI studies published in 2009. Annals of the New York Academy of Sciences 1191:62-88.

201. Price CJ (2012) A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. NeuroImage 62:816-847.

202. Priori A (2003) Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 114:589-595.

203. Rayner K, Springer CJ (1986) Graphemic and semantic similarity effects in the picture-word interference task. Br J Psychol 77 (Pt 2):207-222.

204. Reinkemeier M, Markowitsch HJ, Rauch M, Kessler J (1997) Differential impairments in recalling people's names: a case study in search of neuroanatomical correlates. Neuropsychologia 35:677-684.

205. Robinson G, Blair J, Cipolotti L (1998) Dynamic aphasia: an inability to select between competing verbal responses? Brain 121 (Pt 1):77-89.

206. Roelofs A (1992) A spreading-activation theory of lemma retrieval in speaking. Cognition 42:107-142.

207. Roelofs A (1997) The WEAVER model of word-form encoding in speech production. Cognition 64:249-284.

208. Romero Lauro LJ, Tettamanti M, Cappa SF, Papagno C (2008) Idiom comprehension: A prefrontal task? Cerebral Cortex 18:162-170.

209. Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M (2009) Natural frequencies of human corticothalamic circuits. J Neurosci 29:7679-7685.

210. Ross LA, McCoy D, Wolk DA, Coslett HB, Olson IR (2010) Improved proper name recall by electrical stimulation of the anterior temporal lobes. Neuropsychologia 48:3671-3674.

211. Ross LA, McCoy D, Coslett HB, Olson IR, Wolk DA (2011) Improved proper name recall in aging after electrical stimulation of the anterior temporal lobes. Frontiers in aging neuroscience 3:16.

212. Saetti MC, Marangolo P, De Renzi E, Rinaldi MC, Lattanzi E (1999) The nature of the disorder underlying the inability to retrieve proper names. Cortex; a journal devoted to the study of the nervous system and behavior 35:675-685.

213. Sakai KL, Noguchi Y, Takeuchi T, Watanabe E (2002) Selective priming of syntactic processing by event-related transcranial magnetic stimulation of Broca's area. Neuron 35:1177-1182.

214. Sandrini M, Fertonani A, Cohen LG, Miniussi C (2011) Double dissociation of working memory load effects induced by bilateral parietal modulation. Neuropsychologia 50:396-402.

215. Schnur TT, Schwartz MF, Brecher A, Hodgson C (2006) Semantic interference during blocked-cyclic naming: Evidence from aphasia. Journal of Memory and Language 54:199-227.

216. Schnur TT, Schwartz MF, Kimberg DY, Hirshorn E, Coslett HB, Thompson-Schill SL (2009) Localizing interference during naming: convergent neuroimaging and neuropsychological evidence for the function of Broca's area. Proceedings of the National Academy of Sciences of the United States of America 106:322-327.

217. Schnur TT, Martin R (2012) Semantic picture-word interference is a postperceptual effect. Psychonomic bulletin & review 19:301-308.

218. Schriefers H, Meyer AS, Levelt WJ (1990) Exploring the time course of lexical access in language production: Picture-word interference studies. Journal of Memory and Language 29:86-102.

219. Schuhmann T, Schiller NO, Goebel R, Sack AT (2009) The temporal characteristics of functional activation in Broca's area during overt picture naming. Cortex; a journal devoted to the study of the nervous system and behavior 45:1111-1116.

220. Schuhmann T, Schiller NO, Goebel R, Sack AT (2012) Speaking of which: dissecting the neurocognitive network of language production in picture naming. Cereb Cortex 22:701-709.

221. Schwartz S, Baldo J (2001) Distinct patterns of word retrieval in right and left frontal lobe patients: a multidimensional perspective. Neuropsychologia 39:1209-1217.

222. Semenza C (2006) Retrieval pathways for common and proper names. Cortex; a journal devoted to the study of the nervous system and behavior 42:884-891.

223. Semenza C (2009) The neuropsychology of proper names. Mind & Language 24:347-369.

224. Semenza C (2011) Naming with proper names: the left temporal pole theory. Behavioural neurology 24:277-284.

225. Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR (2008) Enhancing language performance with non-invasive brain stimulation--a transcranial direct current stimulation study in healthy humans. Neuropsychologia 46:261-268.

226. Spek A, Schatorje T, Scholte E, van Berckelaer-Onnes I (2009) Verbal fluency in adults with high functioning autism or Asperger syndrome. Neuropsychologia 47:652-656.

227. Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, Tracey I (2009) Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci 33:11425-11431.

228. Starreveld PA (2000) On the interpretation of onsets of auditory context effects in word production. Journal of Memory and Language 42:497-525.

229. Starreveld PA, La Heij W (1995) Semantic interference, orthographic facilitation, and their interaction in naming tasks. Journal of Experimental Psychology: Learning, Memory, and Cognition 21:686.

230. Starreveld PA, La Heij W (1996) Time-course analysis of semantic and orthographic context effects in picture naming. Journal of Experimental Psychology: Learning, Memory, and Cognition 22:896.

231. Stroop J (1935) Studies of interference in serial verbal reactions. Journal of experimental psychology 18:643.

232. Szaflarski JP, Vannest J, Wu SW, DiFrancesco MW, Banks C, Gilbert DL (2011) Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. Med Sci Monit 17:CR132-139.

233. Szaflarski JP, Allendorfer JB, Banks C, Vannest J, Holland SK (2013) Recovered vs. not-recovered from post-stroke aphasia: the contributions from the dominant and non-dominant hemispheres. Restorative neurology and neuroscience 31:347-360.

234. Thompson CK, Cho S, Price C, Wieneke C, Bonakdarpour B, Rogalski E, Weintraub S, Mesulam MM (2012) Semantic interference during object naming in agrammatic and logopenic primary progressive aphasia (PPA). Brain and language 120:237-250.

235. Tranel D (2009) The Left Temporal Pole Is Important for Retrieving Words for Unique Concrete Entities. Aphasiology 23:867.

236. Turkeltaub PE, Messing S, Norise C, Hamilton RH (2011) Are networks for residual language function and recovery consistent across aphasic patients? Neurology 76:1726-1734.

237. Urgesi C, Berlucchi G, Aglioti SM (2004) Magnetic stimulation of extrastriate body area impairs visual processing of nonfacial body parts. Curr Biol 14:2130-2134.

238. Vallar G, Bolognini N (2011) Behavioural facilitation following brain stimulation: implications for neurorehabilitation. Neuropsychological rehabilitation 21:618-649.

239. Veniero D, Bortoletto M, Miniussi C (2013) Cortical modulation of short-latency TMS-evoked potentials. Frontiers in human neuroscience 6:352.

240. Verstichel P, Cohen D, Crochet G (1996) Associated production and comprehension deficits for people's names following left temporal lesion. Neurocase 2:221-234.

241. Viggiano MP, Vannucci M, Righi S (2004) A new standardized set of ecological pictures for experimental and clinical research on visual object processing. Cortex; a journal devoted to the study of the nervous system and behavior 40:491-509.

242. Vigliocco G, Lauer M, Damian M, Levelt WJ (2002) Semantic and syntactic forces in noun phrase production. Journal of experimental psychology 28:46-58.

243. Vines BW, Cerruti C, Schlaug G (2008) Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC neuroscience 9:103.

244. Virtanen J, Ruohonen J, Naatanen R, Ilmoniemi RJ (1999) Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. Medical & biological engineering & computing 37:322-326.

245. Vitkovitch M, Rutter C, Read A (2001) Inhibitory effects during object name retrieval: The effect of interval between prime and target on picture naming responses. Br J Psychol 92 Part 3:483-506.

246. Vitkovitch M, Cooper E (2012) My word! Interference from reading object names implies a role for competition during picture name retrieval. Quarterly journal of experimental psychology (2006) 65:1229-1240.

247. Warrington EK, Shallice T (1984) Category specific semantic impairments. Brain 107 (Pt 3):829-854.

248. Weiduschat N, Thiel A, Rubi-Fessen I, Hartmann A, Kessler J, Merl P, Kracht L, Rommel T, Heiss WD (2011) Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. Stroke; a journal of cerebral circulation 42:409-415.

249. Wilshire CE, McCarthy RA (2002) Evidence for a context-sensitive word retrieval disorder in a case of nonfluent aphasia. Cognitive neuropsychology 19:165-186.

250. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke; a journal of cerebral circulation 36:1759-1763.

251. Wirth M, Rahman RA, Kuenecke J, Koenig T, Horn H, Sommer W, Dierks T (2011)

Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia 49:3989-3998.

252. Yang FG, Fuller J, Khodaparast N, Krawczyk DC (2010) Figurative language processing after traumatic brain injury in adults: a preliminary study. Neuropsychologia 48:1923-1929.

253. Zacks RT, Hasher L (1994) Directed ignoring: Inhibitory regulation of working memory.

254. Zhao H, La Heij W, Schiller NO (2012) Orthographic and phonological facilitation in speech production: new evidence from picture naming in Chinese. Acta psychologica 139:272-280.

255. Zheng X, Alsop DC, Schlaug G (2011) Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. NeuroImage 58:26-33.

Aknowledgments

First, I want to thank my supervisor, Prof. Costanza Papagno, for encouraging and guiding me in each of the experiments of the present thesis, assisting me in theoretical and practical aspects.

Moreover, I'd like to thank all my colleagues that helped me in designing and performing the experiment:

Dott.ssa Zaira Cattaneo, who greatly helped me in Study 1 and 3;

Dott.ssa Leonor Romero Lauro, who supervised me in Study 2;

Dott.ssa Giulia Mattavelli, who helped me in designing and performing Study 2;

Milena Cerciello, who shared with me the preparation and testing phases of Study 4;

Luigi Iasevoli, who tested with me participants of Study 5.