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NEUROMODULATION BY TRANSCRANIAL DIRECT CURRENT STIMULATION: INVESTIGATION ON READING PROCESSES

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ABSTRACT

Reading is a human skill, fundamental for everyday life, in which a lot of information is given in written form. To explain this process, several theories were advanced: currently there is common agreement on the simultaneous activation of two ways of reading, the direct or lessical one for words, and the phonological one for non-words or novel words. Neuroimaging studies converge in identifying three basic systems for reading, mostly in the left hemisphere: among these, the temporoparietal cortex (TPc) seems to be involved in grapheme to phoneme conversion (phonological route). The aim of the present work is to investigate, through transcranial direct current stimulation (tDCS), the role of TPc in words and non words reading. We also want to investigate different parameters of stimulation. Results of first study suggest bilateral TPc role in reading, and a facilitatory effect of left cathodal-right anodal stimulation on reading onset times. The second study suggest that reference electrode can lead to different effects depending on its position, and that unilateral montage is not as effective as bilateral one, not involving both TPc. The third study suggest that 10 minutes of tDCS are not enough to achieve a modulation, but confirm the role of TPc. The last study with below average readers, suggest that activation state of the stimulated area and difficulty of the task have to be considered too. This work contributes to the study of neural bases of reading and on the functioning of transcranial direct current stimulation on cognitive functions.

RIASSUNTO

La lettura è una competenza umana, fondamentale per la vita di tutti i giorni, in cui molte informazioni sono fornite in forma scritta. Nel tentativo di spiegare questo processo, diverse teorie sono state avanzate: attualmente vi è comune accordo sull’attivazione simultanea di due vie di lettura, quella diretta o lessicale, per la lettura di parole, e quella fonologica per le parole nuove o le non parole. Gli studi di neuroimaging convergono nell'identificare tre sistemi di base per la lettura, per lo più nell'emisfero di sinistra: tra queste, la corteccia temporo-parietale (TPC) sembra essere coinvolta nella conversione da grafema a fonema (via fonologica). Lo scopo del presente lavoro è quello di indagare, attraverso la stimolazione transcranica a corrente continua (tDCS), il ruolo di TPc nella lettura di parole e non parole. Contemporaneamente vogliamo indagare il ruolo dei diversi parametri di stimolazione. I risultati del primo studio suggeriscono un ruolo di TPc bilaterale nella lettura, ed evidenziano un effetto facilitatorio di sui tempi di risposta vocale con stimolazione catodica sinistra-anodica destra. Il secondo studio suggerisce che l’elettrodo di riferimento può portare ad effetti diversi a seconda della sua posizione, e che il montaggio unilaterale non è efficace come quello bilaterale, coinvolgendo solo la TPc sinistra. Il terzo studio mostra che 10 minuti di tDCS non sono sufficienti per una modulazione efficace, ma conferma il ruolo di TPc. L'ultimo studio è sui lettori con una prestazione di lettura inferiore alla media, ed evidenzia l’importanza dello stato di attivazione dell’area stimolata e della difficoltà del compito. Questo lavoro contribuisce allo studio delle basi neurali del processo di lettura e del funzionamento della stimolazione transcranica a corrente continua sulle funzioni cognitive.

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CHAPTER 1

Transcranial direct current stimulation

1.1 Introduction

Transcranial direct current stimulation is a non invasive brain stimulation technique (NIBS) able to induce local and transient changes in cortical excitability and to alter the behaviour for a limited period of time. It consists on the application of a weak electrical current directly to the scalp, on the area of interest, through a pair of electrodes (Nitsche and Paulus, 2000).

First systematic studies with electrical currents were done in the late 18th century by Galvani and Volta for the investigation of animal cell electricity, and by Aldini (Galvani's nephew) who used tDCS to improve mood in melancholic patients. Then the discovery of the electroconvulsive therapy by Cerletti and Bini and the use of drugs to treat psychiatric disorders led to a loss of interest in the electrical stimulation technique, till the 60s, with the studies on animals of Bindman and Purpura which showed that currents of very weak intensity, which did not elicited an action potential, could still influence neuronal activity for hours after a few minutes of stimulation (Bindman et al., 1962; 1964; Purpura and McMurtry, 1965).

Again electrical stimulation was abandoned due to inconsistent or inconclusive results in human studies. Even there are still unresolved questions about the functioning, in recent years tDCS use grow consequently to the use of TMS, in experimental and clinical fields. This interest is also justified by the fact that tDCS is easy to use, relatively cheap and well tolerated. The way to use electrical stimulation has undergone a drastic change, however, resulting in increased scientific rigor, and the administration of weak intensity currents, as Bindman and Purpura suggested.

Currently many researchers are exploring the stimulation mechanisms, investigating different types of NIBS, such as the already mentioned direct current stimulation (tDCS), the random noise (rTNS) and the alternated current stimulation (tACS).

1.2 Modulation or stimulation?

tDCS differs qualitatively from other forms of stimulation, such as transcranial magnetic stimulation (TMS), as it does not induce neuronal action potentials because static fields in this extension does not cause a rapid depolarization required to produce such potentials (Nitsche et al., 2008). Therefore, tDCS does not stimulate, but modulates neuronal activity, causing depolarization or hyperpolarization of the membrane, modifying thus the spontaneous neuronal excitability.

1.3 Methodology

1.3.1 Materials

The current is provided by a battery-driven stimulator (Fig. 1), linked to two conductive rubber electrodes through two corresponding cables (red for anodal, black for cathodal).

Figure 1: Battery-driven stimulator, electrodes and cables (red anode, blue cathode)

The electrodes are put into two saline (NaCl) soaked sponges, and then placed over the scalp with an elastic head band (Fig. 2).

As the technique doesn't have a high spatial resolution, the area to stimulate can be found measuring the scalp and following the EEG 10/20 international system (Nitsche et al., 2008).

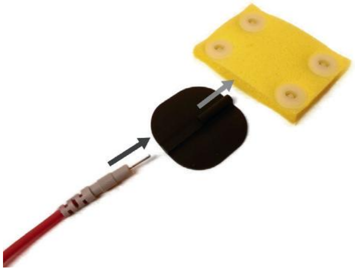


Figure 2: The cable plugs into the rubber electrode, which is then placed into the saline soaked sponge (in Kadosh, 2014)

1.3.2 Parameters

At least five parameters have to be considered and can lead to different neuronal and synaptic effect of stimulation.

The *polarity* refers to the two electrodes and the strength of the field: the anode (positively charged electrode) induces a depolarization, increases the excitability of the stimulated area, and the cathode (negatively charged electrode) leads to a iperpolarization, decreases the discharge rate and the excitability of the area (Nitsche and Paulus, 2000). This is clear and evident when tDCS is applied over motor area, but this distinction is not so clear when other cortical areas and cognitive processes are involved.

The *current density* defines the strength of the electric fields and is proportional to the electrodes size. It is measured in milliAmpere for cm2, and generally goes from 0.03 to 0.08 mA/cm2. A higher current density doesn't correspond to a better efficacy of the stimulation (Batsikadze et al., 2012).

The *size* and the *position* of the electrodes affect the orientation of the electrical field too. The two electrodes can be placed on the scalp (cephalic montage), or one on the scalp and one on the shoulder, on the chin or on the cheek (extracephalic montage), on homologous areas (bilateral montage). In any case, the electrodes should be distant at least 7 cm (Moliadze et al., 2010) and the smaller is the electrode, the more focal the effect. Polarity, size and position of the electrodes determine the current flow direction. Variable size of electrodes limits the spatial resolution of the effects but allows to mantain a low current density, avoiding potential adverse effects on the skin.

The stimulation *duration* is important too, it can affect the duration and intensity of after effects (Nitsche and Paulus, 2000; Fig. 3). To achieve minimal effects the stimulation should last for 3 minutes at 0,9 mA; 5-7 minutes of tDCS lead to 5 minutes of after effects, 9-13 minutes of anodal stimulation increases excitability for up to 90 minutes of after effects (Nitsche and Paulus, 2001).

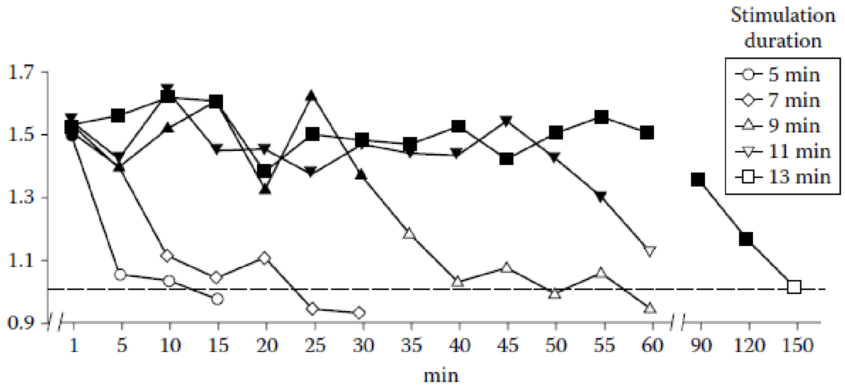


Figure 3. After effects for different anodal stimulation duration, on motor area (Nische and Paulus, 2001).

A longer stimulation does not ensure stronger stimulation effects, as showed by Monte-Silva et al. (2012): 13 minutes of 1 mA anodal tDCS enhances the motor area excitability for 60 minutes, but 13 minutes more of the same stimulation can lead to a decrease of the excitability, leading to a paradoxical effect (Fig. 4).

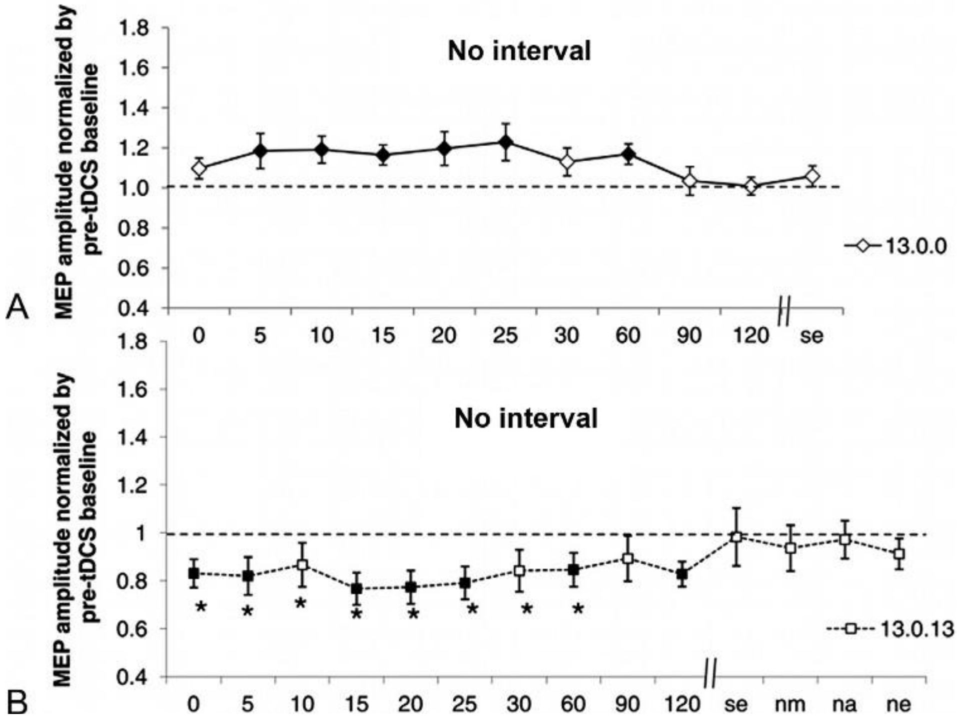


Figure 4. tDCS duration effects. On the top, excitation lasting up to 60' after 13' of anodal tDCS; belown 26' of anodal tDCS, decreasing excitability for up to 120' (Monte-Silva et al., 2012)

There is another factor to be considered, but a difficult to be evaluated without other instrument: the *excitability of the stimulated area*. For example, a motor task usually requires less brain activity than a cognitive task, leading to a less cerebral competition and more clear effects (Jacobson et al., 2012).

1.3.3 Online and offline protocols

The stimulation can be applied during the task of interest (online protocols) or before the task (offline protocols). The choice depends on the type of task administered, in particular on its duration: for example, if the task lasts less than 3 minutes, given that the minimum effects of the stimulation are evident after 3 minutes of current (Nitsche and Paulus, 2000), it is better to stimulate before the task of interest for a sufficient duration to ensure post effects on task. Although stimulation occurs before the task, it is useful to keep the participants engaged in an additional task during this, to be sure that all are engaged in the same activities and that presumably active the same brain circuits, and to try to exclude any noise.

1.4 Neurophysiological mechanisms of action

The term neuroplasticity defines the brain capacity to reorganize his structures and functions, in response to internal or external challenges. tDCS and tES in general could help in understanding this process and provide new knowledge, useful in experimental and clinical rehabilitation fields.

Most of the current delivered through surface electrodes dissipates over the scalp, while just a part of it penetrates the brain. This can alter neuronal resting membrane potentials modulating spontaneous firing frequency through depolarization or hyperpolarization of cortical neurons (Bindman et al., 1964; Creutzfeld et al., 1962; Radman et al., 2009).

Physiological effects of tDCS have been investigated in the last 15 years, and have focused more on motor area, where stimulation consequences are more clear. Generally, stimulating M1, anodal tDCS enhances, while cathodal tDCS decreases cortical excitability, suggesting that direction of the current flow and so polarity are determinant and have a clear functioning (Accornero et al., 2007, Antal et al., 2004, NItsche and Paulus, 2000; Figure 5). This is valid just for motor area stimulation, for resting state condition and was also found in studies on animals (Bindman et al., 1962; 1964; Purpura and McMurtry, 1965). This distinction is not so evident when muscles are activated or cognitive processes are involved, and sometimes there could also be converse effects (Antal et al., 2007).

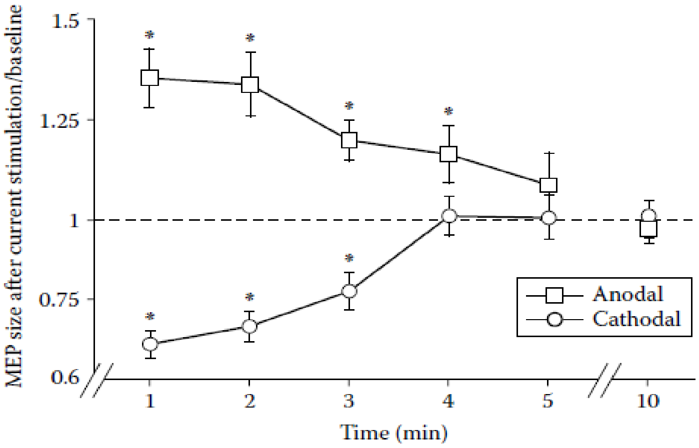


Figure 5. After effects of motor cortex stimulation, lasting 5 minutes at 1 mA (Nitsche and Paulus, 2000)

Few minutes stimulation modulates just during stimulation, while 10-15 minutes sessions are able to induce after effects of about 1 hour, in terms of enhancement of cortical facilitation after anodal stimulation, and of intracortical inhibition after cathodal one (Nitsche and Paulus, 2001, 2005). This effects of plasticity seem to depend on the glutamatergic system and his ionic channels: they disappear with NMDA receptor blocker dextromethorphan; on the other side, excitability prolongs with the enhancement of NMDA receptor D-Cycloserine. tDCS effects are so similar to long-term potentiation (LTP) and long-term depression (LTD) mechanisms: the subthreshold current delivered does not induce action potentials (Bikson et al., 2004) but modulates spontaneous neuronal activity. Specifically, anodal stimulation induces inward current flow in the cortex, depolarizing pyramidal cortical neurons soma and hyperpolarizing apical dendrites; cathodal stimulation leads to outward current flow, hyperpolarizing pyramidal cortical neurons soma and depolarizing apical dendrites (Radman et al., 2009; Zaghi et al., 2010; Figure 6).

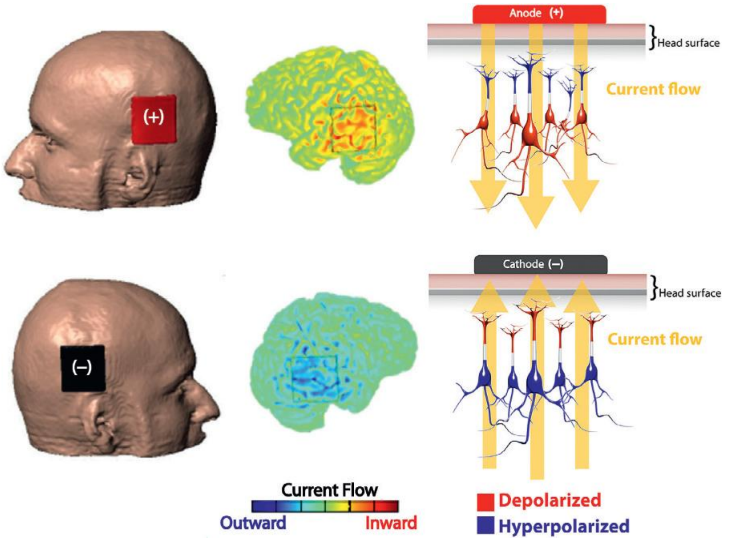


Figure 6. Current flow with tDCS. From anode (scalp, bone, cortical and subcortical regions) to cathode (cortical and subcortical regions, bone, scalp; in Kadosh, 2014).

Stimulation seems to reduce GABA concentration after both anodal and cathodal tDCS (Stagg et al., 2009) and to alter oscillatory cortical activity (Antal et al., 2004), too.

Despite the amount of studies and evidences, there are still many unresolved questions concerning the stimulating current densities, such as whether they reach the scalp and how deeply they influence neural activity; or the clear effect of different electrodes montages; or the consequences of stimulating injured brain areas.

1.5 tDCS effects on healthy people

Since tDCS can cause functional changes in the brain, it can be used to examine connectivity and network communication, for example the influence on resting-state network activity, through fMRI (Kieser et al., 2011; Amadi, 2014). tDCS can also be paired with TMS to investigate causal interactions between brain areas, usually acting contemporary (Cocchi et al., 2013).

Then, tDCS can modulate the frequency and phase of neural oscillations, providing causal insights into communication between distant cerebral sites. For example Marshall et al. (2004) improved declarative memory while sleeping.

The investigation on facilitatory or inhibitory effects of tDCS can explain the possible mechanisms underlying cognitive and motor processes. Generally, cathodal stimulation decrease cortical excitability and leads to impaired performance, while anodal tDCS increases cortical excitability and leads to a facilitation. But this dichotomy anodal tDCS excites-cathodal tDCS inhibits is mainly supported by studies on motor functions (Nitsche and Paulus, 2000; Stagg et al., 2009) and is not always valid: various studies have reported paradoxical effects (improvement with cathodal stimulation and worsening with anodal stimulation; Filmer et al., 2013; Moos et al., 2012), or polarity non-specific effects (both anodal and cathodal stimulation disrupt performance; Ferrucci et al., 2008; Filmer et al., 2013). One possible explanation of these effects has been associated to neural signal-to-noise properties: anodal stimulation could increase excitability and so the signal of the process of interest, or it could also increase noise in the system, disrupting the process; in the same way, cathodal stimulation could decrease excitability, and then reduce the signal of the process or the noise in the system, leading to a better detection of a weak signal. This is real especially for cognitive task which could involve a network of areas, not only the stimulated one, as for motor task (Fox et al., 2006) in which the stimulation acts in a low competitive environment and the effects can be fully expressed (Jacobson et al., 2012). Additionally, studies of the motor area usually use the passive measure of MEP as dependent variable to evaluate tDCS effects; these latter are more complex when the explanation concerns a cognitive task which requires the involvement of active regions and which effects are measured with various indices (RT, accuracy, brain imaging…) leading to more external noise. Another explanation refers to bilaterality of cognitive functions, in this case the possibility to induce an inhibitory cathodal effect decreases because the function is represented bilaterally and other areas can assume that role or function. Similarly, Iuculano and Kadosh et al., (2003) showed how the improvement of a function can lead to the worsening of another one (“mental cost”): after a 6 days training and tDCS, subjects stimulated on posterior parietal cortex improved in numerical learning but worsened on automaticity of learning process, while subjects stimulated on DLPFC enhanced automaticity of learning but impaired the learning process.

In their review, Jacobson et al. (2012), show that especially for language function investigation, the dichotomy anodal excitation-cathodal inhibition is not valid: many studies they considered do not show the inhibitory effect of cathodal stimulation, maybe due to wide language network (Catani et al., 2005): decrease neural activity in a single area is not enough to impair language process.

Research has also shown that tDCS can improve a cognitive function, sometimes better if coupled with cognitive training, both in healthy and clinical adult population, even after one stimulation session. This enhances the potentiality of the technique although the relevance of the improvements in real life, and not in a experimental setting, still need to be investigated (Filmer et al., 2014): for example, an improvement of 70 ms in reaction times of a determined task might be meaningless in everyday life.

Several studies have shown an enhancement of the performance (Floel et al., 2008; Kadosh et al., 2010; Stagg et al., 2011; Nitsche et al., 2003; Iuculano and Kadosh, 2013), but training could also lead to an impairment (Filmer et al., 2013; Ferrucci et al., 2008, Sandrini et al., 2012), depending on stimulation timing (usually offline protocols) and polarity (unilateral montages).

Sometimes, especially for cognitive functions research, the interpretation of tDCS effects is complex and paradoxical, and it is hard to fully understand the mechanisms acting between the cognitive function of interest and the stimulated area. Actually there is not a shared theory or view about tDCS functioning, and more studies are needed, especially testing the effects of different parameters on the performance and

Regarding language, the effects of tDCS have been studied in healthy individuals, and in individuals with aphasia, increasing the knowledge about the role of different brain regions in various aspects of language processing and about brain plasticity.

Studies in healthy subjects have shown that anodal tDCS improves verbal speed (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008), fluency (Cattaneo, Pisoni, & Papagno, 2011; Iyer et al., 2005) and accuracy in naming task (Sparing et al., 2008; Ross, McCoy, Wolk, Coslett, & Olson, 2010). They also show that stimulating (anodal tDCS) the left temporo-parietal junction or Wernicke’s area, verbal learning increase (Fiori et al., 2011; Meinzer et al., 2014). In a study by Meinzer et al. (2014), repeated sessions of anodal tDCS facilitate the recall of novel and familiar words after a word learning task, and the effects lasted up to 1 week, suggesting that repeated sessions of tDCS might lead to long-term effects in the stimulated regions (Kadosh et al., 2010; Reis et al., 2009).

A recent study by Fertonani, Brambilla, Cotelli, and Miniussi (2014) show an improvement in naming task in elderly people only when stimulation is delivered durin the task execution, while in young people both with offline and online stimulation. These studies suggest that stimulation of an area is task related, that age is an important variable to be considered and put the basis for application of tDCS for rehabilitation purposes.

Finally, in a study of Rosso et al. (2014), cathodal stimulation on the right inferior frontal gyrus during a picture naming task, led to faster response times, result explained suggesting the right hemisphere contribution to language process, as already told.

1.6 tDCS effects on patients

Besides the contribution to the understanding of cerebral mechanisms and involved areas, tDCS, as well as other non-invasive stimulation techniques (TMS, tACS, tRNS), finds application in the clinical field for rehabilitation.

Changes induced by cortical excitability can lead to the reorganization (neuroplasticity) of the dysfunctional network involved in a given cognitive function.The functions can be recovered or compensated by mechanisms involving both structural and functional changes of relevant brain circuits (Miniussi et al., 2011).

tDCS has been used to treat several motor and cognitive disorders, especially combined with a training: for example, it has been shown that stimulating stroke patients with anodal tDCS over the affected motor area, contemporary to motor training, leads to a greater improvement than the training alone (Marquez et al. 2013; Floel, 2014). The same results was found by Cotelli et al. (2013) on patients with primary progressive aphasia. Also Marangolo et al. (2013) stimulate Broca’s area in aphasic stroke patients, while attempting verbal description of video clips, and they found enhanced use of connective words in speech discourse. So it seems that, for language function, anodal tDCS combined with training, can enhance the performance.

Some considerations must be done for clinical tDCS application. First of all, results of experimental studies with healthy individuals can not be easily generalized to results in clinical population, because of the features of the stimulated area, the excitability, the inter individual differences. It is very risky to generalize effects more in clinical population than with healthy people. Detailed individual information are necessary (such as the type of language deficit, e.g. semantic or lexical anomia) to identify similar pathologies and to threat them in a different way, basing on the specific problem. Single-case observation allows determining whether an individual benefits from tDCS, avoiding inter subjects variability, but limiting the considerations at the single subject level (De Aguiar et al., 2015).

As in experimental studies with healthy people, is necessary to test and identify the optimal stimulation parameters (electrode montage and size, stimulation site, duration, intensity, number of sessions, online or offline design).

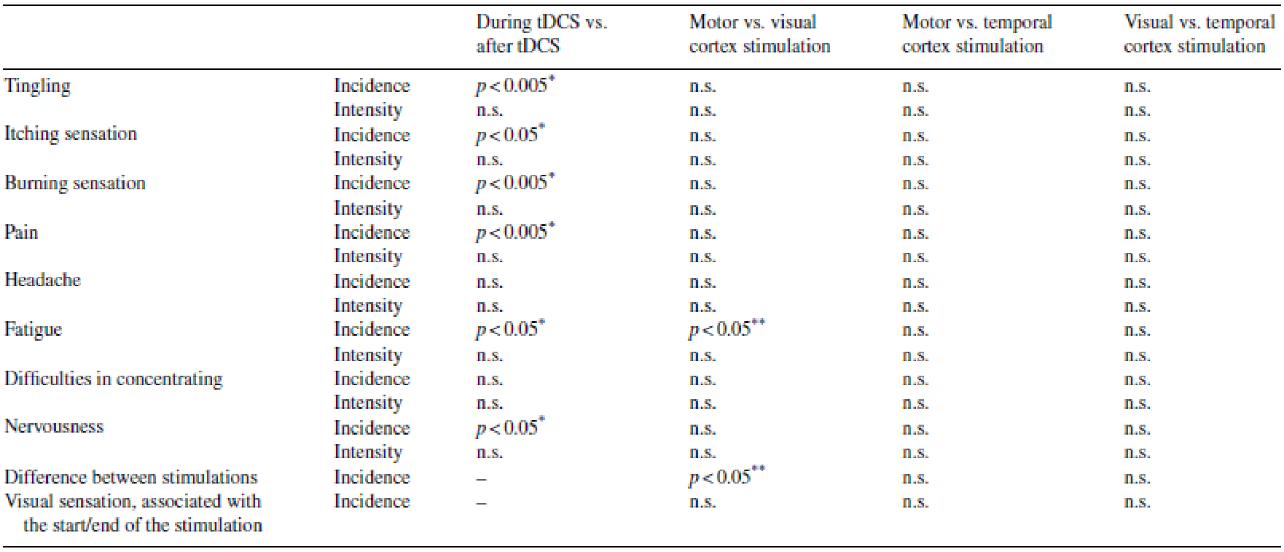
Neuroimaging techniques can help in focusing stimulation to a defined area, the one involved in the patient's deficit; also models of current distribution in damaged tissue can be useful (Datta et al., 2011). This is real especially for language function which network is not restricted to the dominant left hemisphere, but involves homolog areas of right hemisphere.

1.7 Safety and utility

tDCS has been widely applied in experimental and clinical field and has investigated a variety of cognitive and motor functions. This growing and widespread use is due to its features, first of all to its safety.

Normally tDCS does not produce side effects other than a sporadic tingling, itching or burning sensation of the skin under the electrodes (Nitsche et al., 2008; Poreisz et al., 2007. See Table 1). Currently no safety guidelines, established and valid for each application or treatment with tDCS exist. But there are suggested limits, deduced from physiological (Nitsche et al., 2003; Poreisz et al., 2007) and animal studies (Liebetanz et al., 2009). Skin injury or brain damage with tDCS is not possible with tDCS because the electrodes are not directly in contact with the scalp but they are collocated inside water-soaked sponges. Aside from that, to avoid brain tissue heating and neuronal hyperactivity (Agnew and McCreery, 1987), Nitsche et al., also suggest to use a current density (current intensity in mA/electrode surface in cm2) below 0.029 mA/cm2 (such as 1 mA/35 cm2), even if used value is about 0.057 mA/cm2. Similarly they recommend a charge density (current density x time of stimulation in seconds) up to

0.02 C/cm2, but generally the used value is about 0.068 C/cm2, however much lower than the one (216 C/cm2), used by Yuen et al. (1981) which only with strong suprathreshold stimulation elicited some damaging effects. A stimulation intensity up to 2 mA and a duration of 20 minutes is considered safe (Nitsche et al., 2003). Most used ectrodes have a size of 25-35 cm2 and generally intensity is 1-2 mA, generating densities ranging from 0.028 to 0.080 mA/cm2, for up to 18-40 minutes of stimulation.
However, to avoid a skin damage, the stimulation duration should me limited, current and charge densities should me minimized and electrodes which asure low current densities should be used.



		During tDCS vs. after tDCS	Motor vs. visual cortex stimulation	Motor vs. temporal cortex stimulation	Visual vs. temporal cortex stimulation
Tingling	Incidence	$p < 0.005^*$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Itching sensation	Incidence	$p < 0.05^*$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Burning sensation	Incidence	$p < 0.005^*$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Pain	Incidence	$p < 0.005^*$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Headache	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Fatigue	Incidence	$p < 0.05^*$	$p < 0.05^{**}$	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difficulties in concentrating	Incidence	n.s.	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Nervousness	Incidence	$p < 0.05^*$	n.s.	n.s.	n.s.
	Intensity	n.s.	n.s.	n.s.	n.s.
Difference between stimulations	Incidence	–	$p < 0.05^{**}$	n.s.	n.s.
Visual sensation, associated with the start/end of the stimulation	Incidence	–	n.s.	n.s.	n.s.

Table 1. Comparisons between the side effects during and after tDCS and between the stimulated cortical regions. In the first column the results of independent t-test comparing during and after tDCS sensations. In the other columns, the results of t-test comparing side effects depending on stimulated area. * Significantly higher during stimulation. ** Significantly higher during stimulation of motor cortex (Poreisz et al., 2007).

Although if tDCS is considered safe with minimal risk, general exclusion criteria are recommended: subjects must be free of unstable medical conditions, such as epilepsy; they must have no metallic implants in the head, no history of head trauma, head surgery or frequent headache, no heart problems, and they do not have to take tricyclic antidepressants or neurolectics. Pregnant women and people with sensitive skin are excluded too.
Another important feature of tDCS is its usability: it’s very practical and the apparatus is more portable, cheaper and easier to use than other instruments, such as transcranial magnetic stimulation (TMS), especially for clinical purposes. With the last

machines, it’s also possible to plan protocols for rehabilitation, repeated training or experimental sessions.

Then, with tDCS is really easy the control condition, known as sham: subjects hardly discriminate between real and sham stimulation, especially witgh low intensities (Gandiga, Hummel, & Cohen, 2006). Usually, after some seconds of stimulation (10-30 s) the currents ramps down and offsets the current; in this way the participant experiences the typical skin sensation of real tDCS, but without being effectively stimulated.

The possibility to do online rather than offline stimulation provides better adaptation to different experimental conditions. It’s also possible to do repeated tDCS sessions without negative effects (Fregni et al., 2006).

Anyway, to better understand and monitor the stimulation effects, it is useful to do a follow up after some months, test changes also of other cognitive functions investigating cognitive functions, and, if possible, combine methods, especially of neuroimaging, such as fMRI, NIRS or EEG, to better understand the stimulation effects.

CHAPTER 2

Reading Process

> *…and so to completely analyse what we do when we read*
> *would almost be the acme of a psychologist's achievements,*
> *for it would be to describe very many of the most intricate workings of the human mind,*
> *as well as to unravel the tangled story of the most remarkable specific*
> *performance that civilization has learned in all its history.*
> - *Edmund Burke Huey (1908)-*

2.1 Cognitive models of reading process

2.1.1 Reading process in normal readers

Reading is a human skill, fundamental for everyday life, in which a lot of informations are given in a written form. Understanding how to read is at the center of a great debate that has divided the scientific community for about forty years.

Dehaene (2010) talks about the "reading paradox": the human brain appears adapted to read, but its genetic basis is similar to that of a primate that does not read, and it is due to a general hereditary ability of learning and the brain plasticity during the development, based on the ability of neurons to establish new synapses as a result of the relationship with the environment.

Reading is a complex process and includes various components which have given rise to several models. Reading aloud is not just the ability to quickly recognize, correctly name and represent the content of a word, but it involves different cognitive processese such as: computation of several abstract representation of the visual stimulus, starting from a retinotopic representation of the variations in light intensities that lead to visual features and then to a word-centered representation of the graphemes (Hillis and Caramazza, 1990; McCandliss et al., 2003); access to stored ortographic information (spelling) that allows recognition of the word as a familiar one; access to stored lexical-semantic information (meaning); access to the pronunciation; motor planning of respiratory and face muscles (jaw, lips, palate, tongue, vocal folds); movement of the latter (Rapp et al., 2000).

Reading starts from word recognition, all the other processes depend on this (Snowling and Hulme, 2005).

Lots of interpretations about words recognition mechanisms have been suggested so far (Cattell, 1886) but for the purposes of this study, we will only consider the theories concerning the phonological awareness.

When we mentally read can we understand the meaning of the written words without calling their pronunciation or is this fundamental to access the meaning? This is the issue many reserachers tried to answer over the years.

The word recognition is the foundation of reading. The recognition presupposes, therefore, that the known words are stored in the memory, in the mental lexicon, that is an organized set of representation units corresponding to words that are activated in response to sensory stimulation: there is a competition among units and one is engaged before the others up to reach the threshold level of recognition of the corresponding word. If no unit reaches the threshold, this means that the word is unknown to the reader.

Currently there is common agreement on the existence and simultaneous activation of two ways of reading, the phonological and the lexical one, the first leads to words pronunciation, the second directly leads to the meaning of words.

When we read we would assign each grapheme (graphic written sign) to the corresponding phoneme (sound). When we read a rare word the phonological way decodes the letters and then leads to the meaning; but when we read a well known word we do not need to activate the phonological way and to make a grapheme-to-phoneme conversion, but we directly access the meaning of the word and then retrieve the pronunciation. Both ways are necessary for a correct reading: the direct way allows to read frequent words, but not new or irregular ones; the phonological way allows to read new words but not irregular ones.

Several years passed before arriving to this general agreement. We must go back to 1959 to find the first model that tried to explain how we read, through access to the mental lexicon. The pandemonio of Selfridge (1959) represented the mental lexicon as a collection of millions of demons in competition with each other, each representing a word. According to this model, when we read a word, and it then appears on the retina, all demons simultaneously examine it, but only the corresponding demon remains enabled. Despite the simplicity of the metaphor, Selfridge had laid the foundations for future cognitive models on reading, talking about information processing in parallel, simplicity of operation, competition, robustness and flexibility of the model. Exactly as the nervous system, in which different simple cognitive processes are active in parallel, forming coalitions that would compete through excitatory and inhibitory synapses (Dehaene, 2009).

So Selfridge’s model inspired various theoretical models of neural networks involved in reading, especially computational models which tried to describe, through simulations, the mechanisms underlying words recognition and aloud reading. With the emergence of connectionism, models were created to explain this mechanisms but also to simulate reading deficits. They are based on neural networks in which units (input, output and hidden) are linked to each other through connections and have their own weight that changes through learning process. Simulated learning process starts with the presentation of stimuli to input units, for several cycles, and observing how the network changes its weights and connections to achieve the best output. The information is processed in parallel and context-dependent, that is to sa that each unit influence another one. One of the first and most known connectionist model is the *Interactive Activation Model* of McClelland and Rummelhart (1981), in which reading process is described as a network organized in three hierarchical levels: traits, letters and words, linked by excitatory or inhibitory connections (Fig. 7). From competition between lexical units emerges a dominant word, presumably the written and correct one. This model posed a bottom-up flow of information (from features, to letters, to words) and a top-down flow of information at the same time (visual feature, positional letter, word detectors, excitatory and inhibitory connections), and confirmed that the letters learning mechanism was parallel, as argued by Selfridge, and not serial, as previously claimed by Forster (1976) in the Serial Search Model, for example. As a conseguence it indicated that to recognize a word, we use the letters within the word and that the pre-activation of words in mental lexicon, facilitates the words recognition. However this model, arguing that the connection between words and mental lexicon is direct, can just explain the reading of familiar and known words, but not of new ones or pseudo words. On the other side this model can explain the word superiority effect, that means that a letter is more activated when it is inside a word than part of an irregular string of letters. According to McClelland and Rumelhart (1981), in fact, the activation of the units of a word, strengthen the activation of letter representations, which leads to a more accurate perception of the letters in the words than in pseudo words or non words.

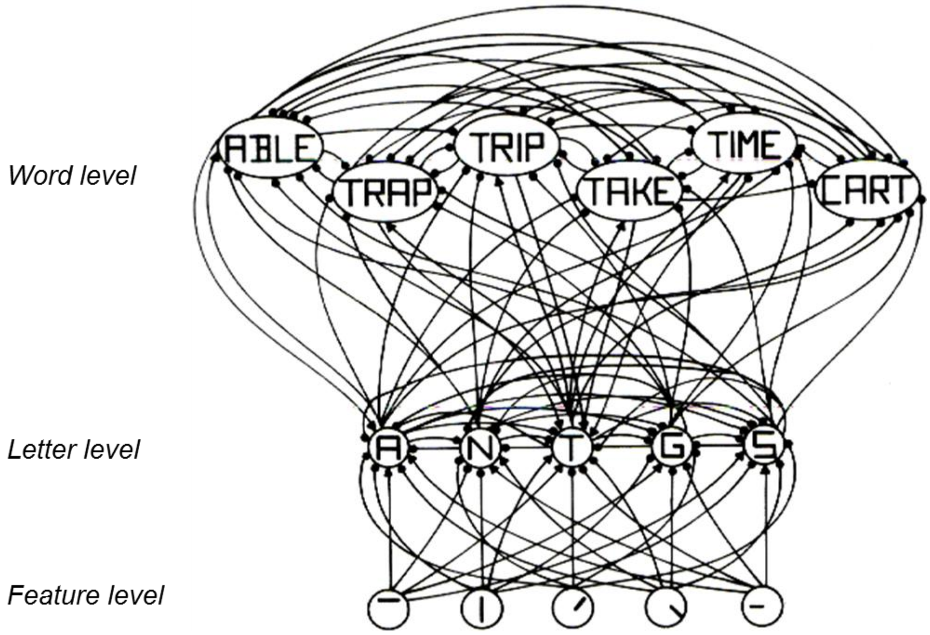


Figure 7. Interactive Activation Model (McClelland and Rummelhart, 1981). In this example, to process the letter T in the first position of a word, the flow of information starts from visual detectors (feature level), which activate the two nodes on the left because of their common features. Excitatory (finishing with an arrow) and inhibitory connections (finishing with a circle) enable or disable nodes till they find the most activated letter, having most incoming excitatory activation, in this example T, and so on for the word level.

This model specifically explains the visual recognition but does not focus on semantic and phonological aspects, taken into account later, always by McClelland group (McClelland and Seidenbergh, 1989), in the *Parallel Distributed Processing Model* (PDP), also known as *Triangle Model*. According to this model, two pathways connect the sound to the spelling: one directly links phonological to ortographic representation; the other links the written word to sound through its meaning. Only the first way was implemented in this model: the phonology of a word or a pseudo word is computed from its orthographic representation through a single process, that is the spread of activation through a neural network, in which the activation patterns of input and output units represent the written and phonological form of the word, respectively.
The PDP was criticized because, tested on several lists of pseudowords, it produced an error rate much higher than the human performance (Besner et al., 1990).

In response to the PDP of Seidenberg and McClelland (1989) based just on one way of reading, Coltheart and colleagues (1993, 2001) focused on two independent ways of reading hyphotesis, and created the *Dual-Route Cascaded model* (DRC model): the lexical (semantic and non semantic) and the non lexical routes. The first has a parallel spreading activation, the second has a serial one. Each route consists of several interaction layers with sets of units, representing the smallest individual part of the model (words in the ortographic lexicon or letters in the letter level). Units of different layers can interact through inhibition or excitation.

The non lexical route operates through grapheme-to-phoneme associations, converting letters or groups of letters (graphemes) into sounds (phonemes); these phonological units are assembled and pronounced. This route operates serially, from left to right and is active for new words and pseudowords reading.

Instead, the lexical route, already in the *Interactive Activation* Model of McClelland and Rumelhart (1981) creates a direct link between ortographic and phonological memory of the word (sound). This route operates for known, frequent and irregular words reading and is faster then the non lexical one. It operates by means of parallel cascaded processing: the features of the word's letters activate the word's letter units, which activate the orthographic lexicon, the phonological lexicon, and finish with the phonological output buffer. The authors included the semantic part in the model, but they did not implement it. Normally, these two routes interact in the phonological output buffer, where lexical and sublexical phonological codes match to find the final and correct pronunciation (Fig. 8).

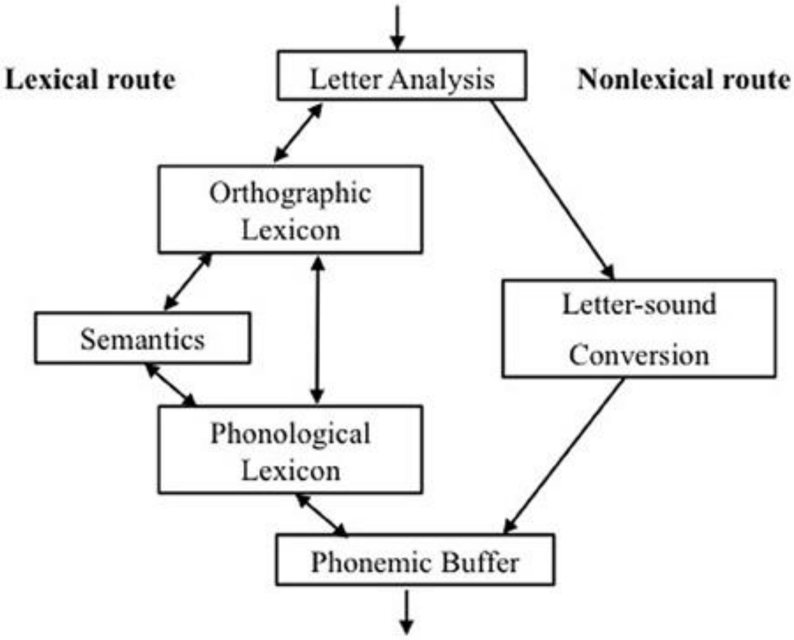


Figure 8. Dual-Route Cascaded Model (Coltheart et. al, 2001)

Perry and colleagues (2007) have criticized the DRC model of Coltheart because it lacks of learning effect and it fails to simulate the consistency of words, important feature in languages as English, where many words are written in the same way but pronuncitaed differently.

The *Dual-Process Model* (DP model; Zorzi et al., 1998), and the more recent *Connectionist Dual-Process Model* (CDP+; Perry et al., 2007), contains a lexical and a non-lexical route, as the DRC model. In this case, however, the non lexical route consists not only in grapheme-to-phoneme conversion rules, but it is a network (sublexical) composed of a input units layer and an output units layer, which learns the most common spelling-sound correspondences at different levels through statistical learning (Perry et al., 2007; Fig.9).

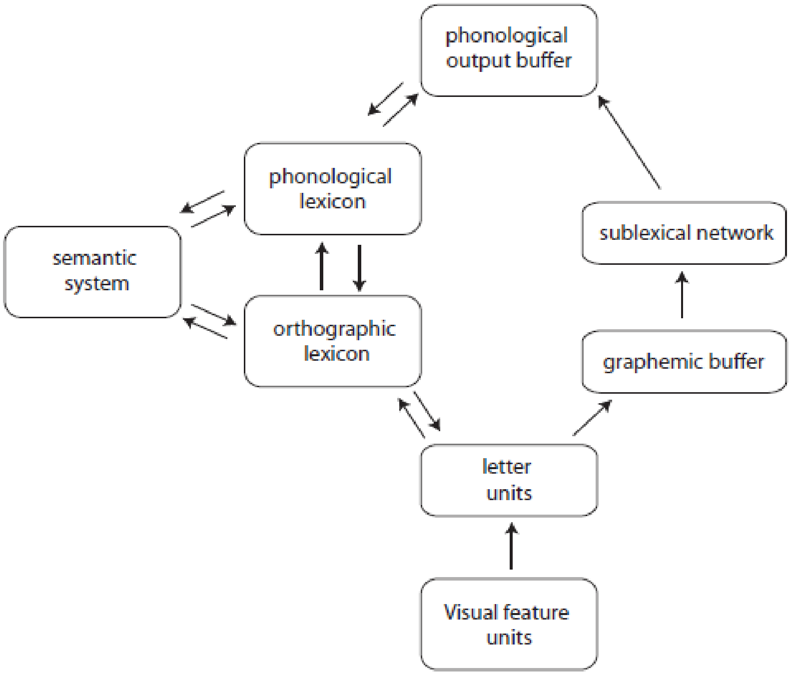


Figure 9. The connectionist dual-process model (Perry et al., 2007).

None of these models are able to explain in a comprehensive manner the reading process, however they make real predictions. DRC model and PDP model predict that frequent words are more quickly and accurately pronuncitaed then rare words, as well as regular words are read more quickly and accurately than irregular ones. Both involve grapheme-phoneme conversion rules, but in the DRC model the context of a word is not taken into account, while in the PDP it is an important factor.

2.1.2 Reading process in dyslexics

According to International Dyslexia Association (IDA):

Dyslexia is a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling, and decoding abilities. These typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge (Lyon, 2003).

The development of fluent reading skill is essential for success in the modern world. Significant numbers of children in all countries fail to acquire adequate literacy skills, and for many this is due to lack of learning opportunities, but for others it is a specific reading disability. Unlike spoken language, that is a biological specialization, written language is a “cultural invention” and for its learning children need explicit adult instructions.

Recent findings indicate the decoding component as more frequent in the dyslexic population (Lyon, 2003; Shaywitz, 2005). According to Boder (1973) in 67% of cases of developmental dyslexia, the child can not do grapheme-phoneme decoding or read simple words and pseudowords.

Reading is not just a phonological deficit, it could affect everyday life in different field and have negative consequences, such as anxiety, academic and employment failure.

Besides explaining the reading process, some of the models exposed above, have also tried to give an interpretation on reading deficits, such as dyslexia.

The DRC and CDP+ models suggest that phonological dyslexia (deficit in pronouncing unknown words and non words; Coltheart et al., 1996)) is caused by a damage to non lexical route, which prevent use of grapheme-phoneme conversion rules and so to achieve the correct pronunciation for novel words. The DRC model also suggests that surface dyslexia (deficit in pronouncing irregular words) is due to a damage to the direct, lexical route, so words can only be pronounced using grapheme-phoneme conversion rules.

The PDP model explains phonological dyslexia as reflecting a damage inside the ortography-to-phonology connections, which leads to pronounce only known words, and to make errors with new words and non words. Regarding surface dyslexia, ortography-to-phonology connections are overly specialized for consistent words and inconsistent words just use semantic route, which is damaged.

Besides phonological deficit, dyslexia may arise from different sources, such as ventral visual and dorsal attention system or a cerebellar dysfunction, so the debate is even more extended.

2.2 Neural bases of reading process in normal readers

At the same time as the first studies of experimental psychology (Cattell, 1886) that tried to explain the reading process steps through models and simulations, studies in neuroscience, from Dejerine (1892) have tried to figure out the presence and identification of specialized neural bases for word recognition.

Déjerine practiced autopsy on one of his patients who could no longer read after cerebral infarction. He demonstrated the presence of lesions in the posterior left lobe, particularly in the occipital lobe, assuming a disconnection, an interruption of the transmission of visual information from the occipital lobe (visual area) to the angular gyrus (visual center of the letters), in left parietal lobe (Fig. 9). This disconnection did not affect oral language, writing, visual recognition of objects, faces, drawings, figures, nor tactile recognition of letters; the patient was still able to see the letters' shapes but not to recognize them as such. This was the first demonstration of verbal blindness or pure alexia.

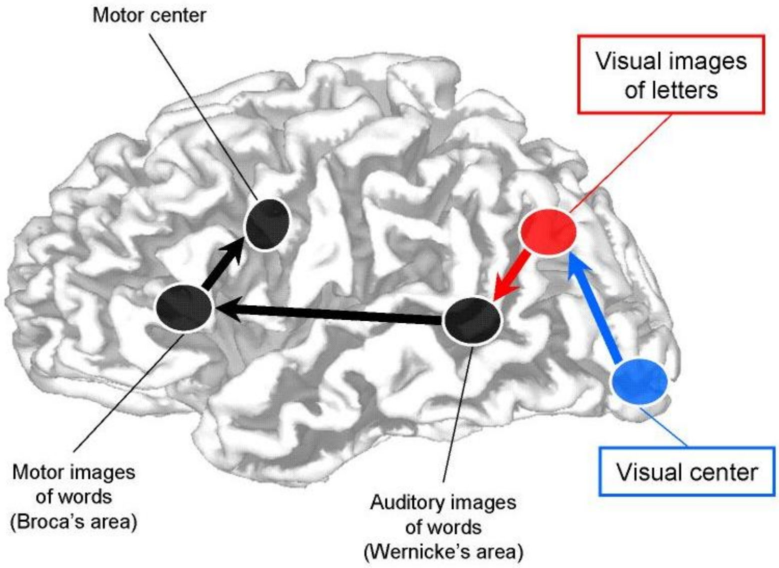


Figure 9. First neurological model of reading, after Déjerine (from Dehaene, 2009)

Dejerine’s theory was not wrong but the model was simple and serial, while the reading process is parallel, many regions would be active simultaneously, as claimed by Dehaene (2009).

The most posterior areas of left hemisphere are not specific for reading, but for the analysis of early visual signals (recognition of shape and color). A lesion in these regions causes a non specific visual deficit. The region involved in the recognition and specifically in the visual analysis of words is more anterior, the left occipitotemporal region, defined as the visual word form area (WVFA; Cohen et al., 2004; Dehaene et al., 2002).

Reading involves the recognition of letters, their combination into words and, their connection with the pronunciation and the meaning.

The circuit for reading is located predominantly in the left hemisphere: it begins in the occipital lobule (recognition of visul stimuli, such as faces and shapes). The visual input then goes to the left occipito temporal area, named “letterbox” area (WVFA; recognition of visual form of letters strings) and then is spread to different regions that encode word meaning, pronunciation and articulation. So reading it’s a visual and auditory process at the same time (Fig. 10).

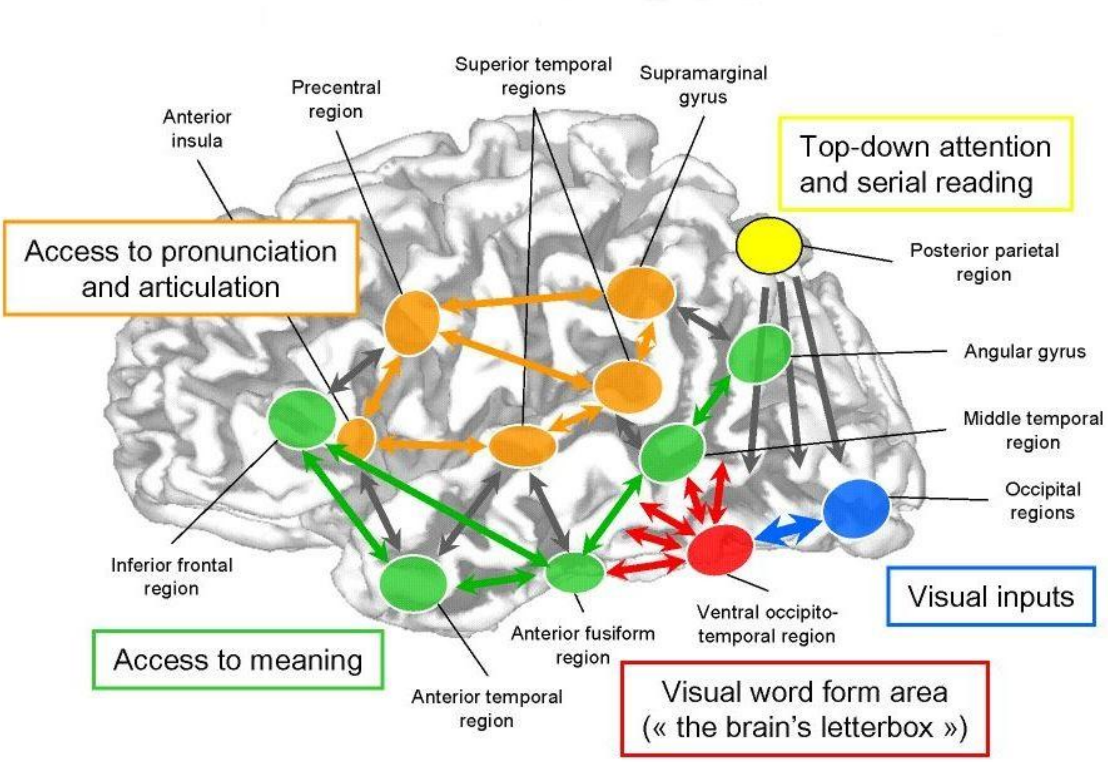


Figure 10. Actual neural model of reading process (from Dehaene, 2009).

When a child learns how to read, initially decipher words, converting each grapheme into a phoneme, with a lot of effort (yellow route). The correct associations between group of graphemes into phonemes

must be taught by an adult/teacher. With learning and practice, reading becomes more automatic and direct (green route), leading to a faster and simultaneous access to the lexicon and to meaning.
At the beginning, the green and the orange areas are used for oral language, they are not specific to reading; learning to read leads to the development of bidirectional interconnection between visual and oral language areas. This model may be simplistic, respect to all the possible connections.

The first images of the brain networks of language come with PET studies (Petersen et al., 1988) and show an activation of bilateral occipital regions to the vision of the written word, associated with early stages of vision, and a more ventral region of the left hemisphere, between occipital and temporal lobe (visual word form area). The latter region would activate only for written and not for pronounced words. The same evidence is conformed by Dehaene and colleagues (2002) in an fMRI study about seven people that activate the same area (occipito-temporal) only for written words (Fig. 11).

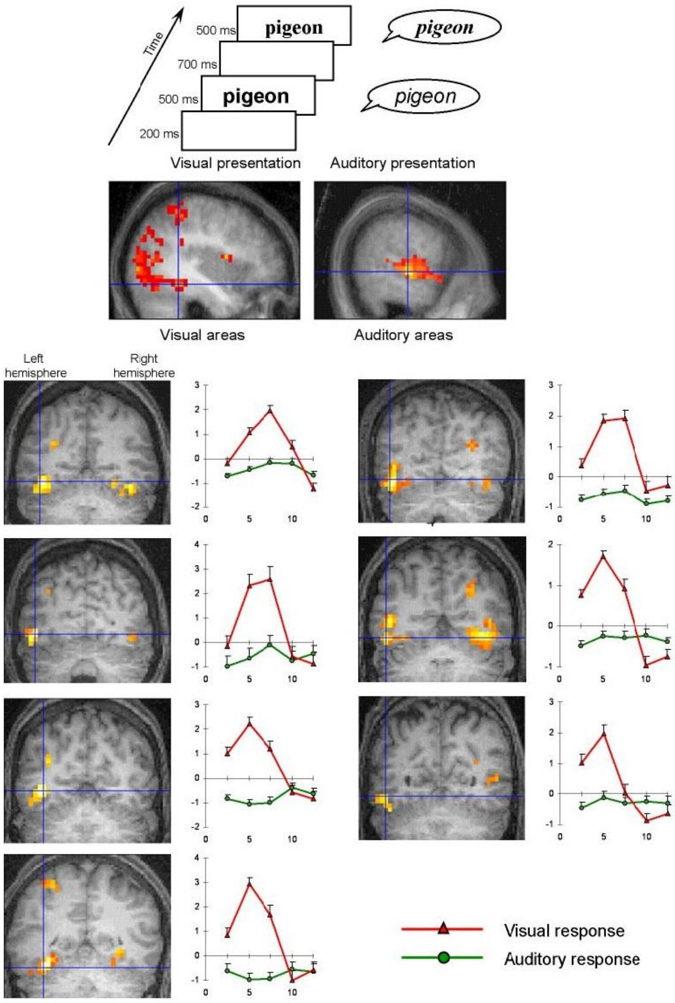


Figure 11. Activation of occipito temporal area in 7 literate people. In the experiment they heard or saw a pair of words and had to judge whether they were identical or different. The VWFA activated just for written words (Dehaene et al., 2002).
In the images a right hemisphere activation can be noted, that could be due to or could predict the extent to which a person will be able to recover reading skills after a lesion in the left hemisphere (Cohen et al., 2004).

fMRI studies then show that left and right hemisphere are initially both stimulated and active, but after a few milliseconds, the words are oriented to the left one, while the faces to the right one. MEG studies also confirm the lateralization of the reading process (Tarkiainen et al., 1999, 2002). Initially, words presented on the right visual field are processed by left hemisphere while words presented on the left are processed by right one but, regardless of where they appear, they all converge in the left occipital temporal area. In this path, the corpus callosum would play a fundamental role: its lesion would lead to emialessia, or interemispheric disconnection syndrome, causing disconnection between visual areas of the right hemisphere (involved in written words visual analysis) and language areas of the left hemisphere (specialized in words identification and meaning), and accordingly, inability or delay in reading words presented in the left visual field.

In 2003 Marinkovic and colleagues, in a MEG study, try to map the path of written and oral words from the first visual decoding till the verbal pronunciation (Fig. 12).

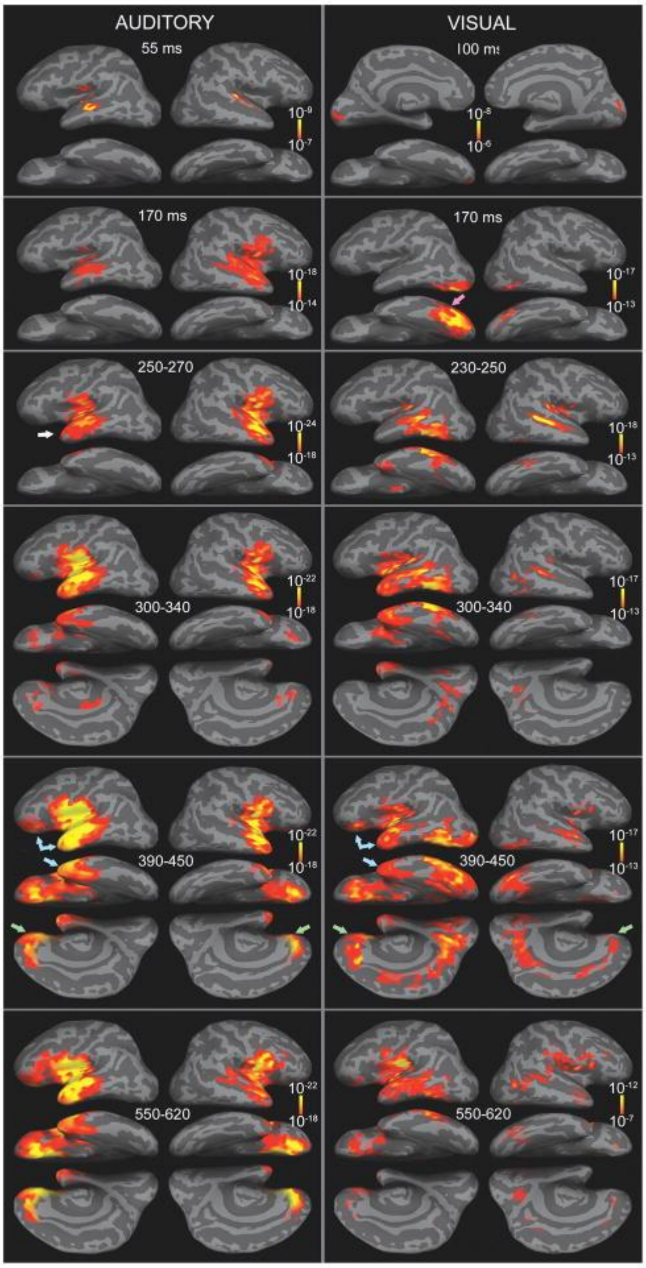


Figure 12. Written and oral words path. Initially, oral or written words are recognized in different areas but then the information converges in the same language area. Specifically, during the reading, after about 100 ms from the presentation of the word, the occipital lobe activate. At 170 ms the information goes to the occipito temporal lobe (VWFA), then at 250 ms it goes to the temporal lobes (bilaterally). At 300 ms activity is oncentrated in left hemisphere, and finally information arrives in more anterior areas to then come back to more posterior regions (Marinkovic et al., 2003).

Different meta-analysis of neuroimaging studies have tried to define reading neural network, especially comparing reading task with other tasks (Fiez and Petersen, 1998; Jobard et al., 2003; Turkeltaub et al., 2002; Taylor et al., 2013; Paulesu et al., 2014). Referring to previously exposed cognitive models and associating areas assumed to be involved in reading with the dual process model, Jobard and colleagues claim that the phonological route (grapheme-phoneme conversion), active for regular, rare words or pseudo words reading, would be localized in the sound brain network, consisting of superior temporal (specifically the planum temporale) and partly of inferior parietal areas, responsible for serial reading; instead, the lexical route, active for frequent and irregular words reading, involves the meaning cerebral network, that is to say the medium posterior temporal convolution, specifically the ventral anterior temporal lobe and the inferior frontal region, that would select a meaning among many for a particular word (Jobard et al., 2003; Fig. 13).

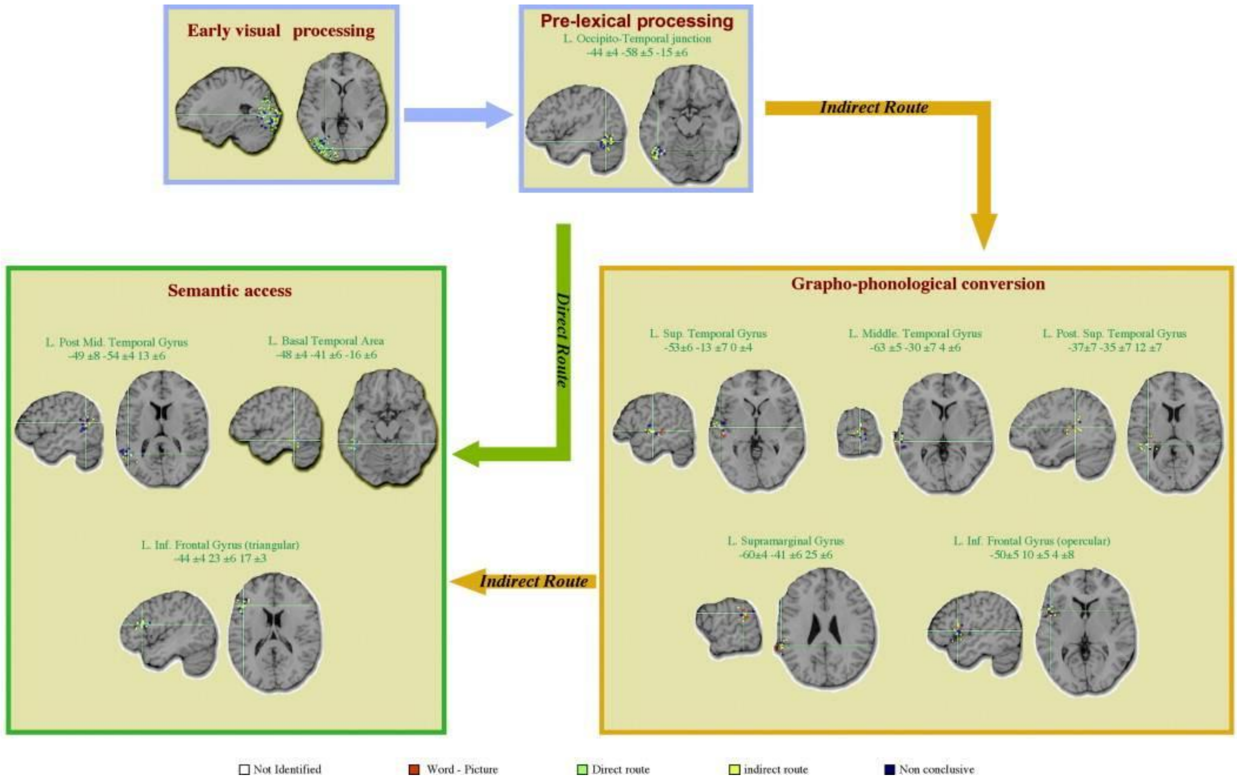


Figure 13. The two reading routes (phonological and lexical) involve different cerebral regions. This model is suggested by the metanalysis of neuroimaging studies (Jobard et al., 2003).

A more recent metanalysis (Taylor et al., 2013) use the quantitative activation likelihood estimation technique to converge results of 36 neuroimaging studies about reading process. Also in this case, they find a convergence between the functional and neural organization of the reading system and the cognitive models, specifically the Triangle model, the DRC model and the CDP+ model (Fig. 14).

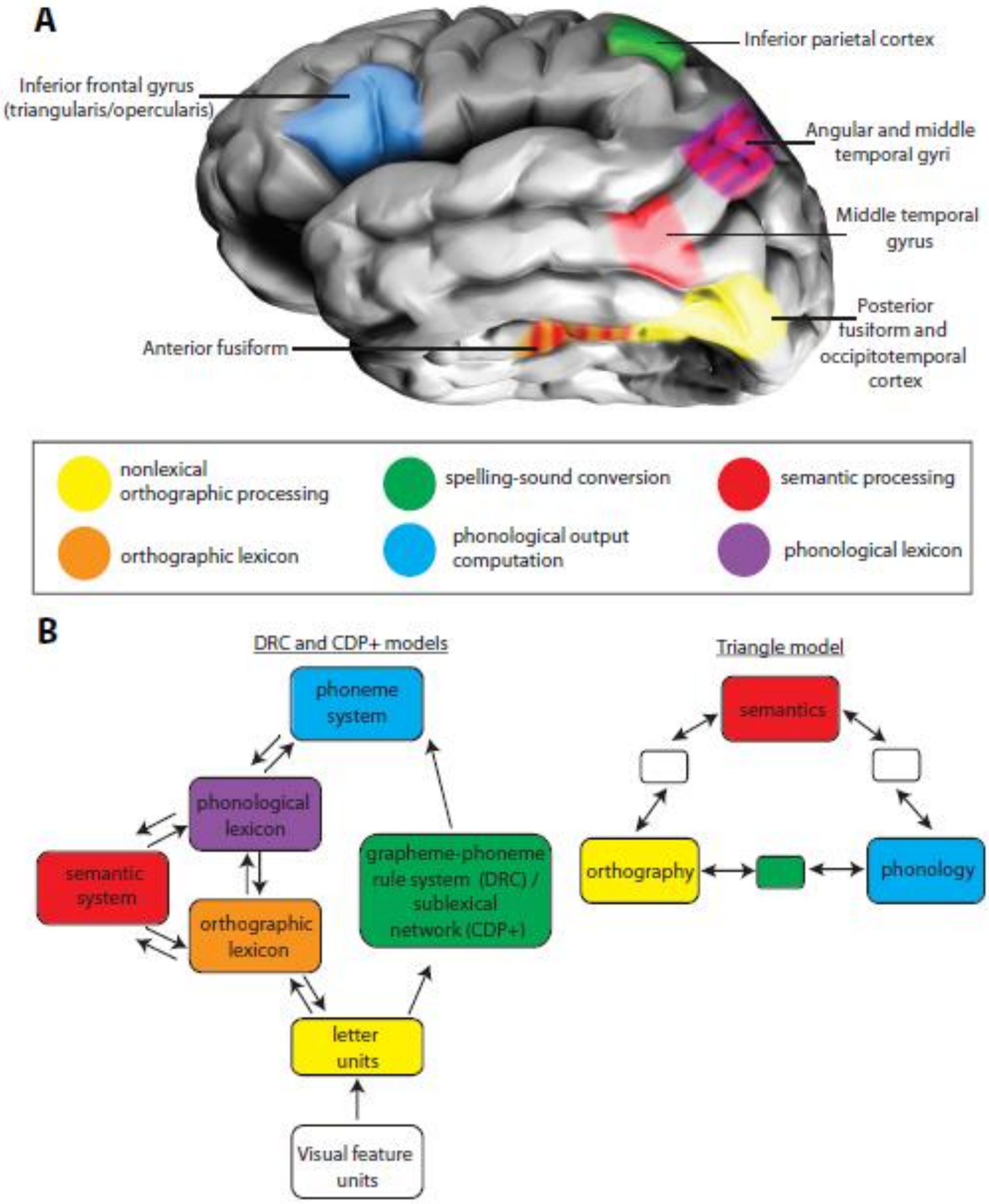


Figure 14. Schematic representation of processes involved in words and pseudowords reading, cognitive model components, and anatomical structures. (A) Inferior temporal lobe. Striped colors indicate that a brain area could perform two processes. (B) Respective components in cognitive models (Taylor et al. 2013).

Currently, most neuroimaging studies (Graves et al., 2010; Philipose et al., 2007; Price, 2000; Price at al., 2005; Shaywitz, 2003; Turkeltaub et al., 2002) and various meta-analysis (Jobard et al., 2003; Taylor et al., 2013) converge in identifying three basic systems for reading, mainly located in the left hemisphere. These include an anterior system and two posterior systems:

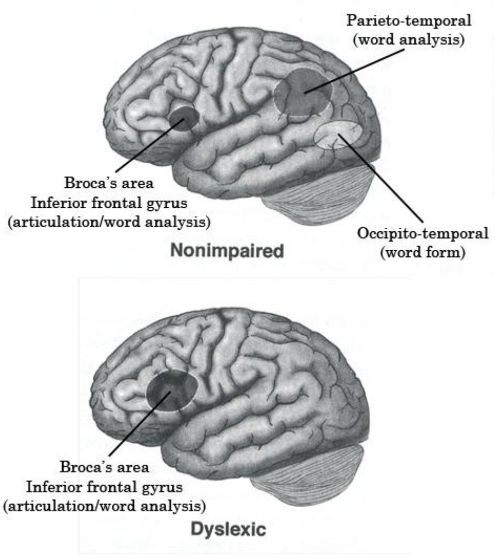
- *Anterior system* in the left inferior frontal region, including the inferior frontal gyrus (Broca's area), an important region for articulation (phonological output), silent reading and naming (Fiez et al., 1998), but also active for attention, working memory and executive processes involved in reading (Graves et al., 2010; Hoeft et al., 2007).
- *Dorsal parietotemporal system* including left inferior parietal lobe and left superior temporal gyrus (dorsal way), active for ortography to phonology conversion (Shaywitz et al., 2003).
- *Ventral occipitotemporal system* including portions of the middle and inferior temporal gyrus, middle occipital gyrus and fusiform gyrus; it also includes VWFA (Cohen et al., 2000). This system seems to be involved In skilled and fluent reading (rapid and automatic).

2.2 Neural bases of reading process in dyslexics

Dyslexia is primarily caused by an abnormality in the phonological processing, and is characterized by difficulty in isolated words reading, both in speed and accuracy, and often by a lack of sentences and texts understanding.

Alternative explanations refer to the cerebellum, head of automation of learning, and to the disorganization of the magnocellular way that transmits faster visual and auditory information. Additional deficits of motor and attentional systems could also be relevant for reading

The first hypothesis, the phonological deficit, is the most shared, and at neural level results in an underactivation of the left temporal lobe, and more extensively of the temporo parietal and occipito temporal areas (Hoeft et al., 2006, 2007; Richlan et al., 2009; Pugh et al., 2000; Shaywitz et al., 2002, 2007). This same area would be the site of dyslexia in different languages, such as Italian, English and French (Paulesu et al., 2001).



the

Figure ?. Normal readers and dyslexics brain activations durig reading. On the top, normal readers activate mostly back regions of the left hemisphere; below, dyslexis underactive these reading system in back of the brain and tend to overactivate frontal areas (Shaywitz et al., 2002).

So dyslexics, after the initial processing of the stimulus, would not activate the left temporoccipital area towards 150/200 ms, because they do not recognize all the letters of a word in parallel, and this would explain the effect of the number of letters on the reading time (effect which disappears in adult normal readers; Zoccolotti et al., 2005). After 200 ms there will be a weak activation in the left lobe, but an intense one in the right temporoparietal area, which would explain the lack of quick access to the phonology of words, because of the compensation of the right hemisphere (Simos et al., 2000 , 2002).

Another group of researchers, starting from the study of Galaburda (1979) who introduced the term "ectopia" or disorganization of cortical neurons, observe with MRI the neural connections and show an alteration of the bundles connections, especially those placed in the deep left temporoparietal region (Klingerber et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005; Silanes et al., 2005; Niogi et al., 2006; Fig. 14). Comparing the location of abnormalities in the left hemisphere with the underactivation of the temporal cortex, it is possible to confirm the hypothesis of the disconnection of the left temporal area from the rest of the brain, particularly from the frontal areas (Paulesu et al., 1996).

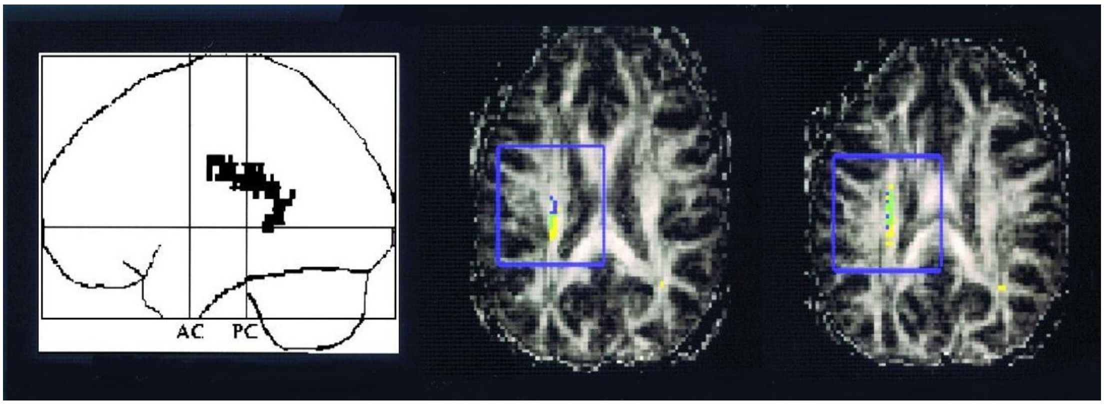


Figure 14. Alteration of long distance cortical connections. This leads to a disorganisation of bundles located in deep left temporoparietal area (Klingberg et al., 2000).

The corpus callosum, the fibers that connect the corresponding areas of the two hemispheres, have also been considered a possible cause of reading deficits (Corballis and Beale, 1976): the left and right visual areas analyse indipendently the information received, changing neural connections, and then transmit the information to the other hemisphere through the corpus callosum. A damage of this latter would provoke a deficit in the transmission of the information to be encoded.

In a more recent meta analysis study (Paulesu et al., 2014), two system have been showed to be involved in reading deficit (Fig.15):

- *Left occipito temporal area* (ventral): a damage would cause a perturbed maturation of the word recognition system (Paulesu et al., 2001; Sandak et al., 2004);
- *Temporo-parietal area* (dorsal): a damage would provoke an early dysfunction of phonological processing, emerging in the initial stage of learning process (Turkeltaub et al., 2003; Sandak et al., 2004).

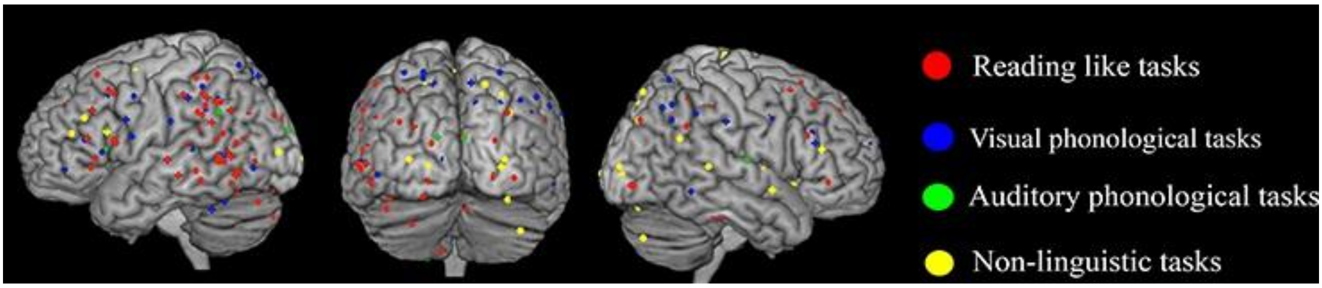


Figure 15. Peaks of ipoactivation in dyslexics during different tasks (Paulesu et al., 2014)

All the studies agree in identifying the same brain regions involved in reading process: the left posterior temporal cortex, both inferior and superior. We know that: a damage to this area causes acquired alexia (Coslett, 2006; left occipito-temporal (Paulesu et al., 2011; Temple et al., 2003), temporo-parietal and inferior frontal regions (Maisog et al., 2008; Richlan et al., 2011) are hypoactive in individuals with developmental dyslexia; left lateralization activity of superior posterior temporal cortex increases after intensive reading remediation in dyslexic children remediation (Simos et al., 2002; Temple et al., 2003); a single case report of a hyperlexic boy showed a hyperactivation of left superior posterior temporal cortex during reading task (Turkeltaub et al., 2004). We also know that transcranial direct current stimulation is able to transiently improve reading efficiency in below average readers, if applied over posterior temporal cortex (Turkeltaub et al., 2012).

Cognitive treatment of critical areas (temporal regions) since the childhood can be effective (Aylward et al., 2003; Eden et al., 2004; Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2003) and can lead to phenomena of normalization (activation of hypoactive areas of the left hemisphere), or of compensation (activation of areas of the right hemisphere; Hoeft et al., 2011).

tDCS can be a very useful tool in rehabilitation field, in reading process investigation and dyslexia treatment, especially with adults.

All these imaging studies and cognitive models led to the decision to stimulate the left temporoparietal area, assuming that it is involved in reading process, especially in grapheme to phoneme conversion.

CHAPTER 3

Studies: The effect of Transcranial direct current stimulation on reading process

3.1 General purpose

Assuming that tDCS applied on a brain area during a task, leads to a change in cognitive or behavioral performance and therefore implies that the area stimulated is involved in that cognitive process, this series of studies aims to investigate the role of temporoparietal cortex, both left and right, in the reading process. In particular they want to explore the reading process from the phonological decoding point of view, using words and non words as stimuli. At the same time the studies investigate the effect of the stimulation on the task, in terms of speed and accuracy, in order to confirm the neuromodulatory effect and to provide useful insights for application in the clinical field, in particular for the treatment of reading disorders.

The temporoparietal area, bilaterally, or with supraorbital reference, was stimulated in different protocols, in normal readers and in students at risk dyslexia.

Using a stimulation technique with no clear and know effects on the cognitive level, various parameters of stimulation (montage and duration in particular) were then taken into account.

3.2 General methods

3.2.1 Recruitment of normal readers

All participants were Italian native speakers with normal or corrected-to-normal vision, and university-level education (most from University of Padua). They were checked for stimulation exclusion criteria (Wassermann, 1998) and had no history of neurologic or psychiatric disorder, significant head trauma, hearing loss, metal in the head, implanted electrical devices or history of seizure. Pre-screening with Revised Adult Dyslexia Checklist (Vinegrad, 1994) and Adult Reading History Questionnaire (Lefly and Pennington, 2000), established that none of them presented personal or family history of learning disorder (including dyslexia). They were right handed according to the Oldfield Inventory (Oldfield, 1971). They gave their written informed consent before participation to the study and were free to leave experiment at any time. The parameters of stimulation (intensity, duration, electrodes size...) were in accordance with the values suggested by Poreisz and colleagues (2007) and approved by the

Ethics Committee of the Department of General Psychology of the University of Padua. All participants were naive as to the purpose of the study.

3.2.2 Recruitment of students at risk dyslexia

The criteria by which students at risk dyslexia were selected corresponded to those used for normal readers, but required further investigation on reading skills. Students who showed in the pre-screening indicative scores of a positive history of disorders of reading, underwent three more tests: the words and non words task (Sartori et al., 1995), the text reading task (Judica and De Luca, 2005) and the Writing Task: dictation with or withouth articulatory suppression (adapted from Colombo et al., 2009).

They were considered at risk dyslexia when at least 2 of their scores (accuracy or speed) were 1.5 standard deviation below the mean average of the adult sample.

3.2.3 Study design

Apparatus and stimuli

All studies were conducted at the Laboratory “Test Soggetti” of the Department of General Psychology - University of Padova.

Participants were seated in the lit room at a distance of 50 cm from a 19-inch monitor controlled by a Pentium Dual Core PC programmed with E-prime (Psychological Software Tool, Pittsburgh, USA). Before starting the experiment they had to read and sign the informed consent; before and after each session they had to answer to Visual Analog Mood Scale (author, year), useful to monitor the mood changes influence on the task performance.

Each participant was tested in three experimental sessions lasting approximately 45 minutes. In each session the main task consisted in words and non words reading aloud, created from Corpus and Vocabulary Frequency of Written Italian (COLFIS; Bertinetto et al., 1995).

Six different lists of stimuli were created, three for the pre-stimulation task and three for the post-stimulation task. Each list included 80 stimuli, 40 words taken from the database, and 40 non-words created by changing a syllable in every word and replacing it with that of another word of another list. In normal readers RTs are independent of word length up to 5 letter words, suggesting a parallel processing, while for longer words, TRs increase linearly, sign of a sequencial processing (in dyslexics TRs increase with increasing length, indicating a sequencial decoding; Spinelli et al., 2010). Moreover, although adults make few mistakes while reading, they may have difficulties when they are dealing with rare words and not-words, which require complex grapheme to phoneme conversion rules (Arduino & Burani, 2004; Burani et al., 2006, 2008). For this reasons we decided to use both words and non- words and to add the length words variable.

The words were selected and matched for length (words of 4 or 5 letters and 2 syllables were considered short; words of 8, 9 or 10 letters and 3, 4 or 5 syllables were considered long) and frequency (high or low). As a result, each list contained 10 short and low frequency words (PCR), 10 short and high frequency words (PCF), 10 words and low frequency words (PLR), 10 long and high frequency words (PLF), 10 short non words (created from PCR), 10 short non words (created from PCF), 10 long non words (created from the PLR) and 10 long non words (created from PLF). Totally, 480 stimuli were selected and created. The lists were presented in a sequential order (words block-non words block; non words block-words block) randomly assigned to participants.

During the stimulation which could last 10 or 18 minutes, depending on the protocol, participants underwent another task to keep them involved in the same cognitive process.

Usually participants had to read aloud paper printed texts, derived from an Italian novel (“Le città invisibili” by Calvino, 1972): they were asked to read until the stimulation time ended; at the end they had to answer to some simple comprehension questions to encourage them to read carefully. The experimenter noted where the subjects stopped and the mistakes made while reading.

Alternatively, some subjects listened to classical music by Beethoven, Mozart or Vivaldi (see the session Task of each study for details).

Procedure and experimental design

Words and non-words were written in black Courier new font 18 and presented individually at the centre of the monitor, with a white background using E-Prime software. A trial started with the presentation of a central fixation cross (subtending 0.5° × 0.5° of visual angle) lasting 500 ms. Then each item was presented for 1000 ms, followed by a 500 ms pause before the subsequent trial (Fig.16). The onset time of participants' vocal response (RTs in ms) was recorded by E-Prime and the experimenter noted accuracy errors; all letter substitution, self-correction or other kind of errors were all considered one error. Each text was presented for the entire duration of stimulation, written single-spaced in black Courier New 10 font on a white sheet of A4 paper. A schematic representation of the trial sequence is depicted in Figure ?.

Each session, which lasted about 45 minutes, was divided into three experimental blocks: first the words and non words reading task without stimulation (before tDCS), second the text reading during stimulation, third a different words and non words reading task without stimulation (after-tDCS). During the first and the third part, between the two blocks of stimuli, there was a break.

The participants were instructed to maintain their gaze on the center of the screen during the words and non words reading task, which lasted about 5 minutes. They were asked to read aloud the presented stimuli, as quickly as possible and trying not to make mistakes, through the microphone.

During the text reading, participants were asked to read aloud with their normal speed, and they were asked few questions at the end of the time. Speed was considered and calculated by the number of syllables read per second (syll/s) and accuracy was calculated as in the screening, one point for letter substitution, inversion or insertion, and half a point for wrong accent, self-correction, same error on the same word (this was made just in Studies 3 and 4). Alternatively, some participants had to listen to classic music (Study 2).

At the end of each session, participants had to answer to VAS scale (10 points scale) and to a questionnaire about the sensations induced by stimulation (Fertonani et al., 2010).

Apart from the first study that had a mixed design, all the other studies presented a within subjects design: each participant took part to three experimental sessions (in a counterbalanced order), one for the control condition (no stimulation was delivered) and the other two per the specific stimulation (See tDCS parameters section of each study for details).

Between each session, at least 48 hours passed.

Before stimulation, participants were shown the stimulator and explained its functioning, and were told they could abandon the experiment at any time. The purpose of the experiment and the type of stimulation received were communicated at the end of the third experimental session.

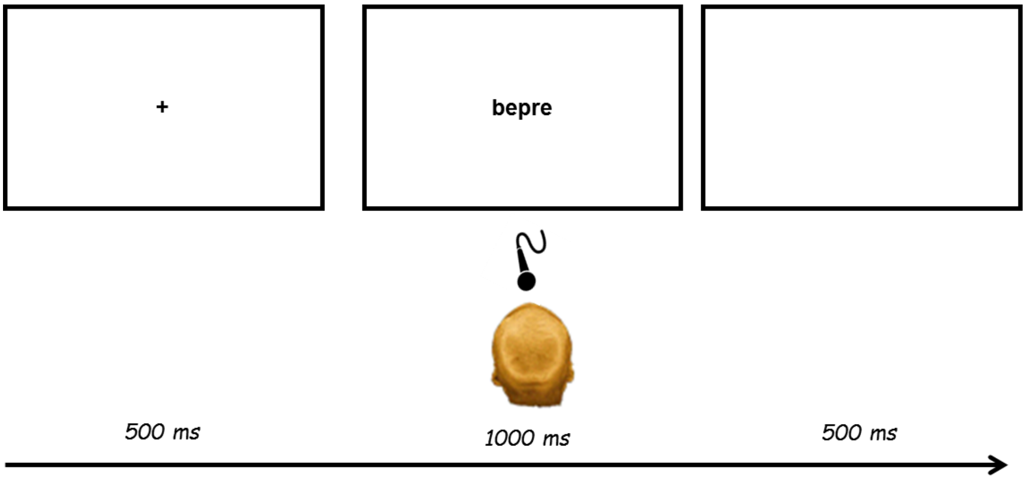


Figure 16. Example of a trial of the words and non words reading task.

3.2.4 Localization of brain targets for tDCS stimulation

Given the poor spatial resolution of tDCS and the size of the electrodes (25-35 cm2), we did not use a location system such as neuronavigation to find the area of interest, but we used the 10-10 eeg system, an extension of the most well known 10-20 international eeg system (Oostenveld and Praamstrac, 2001), used internationally to describe the locations of scalp electrodes.

As in a previous study of Turkeltaub and colleagues (2011), the left temporoparietal cortex was identified between the electrodes T7 and TP7, while the right one between the electrodes T8 and TP8 (Fig. 17).

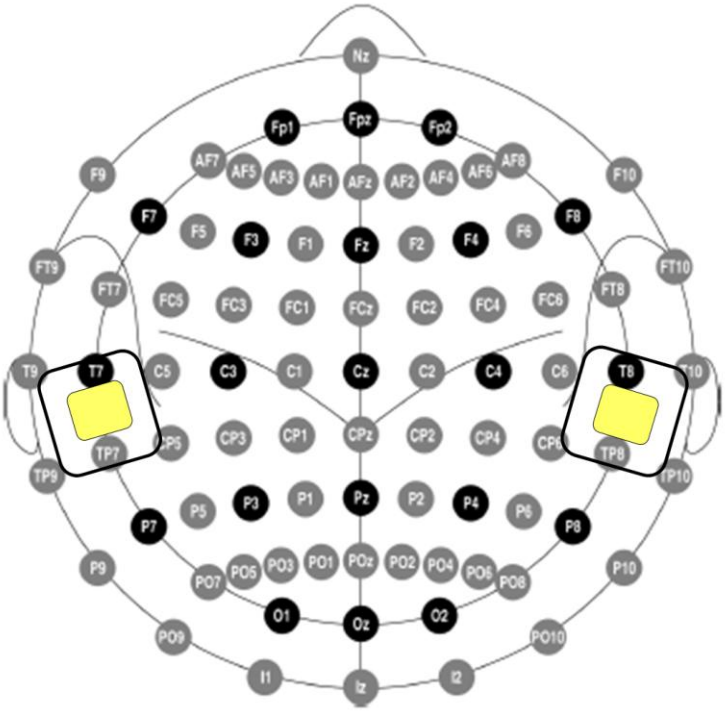


Figure 17. Electrode localization and positioning. In this figure, same size electrodes are collocated over the temporoparietal cortex. Actually, the centre of the electrode is between T7 and TP7, or between T8 and TP8, but its dimension led to cover a wider area, indicated with the black border.

3.2.5 Statistical method

All statistical analyses were performed in SPSS 20 for Windows.

Regarding the words and non words reading task, the mean vocal reaction times (RTs) of each before-tDCS task and of the sham session, were considered as control condition in the analyses. RTs beyond 2 standard deviations of the individual means for each condition were omitted (due to attention collapses, blinks, etc.). The other dependent variable considered is errors, analysed in terms of percentage of accuracy.

Repeated measure ANOVAs were performed on each reading measure (RTs and accuracy) with tDCS (anodal, cathodal, sham), Stimuli (words and non-words), length of stimuli (short and long), frequency (low or high) and time (before and after tDCS) as within-subject factors. In study 1 task (text, music) was included as between subjects factor.

A P value of 0.05 was considered statistically significant. Sphericity was verified by Mauchly's sphericity test. Post-hoc analyses were performed using Bonferroni correction. Partial eta squares (ηp 2) has been reported as effect size measures.

In Study 3 and 4, performance at reading text was considered too, and syllables per seconds and accuracy were analysed (see the section Analysis of each study for more details).

Another ANOVA was performed on mood variable (VAS scale) with tDCS (anodal, cathodal, sham) and time (before and after tDCS) as within-subject factors. Similarly, an ANOVA was performed on sensation after stimulation variable, with tDCS (anodal, cathodal, sham) as within-subject factor.

3.3 Study 1: Effects of tDCS on temporoparietal cortex and of online task on performance, in normal readers

3.3.1 Introduction

tDCS is a relatively new technique and its operation is not clear yet, especially in cognitive field. Before asserting that this tool will be useful in rehabilitation for the treatment of reading disorders, such as dyslexia, it is good to make a first step and investigate the stimulation also from the technical point of view. TDCS, through modulation, can provide a measure of the involvement of a brain region in a cognitive process. The parameters are still poorly investigated and the results are often contradictory. This study is the first of a series of exploratory studies about the functioning and effects of tDCS according to different parameters, focused on reading process.

The temporoparietal cortex (TPC), as part of the reading network (Graves et al., 2010; Philipose et al., 2007; Price, 2000; Price at al., 2005; Shaywitz, 2003; Turkeltaub et al., 2002; Jobard et al., 2003; Taylor et al., 2013) is thought to be implicated in grapheme to phoneme conversion (Shaywitz et al., 2003). This process represents one of the two routes of reading according to the DRC model (Coltheart, 1993, 2001) which argues for the presence of two routes: the lexical which operates for known, frequent and irregular words, and the non lexical (or phonological) which is active for new words and pseudowords reading.

Evidence from clinical cases confirm the involvement of the temporoparietal area: in dyslexic this is hypoactive together with left occipito-temporal and inferior frontal regions (Paulesu et al., 2011; Temple et al., 2003; Maisog et al., 2008; Richlan et al., 2011); a damage to this area can lead to acquired alexia (Coslett, 2006); it is more active after a rehabilitation (Simos et al., 2002; Temple et al., 2003); it shows a hyperactivation in hyperlexics (Turkeltaub et al., 2004).

The implication of right temporoparietal cortex is not excluded: when reading, the two hemisphere are initially both active, just after few milliseconds the information goes to the left hemisphere, but the right one is fundamental for correct reading, also confirmed by its compensation (Simos et al., 2000, 2002); moreover, deficit to the corpus callosum have been suggested as possible cause of reading deficits (Corballis and Beale, 1976).

Few studies have been conducted to assess the influence of tDCS on reading process on healthy people, for example Turkeltaub et al., (2012) showed that tDCS applied over posterior temporal cortex is able to enhance reading accuracy in below average readers. Most of the researchers have investigated tDCS effects on aphasic population during naming task, showing its usefulness for rehabilitation of post stroke aphasic patients. Moreover we know that cathodal stimulation, supposed to be inhibitory, on the right inferior frontal gyrus, improve the performance of picture naming, suggesting not only the “positive” effects of cathodal tDCS, but also the involvement of right hemisphere in language (Rosso et al., 2014).

So, basing on previous studies, the present study examined the contribution of temporoparietal cortex of both hemisphere while dealing with a reading task. If stimulation of this area leads to a change in reading performance, it can be assumed that the activity of a region of the reading network has been modulated. Furthermore, the effects of some parameters of stimulation, such as the polarity, the position of the electrodes, the duration and the task have been investigated.

To test polarity and montage, anode and cathode have been collocated either on the left or on the right hemisphere. In this way, the current flow direction changes and an effect on behavioral results can provide information about the involvement of the stimulated area, and about the lateralization of reading process. Using a different task during tDCS or sham (online task) can suggest the role of the state of excitability during stimulation, whether a task related to the stimulated area is more or less determinant than a not-related task, or whether it does not affect the subsequent reading task.

Other parameters, such as current intensity and duration, have been chosen following previous results, especially of tDCS applied on this area (Turkeltaub et al., 2012), and complying with the suggested and used limits for tDSC applications (Nitsche et al., 2003).

3.3.2 Purpose of the research

The present study investigated the role of temporoparietal area of both hemispheres, during a reading task. Participants performed a words and non-words reading task before and after stimulation or control condition (sham). This kind of protocol is offline because the stimulation was not delivered during the task of interest, but before.

If the performance at the words and non-words reading task changes after stimulation, in terms of speed and/or accuracy, it can be assumed that the temporoparietal area was involved in that cognitive process, as previous studies asserted (Turkeltaub et al., 2011). The aim of this study was to investigate the tDCS effects, depending on the chosen parameters, especially on polarity: if for cognitive functions, stimulation works as for the motor area, anodal stimulation on left temporoparietal area, assumed to be more involved then right one, should activate it and increase the performance on words and non-words reading, while cathodal stimulation on left hemisphere should have an opposite effect, worsening vocal response times and/or accuracy. As parameters of stimulation, we chose to stimulate for 18 minutes, enough to see tDCS effects on reading (Turkeltaub et al., 2011) but within the suggested limits (Poreisz et al., 2007).

Furthermore we hypothesized that the online task, administered during stimulation could have a different influence on next reading task: the one involving the same area stimulated (reading text) could lead to a better performance because of a “double” activation, through the task and through the stimulation; while the listening task, not directly involving the stimulated area, should have a milder effect, because of the single activation due to the stimulation. So, as Turkeltaub and colleagues suggested (2011), participants underwent a “related” task or a “passive” task during stimulation, and as a consequence we could also investigate the role of the task in online protocols and understand if it is another important parameter to consider in tDCS studies using offline designs.

3.3.3 Methods and materials

3.3.3.1 Participants

28 healthy undergraduate students of the University of Padua (all right handed, 18 females and 10 males, mean age of 23,5 years ± 4) with normal or corrected-to-normal visual acuity took part in the first experiment. All subjects were native Italian-speakers and were checked for tDCS and TMS exclusion criteria (Wassermann, 1998) and gave their written informed consent before participation.

3.3.3.2 Tasks

All participants had to read aloud 80 words and non-words, before and after stimulation. During the stimulation, 15 subjects had to read aloud a paper printed text (“Le città invisibili”) till they were stopped and asked some simple questions, after 18 minutes. Other 15 subjects had to listen to classical music with earphones, for the same duration of stimulation, even if they underwent a control condition.

3.3.3.3 tDCS parameters

The electrodes, linked to tDCS stimulator (BrainStim), were put on the scalp, on temporoparietal area, bilaterally. So, participants participated to three sessions in different days and randomly underwent three different conditions: anodal electrode on left temporoparietal area (L an; between T7 and TP7, using 10-10 international EEG system), and cathodal electrode on right temporoparietal area (R ca; between T8 and TP8); anodal electrode on right temporoparietal area (R an; between T8 and TP8), and cathodal electrode on left temporoparietal area (L ca; between T7 and TP7; Fig. 18);

control condition (sham) consisted in the latter montage, but it just lasted 90 seconds (30 seconds of fade in, 30 seconds of stimulation and 30 seconds of fade out). The active stimulation lasted 18 minutes, preceded and followed by 30 seconds of fade in and fade out.

In this case the montage was bilateral as the aim was to investigate the role of temporoparietal area, both left and right, and of lateralization. The electrodes and the sponges were 25 cm^2.

The intensity current was 1,5 mA, within safety limits suggested in prior studies on animals and humans (Nitsche et al., 2003; Iyer et al., 2005; Poreisz et al., 2007; Bikson et al., 2009; Liebetanz et al., 2009).

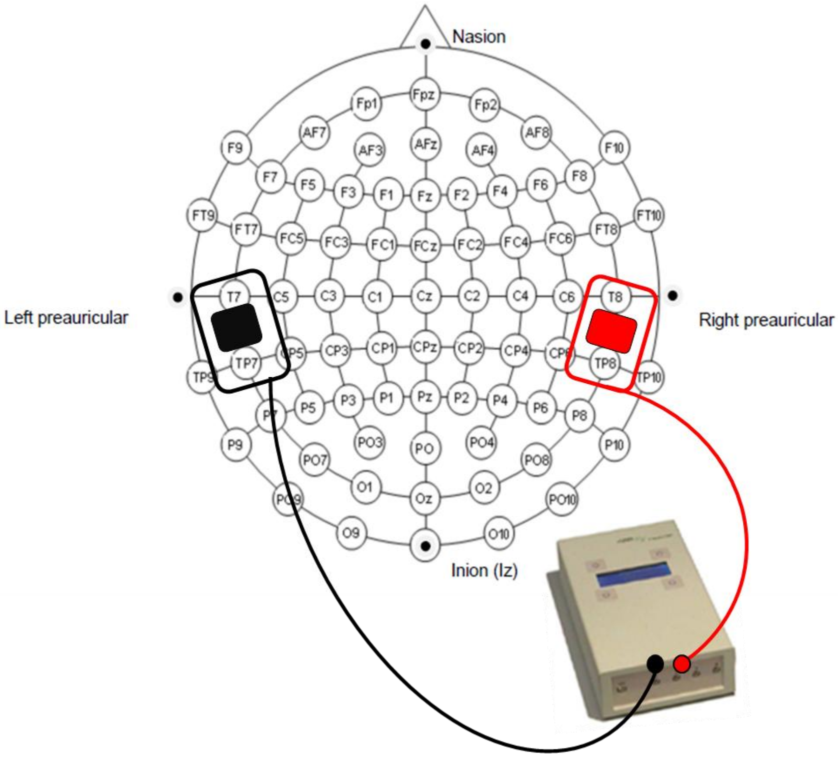


Figure 18. Electrodes positioning, bilateral montage. In this picture, cathode is on left temporoparietal area, and anode is on right temporoparietal area.

3.3.3.4 Procedure

As already described in the general procedure, participants had to fill in informed consent, exclusion criteria and handness test. They started reading aloud words and non-words presented at the center of the screen. They were instructed to read as fast as possible, trying to avoid errors. The stimuli lasted for 1000 ms. RTs were recorded by E-Prime, while errors were noted by the experimenter.

After the first task, lasting about 5 minutes, about 10 minutes were necessary to individuate the area, explain tDCS functioning and put the electrodes on the scalp of the participant.

When the stimulator was turned on, few seconds were left to be sure the participants felt comfortable with it. Then half of them were asked to read aloud the paper printed text, with attention but with their normal reading speed. They were stopped after 18 minutes of real or sham stimulation, and were asked few simple questions about the text they read. Other half of participants were asked to listen to a classical music track, with earphones and in front of a black screen, for 18 minutes. After the listening or the reading, the stimulation was stopped, the electrodes were taken off and they were asked to read aloud other words and non-words, in the same way as before.

Before and after each session, the participants had to answer to VAS scale, about their mood. After each session they also had to answer to sensation induced by tDCS test.

On the last session, they were explained the aims of the study (Fig. 19).

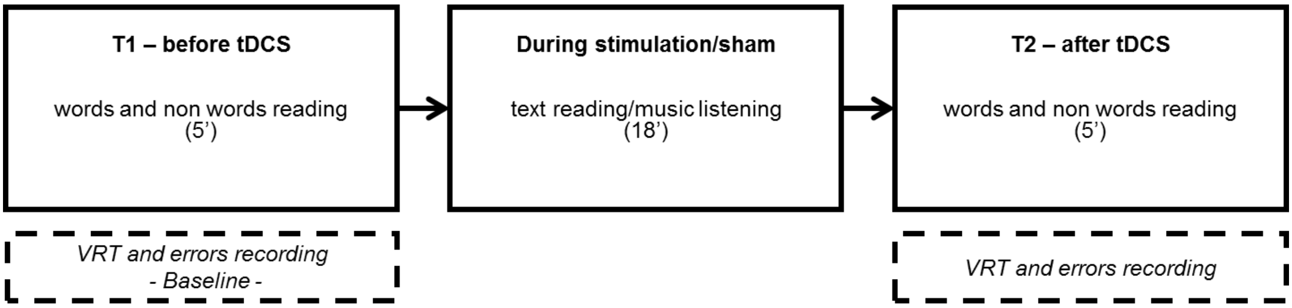


Figure 19. Procedure of study 1.

3.3.4 Analysis

Analysis were performed on RTs and accuracy of words and non-words reading task, before and after stimulation. For reading speed evaluation, a repeated measures ANOVA (3 x 2 x 2 x 2) was performed, with tDCS (anodal, cathodal, sham), Stimuli (words and non-words), length of stimuli (short and long), and time (before and after tDCS) as within-subject factors and group (text, music) as between subject factor.

A second ANOVA (3 x 2 x 2) was performed just on words TRs with tDCS (anodal, cathodal, sham), frequency (low or high) and time (before and after tDCS) as within-subject factors and group (text, music) as between subject factor.

For accuracy evaluation, two repeated measures ANOVA with the same factors as for speed evaluation, were performed. In this first study the online task was not considered from a statistical point of view, it just had the function to keep participants involved in the same task (control). A P value < 0.05 was considered statistically significant. Sphericity was verified by Mauchly's sphericity test. Post-hoc analyses were performed using Bonferroni correction. Partial eta squares (η2p) have been reported as effect size measures.

3.3.5 Results

Speed

Speed for words and non-words reading task was calculated as the mean RTs of corrected items read in each condition.

The Group between subjects factor had no influence on the performance (F(1,25) = 1.875; P = 0.183; η2p = 0.070), showing that the online task, related or not to the stimulated area, is not determinant for the task.

ANOVA on RTs analysed for stimuli length, revealed a main effect of Stimuli (F(1,25) = 113.16; p < 0.001; η2p = .819) with word onset (mean RTs 503.19 ± 75 ms) shorter than non-word onset (mean RTs 589.56 ± 113 ms), of Length (F(1,25) = 111.3; p < 0.001; η2p = .817) with short stimuli (mean RTs 510.95 ± 73 ms) read faster than long stimuli (mean RTs 576.78 ± 119 ms), and of Time (F(1,25) = 5.09; p = 0.033; ; η2p = 0.169) with a faster performance after stimulation (mean RTs 539,52 ± 97 ms) than before stimulation (mean RTs 549.59 ± 111 ms).

The analysis also revealed a significant Stimuli x Length interaction (F(1,25) = 130.29; p < 0.001; η2p = 0.839), showing that short words are read faster than all the other stimuli (Fig. 20).

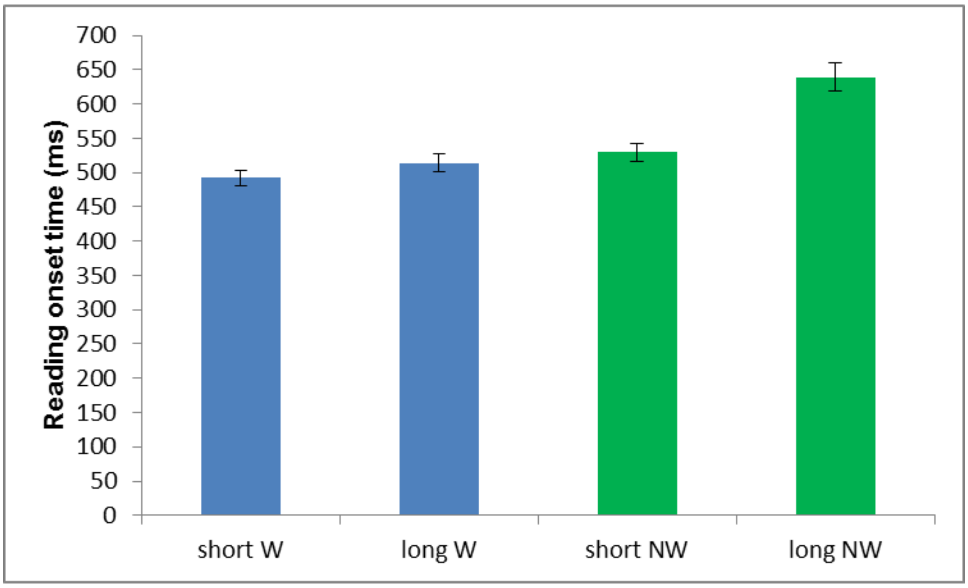


Figure 20. Words are read faster than non-words, especially if short. Non-words are read slower, especially the long ones.

The interaction Stimuli x Time was found significant (F(1,25) = 9.63; P = 0.005; *η*2p = 0.278): specifically non-words were read faster after stimulation (P = 0.002; *η*2p = 0.317). Also Length x Time was significant (F (1,25) = 5.066; P = 0.033; *η*2p = 0.168) and showed that long stimuli (both words and non words) are read faster after any kind of stimulation (P = 0.023; *η*2p = 0.189).

Then, interestingly, interaction tDCS x time was found significant (F(2,50) = 7.15; p = 0.002; *η*2p = 0.222). Bonferroni correction showed that both words and non words reading RTs were faster after right cathodal-left anodal stimulation (P = 0.002; *η*2p = 0.318) and sham (P = 0.019; *η*2p = 0.200) conditions (Fig. 21). No other interactions were found.

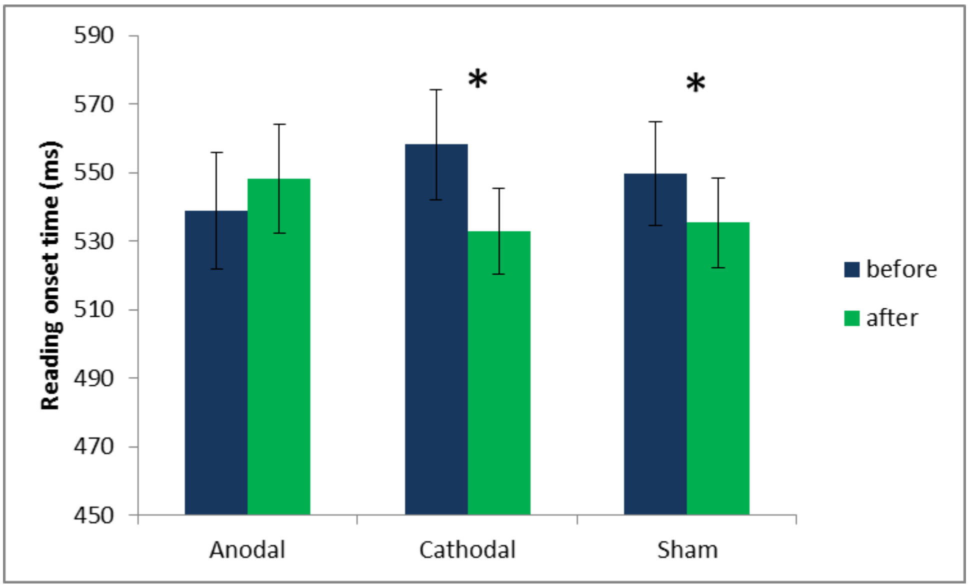


Figure 21. Reading speed is faster for both words and non words, after Left cathodal – Right anodal montage, and after sham condition.

A second ANOVA was performed on RTs just for words frequency. Again, the Group between subjects factor had no influence on words reading task (F(1,26) = 1.35; P = 0.256; *η*2p = 0.049).

The ANOVA revealed a main effect of Frequency (F(1,26) = 42,57; p < 0.001; *η*2p = 0.621) with frequent words onset (mean RTs 497,97 ± 68 ms) shorter than rare words onset (mean RTs 510.87 ± 72 ms). The interaction Frequency x Time was found significant (F(1,26) = 31.1; p < 0.001; *η*2p = 0.545), showing that words RTs are shorter after any stimulation condition (P = 0.003; *η*2p = 0.285).

Moreover, another interaction was significant, between tDCS and Time (F(2,52) = 6.73; p = 0.003; η2p = 0.206): after cathodal tDCS, both rare and frequent words are read faster (P = 0.013; η2p = 0.217; Fig. 22)).

No other significant interaction were found.

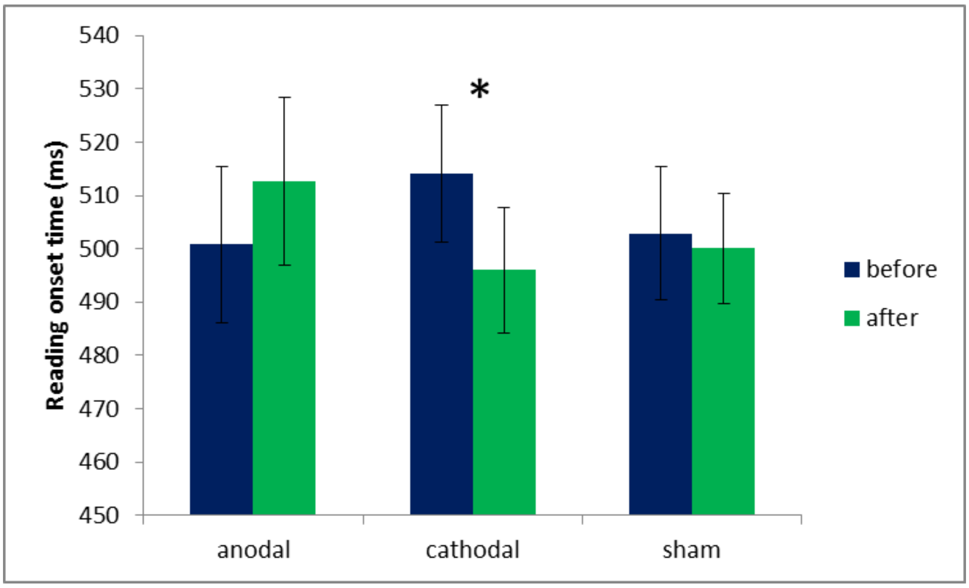


Figure 22. Reading speed is faster for both rare and frequent words, after Left cathodal – Right anodal stimulation.

Accuracy

Measure of reading accuracy was calculated as percentage of accuracy.

The Group between subjects factor had no influence on reading accuracy (F(1,26) = 1.19; P = 0.284; η2p = 0.044).

The ANOVA revealed a main effect of Stimuli (F(1,26) = 23.11; $p < 0.001$; η2p = 0.471) showing more accuracy for words (99,1% ± 5) than non-words (96,5 % ± 6), and of Length (F(1,26) = 10.31; $p < 0.004$; η2p = 0.284), with short stimuli read better (98,9% ± 5) than long ones (96,8 % ± 6).

The ANOVA revealed a significant interaction Stimuli x Length (F(1,26) = 23.61; $p < 0.001$; η2p = 0.476), confirmed by Bonferroni correction ($P < 0.001$; η2p = 0.552), and specifically showing that accuracy for short non-words is higher (98,8% ± 2) than for long non-words (94,37% ± 7).

No other interaction were found.

3.3.6 Discussion

In the present study we investigated the role of temporoparietal cortex (TPc) of both hemisphere, while participants were engaged in a reading task.

The temporoparietal cortex is supposed to be involved in reading process, as demonstrated in various studies (Graves et al., 2010; Philipose et al., 2007; Price, 2000; Price at al., 2005; Shaywitz, 2003; Turkeltaub et al., 2002; Jobard et al., 2003; Taylor et al., 2013), especially in grapheme to phoneme conversion. According to the DRC model (Coltheart, 1993, 2001), a way to investigate this process is to read novel, pseudo or non-words, whiche require a detailed a phonologic step to be read. Words were used too to further investigate possible influence on the lessical route, active for known, frequent and irregular stimuli.

We tested the effects of tDCS on reading process on normal readers, stimulated both hemisphere in order to better understand the right hemisphere role and the polarity effects. Especially for cognitive functions, the tDCS mechanisms is still contradictory, so as first step we decided to use a bilateral montage, reversing the electrodes polarity over temporoparietal cortex, with the same size, assuming an equally current flow o the scalp under the electrodes.

As the words and non words reading task was to slow to use an online design and stimulate during its execution (minimal effects can be disclosed after 5 minutes of tDCS, as argued by Nitsche and Paulus (2000), we added another task all along the duration of the stimulation (or sham condition), which could be a related task (text) or a not-related one (music), in order to understand its influence on tDCS effects on next reading task.

We found no influence of the task given during 18' of stimulation, suggesting that this was not determinant and did not affect the performance on the task of interest. Another explanation could be that the not-related task involved a cerebral region which could have been indirectly influenced by TPc stimulation, such as the auditory cortex; studies of neuroimaging could better answer and explain this result.

Both analysis on speed and accuracy confirmed the importance of length and of type of stimuli: words were read faster than non words, such as short stimuli were read faster than long stimuli, and frequent words were read faster than rare words. Reading onset times were slower with increasing difficulty of the stimuli (short words, long words, short non words, long non words).

tDCS had an effect just on reading onset times, specifically, left cathodal-right anodal montage led to faster TRs both for words and non words, and both for frequent and rare words, suggesting an involvement of the stimulated region in both lexical and non lexical route. A decrease of TRs was also found with sham condition (no stimulation), revealed for stimuli in general suggesting that the task was quiet easy and could led to a better performance, maybe due to learning process.

Accuracy was not improved by stimulation.

Thus, these first findings suggest that the stimulation (cathode on the left hemisphere) has an effect on words and non-words reading, in terms of speed, and that the stimulated area, the temporoparietal cortex, could have a role in this process. With a bilateral montage is difficult to understand which hemisphere is involved and which polarity is determinant to modulate the performance, especially if cognitive and involving a network of regions. One might think that interemispheric connections are fundamental for reading, as suggested by supporters of corpus callosum role in reading deficits (Corballis and Beale, 1976). This is difficult to say when using a bilateral montage, because we don’t know the exact influence of anode or cathode.

Several parameters could be changed in this study, but to first investigare a bit more the TPc role and the polarity functioning, next study focused on the montage influence.

3.4 Study 2: Effects of different montages on reading task

3.4.1 Introduction

One important aspect to consider when stimulating with tDCS is the electrode positioning, which determines the spatial distribution and direction of the flow of current, and so the distribution of induced electric fields in the brain. First studies with tDCS on motor cortex found a decreasing of motor cortex excitability with anodal stimulation (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998) or with cathodal stimulation while anodal tDCS enhanced the activity (Nitsche & Paulus, 2000). This result could be explained by the different positioning of the reference electrode: under the chin, in the first study, and over the contralateral supraorbital in the second one.

Normally, bilateral montage is used to simultaneously modulate activity in two cerebral areas, increasing activity on one side, and decreasing it on the other (Sela et al., 2012), or to investigate and involve interemispheric connections between the stimulated areas (Cohen Kadosh et al., 2010). So it is useful to investigate mechanisms involving both hemisphere or two regions (Hecht et al., 2010) but can leads to confounding effects because of two different polarities acting at the same time on the brain, especially using the same size for both electrodes. This problem is more evident when applying tDCS for cognitive function involving a network of regions. One possible solution to better understand the mechanism of interest is to increase the size of the reference electrode to reduce local current density without compromising the effects under the active electrode (Nitsche et al., 2007; Stagg & Nitsche, 2011; Meinzer et al., 2012); another alternative is to use an extracephalic montage or collocate the reference electrode over an area supposed not to be involved in the studied function. This is though to modifying a specific area of interest, but could also lead to stimulate an area linked or close to the stimulated region. For this reason, some reserachers preferred to use arm montages (Cogiamanian et al., 2007; Priori et al., 2008).

Another important aspect to consider and investigate, is the distance between the electrodes: more distant electrodes can increase brain modulation due to less scalp shunting (Datta et al., 2008). The knowledge about the functioning of extracephalic electrodes is still little, the only two suggestions are that maybe conductivities in the arm and body are not homogenous and that with larger distances between electrodes, voltage should adapt according to this distance to achieve similar aftereffects to cortical reference sites.

3.4.2 Purpose of the research

In the first study we used a bilateral montage which led to an influence on the reading task, but we could not discriminate between the two stimulations, even if data suggested a certain involvement of the stimulated area, and as already said, maybe the explanation could refer to the wide reading network modulated.

Although many studies support that reading is a left hemisphere lateralized process (Tarkiainen et al., 1999, 2002; Simos et al., 2002; Temple et al., 2003; Turkeltaub et al., 2004), there are also plenty of evidence of the involvement of both hemispheres in this process. The aim of the second study was to investigate the effects of tDCS using a montage with active electrode (anode, cathode or sham) over left temporoparietal area, and reference electrode, larger and over contralateral orbitofrontal area (right hemisphere), supposed to be not involved in reading process, at least not directly.

The aim was to "isolate" the left hemisphere, dominant for language, and assess the effects of stimulation during a reading task.

3.4.3 Methods and materials

3.4.3.1 Participants

12 healthy undergraduate students of the University of Padua (all right handed, 9 females and 3 males, mean age of 26 years ± 4) with normal or corrected-to-normal visual acuity took part in the second experiment. All subjects were native Italian-speakers and were checked for tDCS and TMS exclusion criteria (Wassermann, 1998) and gave their written informed consent before participation.

3.4.3.2 Tasks

The task was exactly the same as the one used for the first study. The only difference was that during stimulation all participants read a text aloud ("Le città invisibili").

3.4.3.3 tDCS parameters

The electrodes linked to tDCS stimulator (BrainStim), were put on the scalp, one on left temporoparietal area and the other on right orbitofrontal area. So, participants came three times in different days and randomly they underwent three different conditions: anodal electrode on left temporoparietal area (between T7 and TP7, using 10-10 international EEG system), and cathodal electrode on right orbitofrontal area; anodal electrode on right orbitofrontal area, and cathodal electrode on left temporoparietal area (between T7 and TP7); control condition (sham) consisted in the latter montage, but it just lasted 90 seconds (30 seconds of fade in, 30 seconds of stimulation and 30 seconds of fade out). The active stimulation lasted 18 minutes, preceded and followed by 30 seconds of fade in and fade out (Fig. 23).

In this case the montage was orbitofrontal: electrodes and sponges were 25 cm^2 (on left temporoparietal area) and 35 cm^2 (on right orbitofrontal area).

The intensity current was 1,5 mA, following safety limits suggested in prior studies on animals and humans (Nitsche et al., 2003; Iyer et al., 2005; Poreisz et al., 2007; Bikson et al., 2009; Liebetanz et al., 2009).

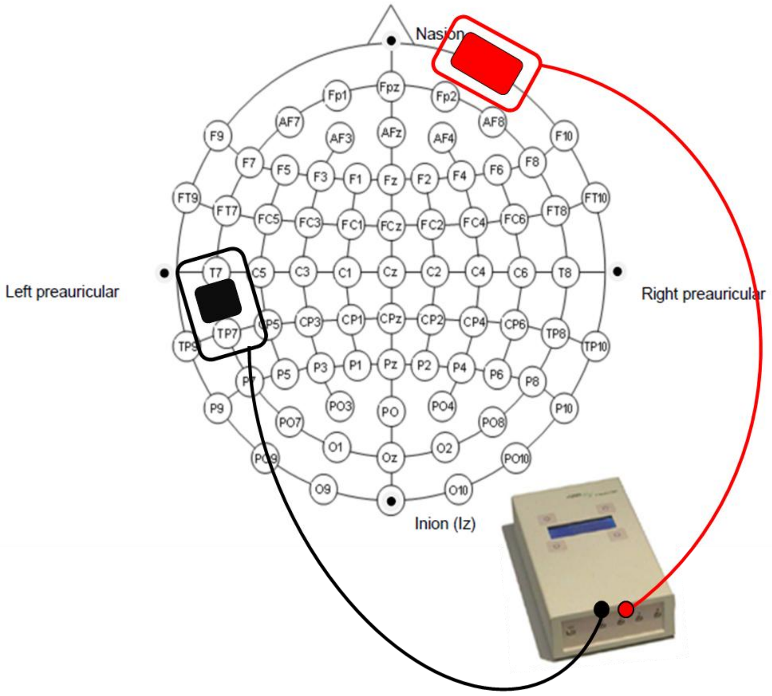


Figure 23. Electrodes positioning, supraorbital controlateral montage. In this picture, cathode is on left temporoparietal area, and anode is on right orbitofrontal area. The latter is bigger.

3.4.3.4 Procedure

Procedure was the same as the first study. This time, alla participants read a text during active stimulation or sham.

3.4.4 Analysis

Analysis were performed in the same way as in the first study. No between subject factor was evaluated.

3.4.5 Results

Speed

ANOVA on RTs for Stimuli length, revealed a main effect of Stimuli ($F(1,12) = 103.86$; $p < 0.001$; $\eta 2p = .896$) with word onset (mean RTs 485.27 ± 61 ms) shorter than non-word onset (mean RTs 582.62 ± 121 ms), of Length ($F(1,12) = 60.92$; $p < 0.001$; $\eta 2p = .835$) with short stimuli (mean RTs 487 ± 69 ms) read faster than long stimuli (mean RTs 580.8 ± 118 ms).

The analysis also revealed a significant Stimuli x Length interaction ($F(1,12) = 60.17$; $p < 0.001$; $\eta 2p = 0.834$), showing an increase in TRs parallel to the increase of difficulty of the stimulus to read (short words, long words, no words short, not long words).

No significant interaction was found for tDCS x time (F(2, 24) = 0.253; p)= 0.778; *η*2p = 0.021; see Fig. 24).

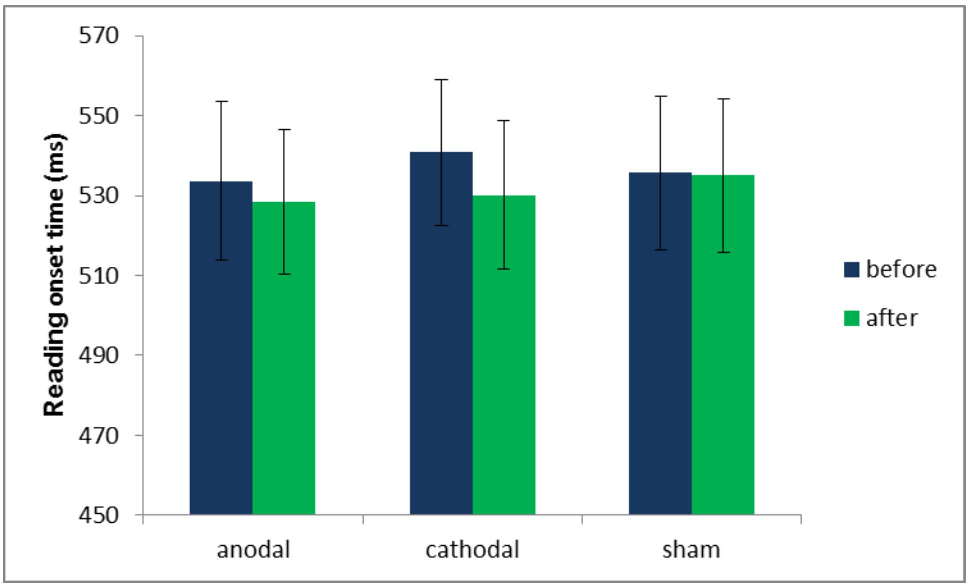


Figure 24. Reading performance after real or sham stimuation is not different than before, in terms of speed.

The ANOVA performed on RTs for words frequency revealed a main effect of Frequency (F(1,12) = 15.49; p = 0.002; *η*2p = 0.563) with frequent words onset (mean RTs 475 ± 52 ms) shorter than rare words onset (mean RTs 488 ± 60 ms).

A significant tDCS x frequency x time interaction (F(2,24) = 3.5; p = 0.046; *η*2p = 0.226), confirmed by post hoc analyses: specifically there was a significant improvement on performance and so a decreasing of RTs for rare words after cathodal stimulation (P = 0.044; *η*2p = 0.296).

No other significant interactions were found.

Accuracy

The ANOVA revealed a main effect of Stimuli (F(1,12) = 44.2; p < 0.001; *η*2p = 0.787) showing more accuracy for words (98,1% ± 3) than non-words (91 % ± 9), and of Length (F(1,12) = 43.78; p < 0.001; *η*2p = 0.785), with short stimuli read better (98 % ± 3) than long ones (92.1 % ± 9). The ANOVA also revealed a significant interaction Stimuli x Length (F(1,12) = 46.65; p < 0.001; *η*2p = 0.795), confirmed by Bonferroni correction, and specifically showing that accuracy for long non-words is lower than for short non-words (P < 0.001; *η*2p = 0.801) and for long words (P < 0.001; *η*2p = 0.802).

No other interaction were found.

3.4.6 Discussion

When stimulating with a bilateral protocol, it si more possible that a reported effect on behaviour is due to reference electrode stimulation or to the interaction between the target and the reference electrode. One possibility to focus on the target area is to put the reference not over the homologue contralateral area, but on supraorbital region, better if larger.

With the second study we aimed to focus on left temporoparietal cortex, using an orbitofrontal montage. We just found a selectively effect of cathodal tDCS on speed, decreasing rare words TRs. No other significant effect was found besides stimuli and length influence. Nevertheless, reading times after left cathodal stimulation diminished, and although the difference between before and after tDCS was not significant, this couls suggest, together with the results of the first study, that the parietotemporal cortex was still involved in the reading process. It could be that the influence on the task was lower due to the distance between the electrodes and the consequent current shunting on the scalp, which lead to less current delivered on the target area. The advantage of an orbitofrontal montage is the focusing of the stimulation on one area or hemisphere, but we are not completely sure that the reference electrode has no influence on the other area, although it is bigger.

Maybe to achieve a stronger effect, increasing distance between the two electrodes we shoul have increased the current intensity too, as suggested by Moliadze

To achieve a more clear view of the stimulation functioning, we decided to modify one variable at a time, and considered the more salient result of the first experiment, in the third study, we decided to use again the bilateral montage an to investigate another parameter: the duration of the stimulation.

3.5 Study 3: Effects of stimulation duration on reading task

3.5.1 Introduction

In the first study we found a facilitatory effect on left cathodal-right anodal stimulation, which could seem a contradictory effect if we think that cathode normally inhibits the below area, while the anode excite it. But this dicothomy seems to be true just for motor area stimulation. Without the help of neuroimaging techniques, it is very difficult to say with certainty how really stimulation works, but we could draw indirect conclusions from behavioral results. Before to argue that the temporoparietal cortex is really involved in reading, or at least in isolated words and non-words reading task, we could change another parameter of stimulation which seems to be determinant too.

The duration of tDCS can determine the direction of current. First studies showed that a minimal effect could be achieved stimulated for 5 minutes, and that 9-13 minutes could lead to 90 minutes of aftereffects (Nitsche and Paulus, 2001). But it was also shown that 13 minutes of anodal stimulation really increased motor cortical excitability, still other 13 minutes were applied after and led to a significant decrease of the area (Monte-Silva et al., 2012). The authors suggested that this could be due to regulatory mechanisms which prevent over-excitability: they would activate hyper-polarizing potassium channels, which are dependent on intracellular calcium level (Monte-Silva et al., 2012). If for motor area the mechanisms is not so clear, for cognitive function, the question is still open.

3.5.2 Purpose of the research

The aim of this study was to investigate the stimulation duration influence.

Taken together the facilitatory effect of left cathodal-right anodal montage, and the hyphotesis of an over-excitation (Monte-Silva et al., 2012), we though that maybe our findings was due to the duration of stimulation who could have led to a paradox effect, with the cathode facilitating instead of inhibiting the area and the anode inhibiting instead of exciting the stimulated region.

To test the hyphotesis of a prolonged and paradoxical stimulation, we decided to stimulate only for 10 minutes, supposed to be enough to achieve an aftereffect of at least 30 minutes. We also wanted to compare the effects of a “limited” stimulation to the one we had used before.

3.5.3 Methods and materials

3.5.3.1 Participants

14 healthy undergraduate students of the University of Padua (all right-hand handed, 6 males and 8 females, mean age of 21 years ± 2) with normal or corrected-to-normal visual acuity took part in the first experiment. All subjects were native Italian-speakers and were checked for tDCS and TMS exclusion criteria (Wassermann, 1998) and gave their written informed consent before participation.

3.5.3.2 Tasks

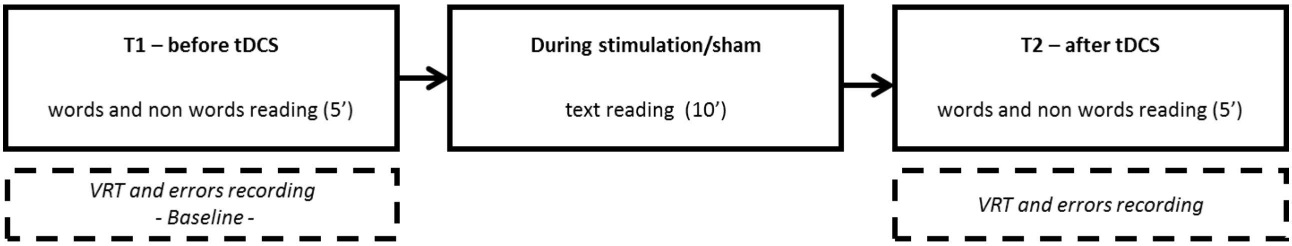
The task was exactly the same as the one used for the second study: words and non-words reading task, and aloud reading of a text during stimulation.

3.5.3.3 tDCS parameters

The electrodes, 25 cm^2, were put on the scalp, on temporoparietal area, bilaterally. The experiment design was again within subjects, each participant took part to three daily sessions. The electrodes were put using the 10-10 international EEG system.

This time the duration of the stimulation was 10 minutes. The intensity current was 1,5 mA, as in first two studies.

3.5.3.4 Procedure



3.3.4 Analysis

Analysis were performed in the same way as in the second study.

3.3.5 Results

Speed

ANOVA on RTs analysed for Stimuli length, revealed a main effect of Stimuli (F(1,13) = 100.63; p < 0.001; η2p = .886) with word onset (mean RTs 540 ± 80 ms) shorter than non-word onset (mean RTs 657 ± 121 ms), of Length (F(1,13) = 71.9; p < 0.001; η2p =

.847) with short stimuli (mean RTs 560 ± 85 ms) read faster than long stimuli (mean RTs 637 ± 133 ms). The significant interaction Stimuli x Length further explain this effect (F(1,13) = 128.7; p < 0.001; *η*2p = 0.908): TRs for long non-words (730 ± 84 ms) are significantly slower than for short non-words (730 ± 108 ms).

Two more interactions were significant: stimuli x time (F(1,13) = 8.9; p < 0.001; *η*2p = .409) showing that non-words are read faster after each condition of stimulation, but this effect disappeared with pairwise comparisons (all p > 0.07); length x time (F(1,13) = 25.5; p < 0.001; *η*2p = 0.663) resulting in faster TRs for long stimuli (650 ± 132 ms) after each stimulation condition (625 ± 134 ms), confirmed by Bonferroni correction (p = 0.03; *η*2p = 0.306).

The interaction tDCS and Time was not significant (F(2,26) = 2.104; p = 0.142; *η*2p = 0.139; Fig. 24). No other interactions emerged.

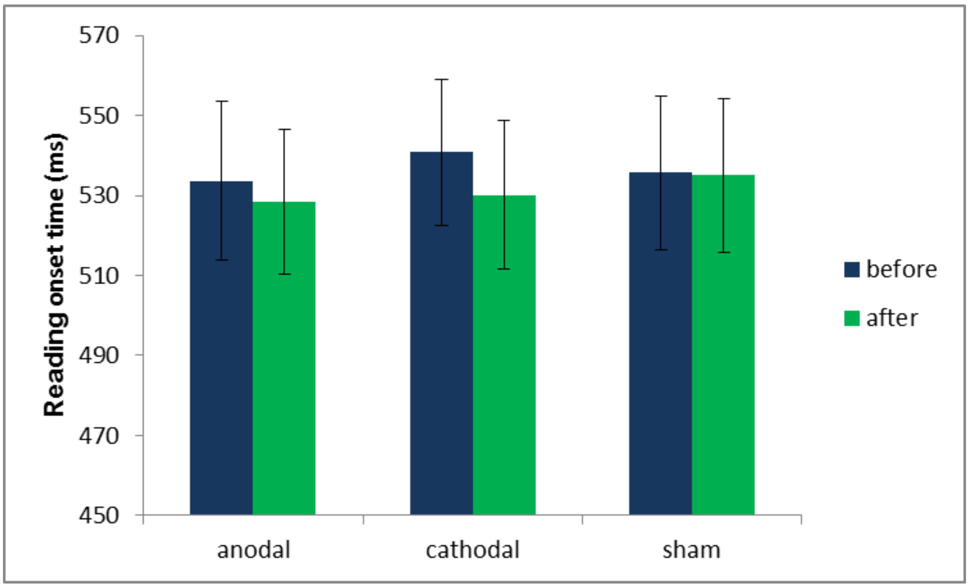


Figure 24. Reading times are not significatly slower after real or sham stimuation.

The ANOVA performed on RTs for words frequency revealed a main effect of Frequency (F(1,13) = 22.48; p < 0.001; *η*2p = 0.634) with frequent words onset (mean RTs 531 ± 76 ms) shorter than rare words onset (mean RTs 548 ± 80 ms).

A significant frequency x time interaction emerged (F(1,13) = 7.24; p = 0.002; *η*2p = 0.358), but it resulted no more significant with post hoc analyses (p > 0.329).

The interaction tDCS and Time was not significant (F(2,26) = 3.3; p = 0.052; *η*2p = 0.203).

Accuracy

The ANOVA revealed a main effect of Stimuli (F(1,13) = 16.42; $p < 0.001$; $\eta 2p = 0.558$) showing more accuracy for words (98,9% ± 8) than non-words (94,4 % ± 8), and of Length (F(1,13) = 43.29; $p < 0.001$; $\eta 2p = 0.769$), with less errors for short stimuli (99,1 % ± 2) than for long ones (94.1 % ± 10). Further a significant interaction Stimuli x Length emerged (F(1,13) = 14.27; $p = 0.002$; $\eta 2p = 0.523$) as confirmed by Bonferroni correction ($p < 0.001$; ; $\eta 2p = 0.809$): long non-words lead to more errors (90,2 % ± 8) than short non words (98,8 % ± 3)

The interaction tDCS x time was not significant (F(2,26) = 0.954; $p = 0.398$; $\eta 2p = 0.068$). No other interaction were found.

3.3.6 Discussion

In this study, we found again an effect of stimuli, length and frequency. We did not find a facilitation for accuracy, nor for reading speed.

Anyway, although the result was not significant, reading times diminished again after cathodal stimulation, going in the same direction as the first study. One possible explanation is that 10 minutes of stimulation of 1.5 mA intensity are not enough to significantly improve a reading performance. We did not find an opposite effect to the first study, and this could suggest that the bilateral montage, among the one tested, and a duration of 18 minutes, are the most effective.

Considering that in these studies we tested normal readers and that they had no hypoactive or lesioned area, it is also hard to achieve a facilitation because of a possible ceiling effect, due to the state of excitability of the stimulated area, but also to the simplicity of the given task.

So, this finding seems to confirm a facilitatory effect of cathode over left parietotemporal area, or at least could exclude an inhibitory effect of cathodal stimulation.

3.6 Study 4: Effects of tDCS on bilateral temporoparietal cortex in students at risk dyslexia

3.6.1 Introduction

All the previous studies investigated stimulation after effects on normal readers, focusing on different parameters. We found a facilitatory effect with left cathodal-right anodal stimulation, both for words and non words, suggesting that the bilateral montage with a duration of 18 minutes modulates temporoparietal area and affects reading process.

Dyslexia, from the neurological point of view, results in an underactivation of the left temporal lobe, and more extensively of the temporo parietal and occipito temporal areas (Hoeft et al., 2006, 2007; Richlan et al., 2009; Pugh et al., 2000; Shaywitz et al., 2002, 2007). Dyslexics have a deficit in the phonological process, in the grapheme to phoneme conversion, and would read words sequentially and not in parallel, ssuffering the effect of the number of letters (Zoccolotti et al., 2005). Without any brain image, we can just hypothesize that below average readers have some difficult in reading and the task is of course more difficult for them. According to Miniussi et al., (2013) stimulation would be more effective when doing a “medium coherent” task, that is to say that to achieve good results, a task should not be “incoherent”, too difficult, with a lot of noise, or “high coherent”, too easy. Maybe the previous results are influenced by the “high coherent” task given to the participant. With below average readers, the same task could result of medium difficulty, and so it could led to different results.

3.6.2 Purpose of the research

The aim of this study was to investigate the effects of tDCS on below average readers. Following previous results, we used the bilateral montage and stimulated for 18 minutes.

We wondered if this montage, with this parameters, could have the same effect on below average students in reading performance, with a presumed different state of activation of the stimulated area and for which the task would be more difficult.

3.6.3 Methods and materials

3.6.3.1 Participants

The participants were selected through a pre-screening which indicated reading problem history and a subsequent assessment about: they were given the words and non words task (Sartori et al., 1995), the text reading task (Judica and De Luca, 2005) and the Writing Task (adapted from Colombo et al., 2009).

10 students (all right-hand handed, 6 males and 4 females, mean age of 23 years ± 4,5) with normal or corrected-to-normal visual acuity took part in the study. All subjects were native Italian-speakers and were checked for tDCS and TMS exclusion criteria (Wassermann, 1998) and gave their written informed consent before participation (Table 2).

subject	**sex**	**age**	**education**	**Word**		**Non words**		**Text**		**Dictation**	
				acc	**speed**	**acc**	**speed**	**acc**	**speed**	**omissions**	**errors**
1	M	23	15	--	--	-	--	+	--	--	+
2	F	20	15	--	+	--	-	--	--	+	--
3	M	22	17	+	+	--	+	-	-	+	+
4	F	21	16	+	+	--	+	+	-	+	--
5	M	21	16	--	+	+	--	+	+	-	--
6	F	20	15	--	+	--	+	-	+	+	--
7	M	21	16	--	+	-	+	+	+	+	+
8	M	34	18	--	--	--	--	-	--	-	--
9	M	29	18	--	+	--	+	+	--	--	+
10	F	22	17	--	+	--	--	+	--	-	--

Table 2. participants demographic data and assessment result. Acc = accuracy
(-) below 1,5 DS (--) below 2 DS or more (+) no impairment

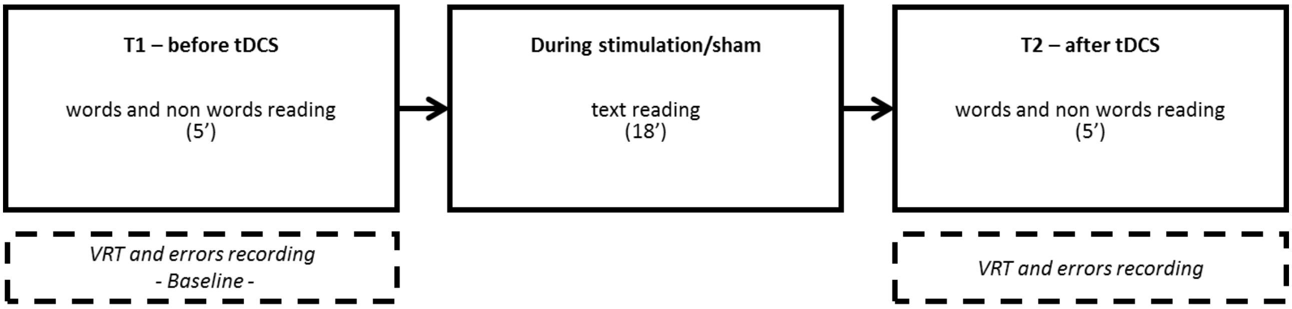
3.6.3.2 Tasks

The task was exactly the same as the one used for the other studies: words and non-words reading task, and aloud reading of a text during stimulation.

3.6.3.3 tDCS parameters

The parameters used were the same as in the first study. 18 minutes of stimulation, 1 mA, electrodes of 25 cm2, during a text reading.

3.6.3.4 Procedure



3.6.4 Analysis

Analysis were performed in the same way as in the first study, without Group as between subjects factor.

3.6.5 Results

Speed

ANOVA on RTs analysed for Stimuli length, revealed a main effect of Stimuli (F(1,6) = 35,66; $p < 0.001$; η2p = 0.856) with word onset (mean RTs 716 ± 133 ms) shorter than non-word onset (mean RTs 828 ± 169 ms) and of Length (F(1,6) = 9.87; $p = 0.02$; η2p = 0.622) with short stimuli (mean RTs 713 ± 127 ms) read faster than long stimuli (mean RTs 831 ± 167 ms).

ANOVA on RTs analysed for words frequency, revealed a main effect of Frequency (F(1,7) = 10.44; $p = 0.014$; η2p = 0.599). No interaction was significant

Accuracy

The ANOVA revealed a main effect of Stimuli (F(1,7) = 14.89; $p = 0.006$; η2p = 0.680) showing more accuracy for words (97,5% ±) than non-words (90 % ±), and of Length

(F(1,7) = 12.59; p = 0.009; *η*2p = 0.643), with less errors for short stimuli (97,4 % ±) than for long ones (90.1 % ±).

Further a significant interaction tDCS x Time emerged (F(2,14) = 8,5; p = 0.004; *η*2p = 0.549) as confirmed by Bonferroni correction (p = 0.014; *η*2p = 0.605): after left anodal-right cathodal stimulation, accuracy was higher than before, respect to all the other conditions (all p > 0.584). The interaction tDCS x length x time was significant too (F(2,14) = 4.226; p = 0.37; *η*2p = 0.376) indicating that left anodal-right cathodal stimulation increased accuracy especially for long stimuli (p = 0.007; *η*2p = 0.349; Fig. 25). No other interaction was found.

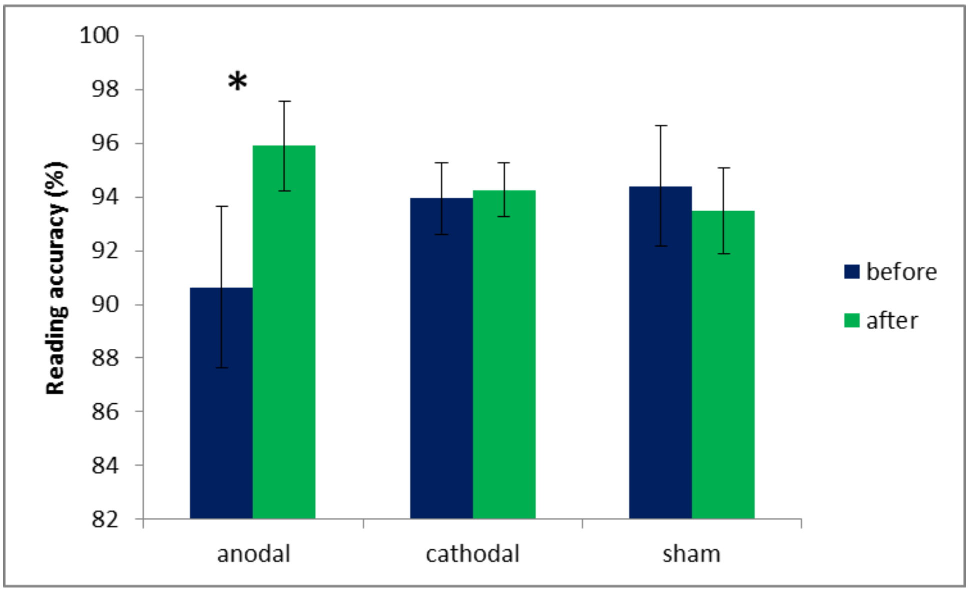


Figure 25. Reading accuracy improves after left anodal-right cathodal tDCS, especially for long stimuli.

3.6.6 Discussion

Also in this study, we found an effect of stimuli, length and frequency. tDCS had no facilitatory or inhibitory effect on reading onset times, but showed its influence on accuracy. Specifically, left anodal-right cathodal stimulation improved words and non words reading accuracy, most for long ones. A similar effect was already found by Turkeltaub et al., (2011) which found an improved reading efficiency after anodal stimulation in below average readers.

Regarding the montage, the bilateral seems to be effective, at least after one session of tDCS of one type. In previous studies, accuracy was less relevant, and the effective montage was the bilateral one but with inverted polarities.

In this study, instead, tDCS had no effect on reading times, but this could be due to different level of difficulties the participants showed.

To conclude that tDCS and this specific parameters are effective, especially for rehabilitation, more sessions would be necessary. We just could suppose that the stimulated area could be involved in reading process, and that other montages should be tested to achieve the most effective parameters.

CHAPTER 4
Conclusions

Reading is a human skill, fundamental for everyday life. It involves several cognitive processes, such as the recognition of letters, their combination into words, pronunciation and meaning. Curretly there is common agreement on the simultaneous activation of two ways of reading, the phonological and the lexical one, both necessary for a correct reading: the first leads to words pronunciation, through grapheme to phoneme conversions, and allows to read new words or not-words; the second leads to the meaning of words, and allows to read frequent words. This theory was suggested in the *Dual-Route Cascaded model* (DRC model) by Coltheart and colleagues (1993, 2001). According to this model, from the neural bases point of view, most regions involved in reading process are located predominantly in left hemisphere, as confirmed by neuroimaging studies (Graves et al., 2010; Philipose et al., 2007; Price, 2000; Price at al., 2005; Shaywitz, 2003; Turkeltaub et al., 2002) which converge in identifying three basic systems for reading: an *anterior system* in the left inferior frontal region for articulation (phonological output); a *dorsal parietotemporal system* including left inferior parietal lobe and left superior temporal gyrus for orthography to phonology conversion (Shaywitz et al., 2003); and a v*entral occipitotemporal system* including, among others the VWFA and involved for rapid and automatic reading. Similarly, studies on patients found these same regions involved in dyslexia (Paulesu et al., 2001; Turkeltaub et al., 2003; Sandak et al., 2004). The distinction is not so clear, other cognitive theories have been suggested, together with neural findings, such as the involvement of corpus callosum (Corballis and Beale, 1976) and its disconnection.

Transcranial direct current stimulation is a non invasive brain stimulation technique which induce a transient changes in cortical excitability and is able to alter the behaviour for a limited period of time. Thanks to its neuromodulatory feature, it could be very useful to understand the role of brain regions, the mechanisms of cognitive functions, and for rehabilitative purposes too. tDCS mechanisms is still not well known, especially regarding cognitive function.

These studies aimed to investigate the effects of tDCS over temporoparietal cortex during and on reading process in healthy and below average people. We also wanted to investigate the stimulation parameters, supposed to be determinant for the desired effects. In the first study we stimulated temporoparietal cortex bilaterally, while dealing with a reading task, in which participants had to read aloud words and non-words: the first test the grapheme to phoneme conversion ability, while the second were used to test the influence of lessical route of reading, according to DRC model (Coltheart, 1993, 2001).

We also investigated the online task (related or not to the stimulated area) given during stimulation. This seemed to have no influence on next reading task, suggesting that the online task is not determinant or that stimulation activated also regions close to the area involved in the control task (music listening). As in all the studies, words were read faster than non words, short stimuli were read faster than long stimuli, and frequent words were read faster than rare words, suggesting that the task was adapt to achieve our purpose and that this variable have to be considered. Stimulation had an effect on task, specifically with left cathodal-right anodal montage TRs were faster for all the stimuli, short and long, frequent and rare. This could suggest that we both stimulated the two routes of reading, both lexical and phonological, and this could be true considering the electrodes size (25 cm2). We also found an improvement after control condition, maybe due to task facility. From this first evidences we suggested that TPc was involved in the reading process, but we could not argue if left , right or both hemisphere. With the aim to better understand the lateralization of reading, we did a second experiment changing reference electrode positioning from contralateral to supraorbital controlater. We just found a decreasing of TRs with left cathodal tDCS just for rare words: although not significant, TRs for all stimuli diminished after cathodal tDCS, suggesting that with this montage TPc is still involved but the effect is lower, or maybe the current is not enough to achieve an improvement.

In third experiment we focused on duration parameter and we used the bilateral montage, as it resulted more effective. We wanted to avoid a paradoxical effect due to “too much” current delivered and understand better our first finding. Although not significant also in this study, TRs decreased after left cathodal stimulation, going in the same direction as the first study, suggesting that 10’ are not enough and that maybe stimulating for more time or with a different intensity, we can achieve the same results.

Till this point, our data seemed to suggest that the most effective result was found with bilateral montage and stimulating for 18 minutes. It could be that cathodal tDCS over the dominant hemisphere excited the TPc because, inhibiting, it lead to less neuronal competition, and so to a performance improvement (Antal et al., 2004). We also have to remember that the dichotomy anodal excite-cathodal inhibits derives from motor area studies, and is not always found in cognitive applications. It could also be that as Catani et al., (2005) suggested, the language network is wide and inhibition in one area does not lead to real inhibition because of other regions involved in the process. According to Boggio et al. (2006) a ceiling effect could be responsible for the inefficacy of anodal tDCS on dominant hemisphere, while the the other one "under use" could beneficiate from the stimulation. Specifically regarding language functions, then, some researchers (Corballis and Beale, 1976; Coslette et al., 1994; Costanzo et al., 2013; Knecht et al., 2002) hypothesize the implication of corpus callosum, whose interhemispheric disconnection could lead also to reading deficit (bilateral in this case); and this could explain not only the efficacy of bilateral montage, but also the lower and not significant effect of left TPc stimulation.

In these three studies we tested our hypothesis in normal readers, in which a modulation due to tDCS is not always evident because of ceiling effect or too simple task. So in the last study we tested the same protocol as the first study, bilateral for 18 minutes, which seemed to be the most effective, on below average readers. We found an improvement for accuracy, not emerged in previous experiments, after left anodal-right cathodal tDCS, already found by Turkeltaub et al. (2011).

So, it seems that the bilateral montage for 18 minutes is able to modulate TPc excitability, at least after one session of tDCS. The fact that tDCS did not improve below average readers TRs can be due to participants variability. The TPc of both groups (first and fourt study) were modulated but with inverted polarities: while normal readers improved TRs with left cathodal-right anodal tDCS, below average readers beneficiated from left anodal-right cathodal tDCS. And this can be explained according to the theory of the "under use" hemisphere (Boggio et al., 2006): maybe in normal readers the effect is not produced by left cathode, but by right anode. This are just hyphotesis.

tDCS seems to be a useful tool able to increase knowledge about neural functioning, thanks to its modulating feature. Infer that tDCS has a modulatory effect on reading process basing on behavioral data would be early. It would be interesting to combine the stimulation with neuroimaging techniques such as fMRI and NIRS to achieve more detailed information on the mechanism of functioning of tDCS.

A limitation of these studies is the small sample tested and the lack of follow-up.

Future studies, in addition to combine tDCS with neuroimaging techniques, should test different stimulation parameters to provide general guidelines, and take into account the different variables that could affect the effects of stimulation, such as: handedness (Schade et al., 2012), age (Moliadze et al., 2007), interindividual variability and level of expertise (Furuya et al., 2014; Ridding and Ziemann, 2010), gender (Chaieb et al., 2008), among others.

These steps are needed before we can say that tDCS is a useful technique for the rehabilitation of dyslexia, considering also the always more evident need to set up personalized protocols (Bikson et al., 2011; Wiethoff et al., 2014).

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SCHEDA DI CONSENSO INFORMATO

Questa ricerca ha come obiettivo la valutazione degli effetti della stimolazione transcranica a corrente diretta (tDCS) in un compito di lettura. La tDCS è una metodica già in uso da diversi anni a scopo di ricerca ed è stata applicata ripetutamente su migliaia di individui sani e su pazienti di vario tipo senza effetti collaterali particolari. Si tratta di una tecnica in cui, attraverso una corrente elettrica bassa intensità (1,5-2 mA) applicata mediante due elettrodi posizionati sullo scalpo, si induce una transitoria polarizzazione/depolarizzazione delle membrane dei neuroni corticali. Gli elettrodi sono posti sul capo in modo tale da permettere alla corrente di raggiungere la regione del cervello di interesse. Lo stimolo elettrico può produrre un'iniziale sensazione di prurito sulla pelle del capo. Ad oggi non sono stati riportati effetti collaterali legati all'utilizzo della tDCS, tranne la possibilità di indurre un leggero e transitorio mal di testa e/o nausea che passa spontaneamente dopo poco tempo e che viene facilmente eliminato con l'ausilio di comuni analgesici da banco.

La tDCS verrà applicata per 20 minuti in ciascuna sessione sperimentale. La durata complessiva di ciascuna sessione sperimentale è di 30 minuti circa. Ti chiederemo di partecipare a tre sessioni separate in tre giorni diversi (con un intervallo di almeno due giorni tra una sessione e l'altra). L'esperimento consiste nella registrazione di Tempi di Reazione. Prima di eseguire la prova ti saranno mostrati l'apparecchio e lo stimolatore che saranno utilizzati, in modo che possa renderti conto di persona di cosa si tratta. Non esitare a chiedere ulteriori informazioni e/o specificazioni.

Ti ricordiamo che potrai decidere di ritirarti dall'esperimento in un qualsiasi momento, senza fornire spiegazione e senza incorrere in alcun tipo di penalizzazione, ottenendo il non utilizzo dei tuoi dati.

Il/La sottoscritto/a dichiara:

- di essere stato/a messo/a a conoscenza delle procedure sperimentali relative all'indagine scientifica alla quale liberamente partecipa come soggetto sperimentale, al fine di contribuire all'avanzamento delle conoscenze nel campo delle funzioni cerebrali superiori; i risultati di tale ricerca potranno eventualmente essere comunicati ad altri ricercatori in occasione di congressi o riunioni scientifiche in forma anonima;
- di essere stato/a informato/a riguardo alle finalità e agli obiettivi della ricerca in questione;
- di aver preso visione diretta dell'ambiente in cui avverranno i rilievi sperimentali e degli apparati che saranno utilizzati a tale scopo;
- di essere a conoscenza che l'applicazione correnti continue a bassa intensità può indurre lievi effetti collaterali in soggetti predisposti e di essere stato/a informato/a che la stimolazione utilizzata nell'ambito del presente studio rientra ampiamente all'interno delle norme di sicurezza stabilite nelle linee guida internazionali;
- di essere stato informato che nel caso accusasse effetti collaterali quali mal di testa o bruciori cutanei, deve avvisare immediatamente lo sperimentatore che provvederà all'immediata interruzione dell'esperimento;
- di aver ricevuto soddisfacenti assicurazioni relativamente al principio dI mantenimento della riservatezza delle informazioni relative e/o scaturite dall'esame della propria persona.

Si informa che tutti i dati personali a Lei relativi verranno trattati in conformità al Decreto Legislativo 30 giugno 2003 n. 196 "Codice in materia di protezione dei dati personali". Si informa inoltre che tutti i risultati ottenuti dalle analisi connesse alle attività di ricerca o sperimentazione, così come ogni altro atto medico, sono da considerarsi strettamente confidenziali e sottoposti al vincolo del segreto professionale e della legislazione vigente in materia.

Padova, lì________________________

Firma ________________________

Firma del Ricercatore che ha raccolto consenso ______________________________

Per cortesia, prima di sottoporsi a stimolazione elettrica transcranica (tDCS) risponda alle seguenti domande. Le informazioni che fornirà sono strettamente confidenziali.

Soffre o ha mai sofferto di crisi epilettiche, convulsioni febbrili o ricorrenti svenimenti?	SI	NO
Ci sono in famiglia casi di epilessia? Se SI, indichi il grado di parentela del/dei familiare/i.	SI	NO
Ha mai subito un trauma cranico? Se SI, fornisca di seguito i dettagli.	SI	NO
Ha inserti metallici o clip chirurgiche “in testa” (eccetto per i denti)?	SI	NO
Ha problemi di cuore?	SI	NO
È portatore di pacemaker cardiaco?	SI	NO
È portatore di protesi acustiche?	SI	NO
Prende antidepressivi triciclici?	SI	NO
Prende farmaci neurolettici?	SI	NO
Soffre di severi e frequenti mal di testa?	SI	NO
Ha bevuto più di 3 unità alcoliche nelle ultime 24 ore?	SI	NO
Nelle ultime 2 ore, ha bevuto più di 2 tazze di caffè o assunto caffeina da altre fonti?	SI	NO
Ha usato sostanze stupefacenti nelle ultime 24 ore?	SI	NO
Ha già partecipato ad altri esperimenti con la TMS?	SI	NO
Solo per le donne: Potrebbe essere incinta?	SI	NO
E’destrimane o mancino?	destrimane	mancino

Data di nascita ____/____/____

Padova, lì ______________________

Firma ____

COGNOME E NOME:

DATA DI NASCITA: **ETA':** **M** **F**

QUESTIONARIO DI DOMINANZA MANUALE

Edinburgh handedness inventory (Oldfield, 1971)

Metta una crocetta sul numero appropriato nella tabella qui rappresentata per indicare quale mano preferisce usare per ciascuna delle attività indicate.
Se la sua preferenza per una mano è così forte che non proverebbe mai ad usare l'altra se non assolutamente costretto\a, metta una crocetta su "**-2**" o "**2**" (a seconda della mano). Se preferisce una mano all'altra in modo meno categorico, metta una crocetta su "**-1**" o "**1**" (a seconda della mano). Se per lei è realmente indifferente usare l'una o l'altra mano, metta una crocetta sullo "**0**".
Alcune delle attività descritte richiedono entrambe le mani. In questi casi, il compito, o l'oggetto, per cui è richiesta la preferenza è indicato in parentesi.
Per favore cerchi di rispondere a tutte le domande e di lasciarle in bianco solo se non ha mai avuto alcuna esperienza dell'attività indicata.

Attività	Mano Preferita				
	Sinistra				**Destra**
Scrivere	-2	-1	0	1	2
Disegnare	-2	-1	0	1	2
Lanciare un oggetto	-2	-1	0	1	2
Usare le forbici	-2	-1	0	1	2
Usare lo spazzolino da denti	-2	-1	0	1	2
Usare il coltello senza forchetta	-2	-1	0	1	2
Usare il cucchiaio	-2	-1	0	1	2
Impugnare la scopa (mano più in alto)	-2	-1	0	1	2
Accendere un fiammifero	-2	-1	0	1	2
Aprire una scatola (coperchio)	-2	-1	0	1	2

SCALE VAS

Come definiresti il tuo stato attuale rispetto alle seguenti espressioni dell’umore?

Triste Felice
0 1 2 3 4 5 6 7 8 9 10

Calmo Ansioso
0 1 2 3 4 5 6 7 8 9 10

Concentrato Distratto
0 1 2 3 4 5 6 7 8 9 10

Apatico Dinamico
0 1 2 3 4 5 6 7 8 9 10

Confuso Lucido
0 1 2 3 4 5 6 7 8 9 10

Pieno d’energie Debole
0 1 2 3 4 5 6 7 8 9 10

Soddisfatto Inappagato
0 1 2 3 4 5 6 7 8 9 10

Preoccupato Sereno
0 1 2 3 4 5 6 7 8 9 10

Teso Rilassato
0 1 2 3 4 5 6 7 8 9 10

Modulo di rilevazione delle sensazioni di fastidio legate alla Stimolazione Elettrica Transcranica (tES)

Codice Soggetto: ____ Data:_____/_____/____

Esperimento/Sperimentatore:____

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

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

Nel primo blocco di stimolazione

Prurito: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Dolore: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Bruciore: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Calore: ☐ Nessuno ☐ Lieve ☐Moderato ☐ Abbastanza ☐ Molto

Pizzicore: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Sapore Ferroso: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Affaticamento: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Altro__________________: ☐ Nessuno ☐ Lieve ☐ Moderato ☐ Abbastanza ☐ Molto

Quando sono insorte le sensazioni?

☐ All’inizio ☐ Verso la metà del blocco di stimolazione ☐ Verso la fine

Per quanto tempo sono durate?

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

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

☐ Per Nulla ☐ Poco ☐ Abbastanza ☐ Molto ☐ Moltissimo

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

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