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**BRAIN OSCILLATIONS: DISCOVERING THEIR ROLE IN MEMORY USING  
TRANSCRANIAL ALTERNATING  
CURRENT STIMULATION**

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## **Introduction**

Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation technique (NIBS) allowing the application of weak sinusoidal electric currents through the scalp. TACS is a rather inexpensive and easily administrable tool for cognitive and clinical purposes. These sinusoidally shaped currents can be applied to directly interfere with cortical rhythms, allowing to understand the functional role of oscillations in the brain and, consequently, to treat those kind of neural disorder dependent on alteration of the brain rhythms functioning.

More than other brain stimulation techniques, tACS brings with it the need for a better understanding of the effective functional role of brain oscillations in cognition.

If the potential of tACS is to be used to interfere with neural oscillations and to treat neural disorders, it is crucial to understand how tACS works and how it can be used to reach the desired effects, as well as to understand how those brain rhythms that can be modulated with tACS have a functional role in cognition.

To date, such a knowledge has not been reached and although several strands of research are exploring the role of this technique in different cognitive domains, the neuroscientific community underlines the need for an optimization of the parameters and the combination of different tools to clarify the effectiveness of this new technique in entrainment of brain oscillations and, consequently in modulation of their functioning. In the same time, a growing number of researchers is clarifying the role of brain oscillations in cognition pulling them out of the noise they have been associated with, for several years.

Finally, the possibility to apply tACS to improve cognitive performances, like memory

processes, could make this tool reliable and safe to help people with cognitive disorders.

The present work describes two experiments conducted to elucidate the mechanisms by which tACS interacts with underlying neural network activity and, consequently, improves memory performance.

The aim is to explore the role of tACS in modulating brain oscillations, reviewing the existent literature and applying it to modulate a specific brain rhythm, i.e. alpha rhythm, investigating, consequently, the role of this rhythm and of its modulation in working memory. Particularly, the attention will be focused on more posterior brain regions such as the posterior parietal cortex (PPC) and the occipital cortex, traditionally associated with higher power of alpha rhythm.

The present work is structured in four chapters. **Chapter 1** presents an overview of the most important concepts in the existing literature about brain oscillations. Some basic principles about encephalography are also presented. **Chapter 2** presents researches and literature about tACS and its effects in modulating brain oscillations. Previous studies reporting its efficacy as well as mechanisms of action are reported. Evidences coming from different fields of research are discussed.

Finally, **Chapter 3 and 4** report two experimental works. The first one presents the data about an intheremispheric montage of tACS administered at alpha frequency band in the occipital cortex, the second one shows the effect of an intraemispheric, intermittent, tACS stimulation in a working memory task in which both relevant items and distractors are presented together.

# **CHAPTER I**

## **BRAIN OSCILLATIONS: SAILING IN A SEA OF NOISE**

### **A brief introduction**

In the last years there have been a growing enthusiasm about brain oscillations, this enthusiasm has lead to a huge field of studies and theories about electrical activity in the brain and its role in cognition. All these studies try to account for an answer to one of the first questions about oscillations, since when Berger discovered the alpha rhythm in the 1929: “Do brain oscillations play a functional role in cognition?”

To date more evidences are needed to certainly state if electric fields in the brain have a causal role in cognitive processes. Despite this, recording of brain oscillations and their modulation is one of the most interesting field of research to which thousands of scientists in the world are devoted to.

### **1. Brain oscillations: history and taxonomy**

Interest in brain oscillations began in 1929, when Hans Berger after having performed several experiments to prove the existence of telepathy, found, when subjects had their eyes closed an electrical activity in the occipital part of the skull. This rhythm was characterized by a large amplitude.

Berger called this rhythm “alpha” (Berger,1929). When subject’s eyes were open, electrical activity became faster and Berger named this rhythm “beta” waves. In the following years, oscillations were found in several mammalian species. The speed of the oscillations ranges from very slow to very fast, up to 600 Hz.



For convenience, scientists group brain rhythms in five different bands:

- Delta: 0.5 - 3 Hz;
- Theta: 4 - 7 Hz;
- Alpha: 8 - 12 Hz;
- Beta: 13 - 30 Hz;
- Gamma: > 30 Hz.

There are also oscillations in the sub-delta and omega (up to 600 Hz), but the bands usually involved in behaviour are between 2 Hz and 150 Hz (Buzsàki,2012).

Frequency, power and phase are specific and different for each brain rhythm. Namely, frequency is the speed of each cycle of the rhythm; Power is the amount of energy for a given frequency; Phase is the position along the sine-wave at any given time point (Cohen, 2014).

Neural oscillations arise from rhythmic fluctuation in the local field potential (LFP) (Thut, 2012) and they are dependent on intrinsic properties such as ions channels as well as on extrinsic properties such as input strength and noise levels (Wang 2010; Buzsàki, 2012).

For long time oscillations have been ignored and considered as a neural background noise (Lopes da Silva et al., 1997; Niedermeyer, 1997). Recently, evidences coming from several neuropathologies such as Alzheimer's disease and schizophrenia (Başar, 2008; Uhlhaas, 2008) have shown alterations in oscillatory activity in such a kind of diseases, suggesting, thereby, the importance of neural rhythms for normal brain's functions.

Additionally, these neural oscillations have been found to be modulated by different cognitive tasks and motor processes also in healthy subjects (Başar, 2001).

Finally, the relation between brain rhythms and cognition has been studied, mostly, using electroencephalography (EEG) and magnetoencephalography (MEG).

Noteworthy, it is almost impossible to link linearly a given cognitive function to activity in a given frequency band, as well as is unlikely that a given brain rhythm could be related just to a single cognitive function in the brain.

In this chapter we will briefly introduce the commonly known brain rhythms. A deeper discussion about alpha frequency band, due to its role in the studies presented here, will be provided in the relative chapter.

### *Delta rhythm*

Widely investigated during sleep, to date less studies have been dedicated to the role of delta oscillations in cognitive domain. Despite this, recently, attention process related delta oscillations have been found in frontal and cingulate cortex and their appearance seems to be related to detection of a target when several distractors are presented (Harmony, 2013). Additionally, delta oscillations increases have been recorded in frontal cortex during different tasks such as mental calculation and working memory (Harmony, 1996). Noteworthy, it seems to be a correlation between delta activity, signal detection and decision making (Basar, 1992).

### *Theta rhythm*

In the hippocampus of the rats, theta rhythm arises during specific movements (Vanderwolf, 1969) while in humans, it has been recorded during the behaviour associated with the intake of new stimuli (Kayser, 2012). Recently, some authors suggested that each theta cycle may contain informations about the ongoing behavioural condition at any given moment (Jezek, 2011).

Additionally, it is widely accepted the involvement of theta rhythm in memory processes (Klimesch, 1999; Jensen, 2002; Buzsaki, 2005), especially, this slow rhythm is thought to establish a phase coupling with higher rhythms, such as gamma frequencies band, to allow the consolidation of new memory traces (Canolty, 2006). It has been proposed that theta oscillations reflect communication processes between the neo-cortex and the hippocampus (Lega, 2011) and that it is prominent in the frontal cortex, in which this rhythm could be involved in the executive functions (Huster et al., 2013).

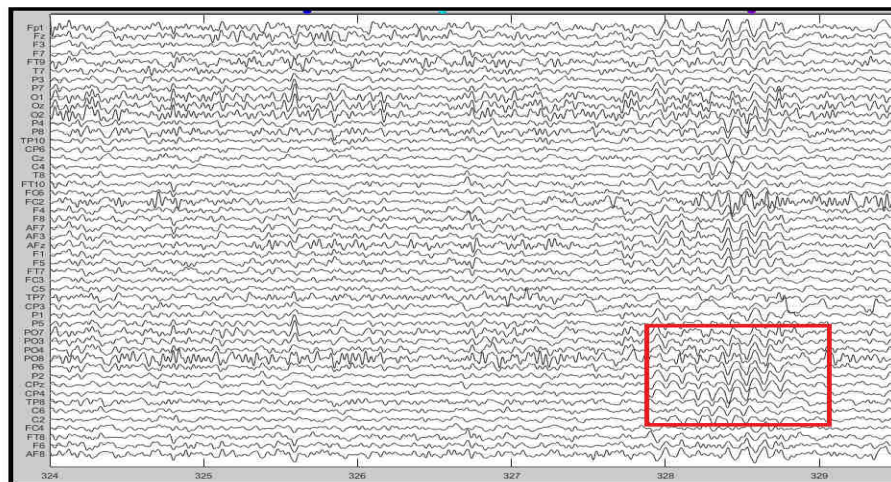
### *Alpha rhythm*

When a healthy subject is relaxed, with eyes closed, alpha rhythm synchronizes over the posterior scalp regions (Berger, 1929). Even if alpha activity is prominent in these posterior regions, it can be recorded in several regions of the awake brain and it is thought to arise from the oscillation of postsynaptic potentials in the cortex (Berger, 1929; Cooper, 1965; Nunez, 2001) (**Fig.1**).

Traditionally, alpha oscillations range from 8 to 12 Hz but individual variations can be found and electrical activity in the alpha frequency band is susceptible to changes with age and gender (Basar, 1997; Fink, 2006).

In the occipital cortex the ongoing occipital alpha oscillations can be manipulated with different tasks, such as visual imagery, mental activity, eyes open or closed (Cooper, 2003; Doppelmayr, 2002). Indeed, coexisting with the eyes closed related alpha rhythm there are different alpha synchronizations during sensory and cognitive processes (Klimesch, 2012). For example, auditory and visual stimuli elicit alpha responses in the auditory and visual pathways, hippocampus and reticular formation (Basar, 1998). Although in the past years alpha was considered as an “idling” rhythm (Pfurtscheller,

1997), recently evidences for a link to cognitive processes, such as working memory and long term memory, have been provided (Klimesch, 1994). In line with these evidences, numerous recent studies suggest that alpha may reflect internal mental processing (Jensen, 2010).



**Fig.1. Alpha rhythm.** The red square highlights alpha rhythm in a 64 channels EEG recording. Alpha rhythm is prominent in the posterior scalp sites.

### *Beta rhythm*

Classically considered as related to motor functions (Engel, 2010; Jenkinson, 2011), the beta band rhythm has been reviewed in the last years. Indeed, because of its occurrence in motor cortex in the resting state, for a long time, it has been seen as an idling rhythm in the motor system (Pfurtscheller, 1996). Recently, some authors suggested that beta band activity could signal the tendency of the sensori-motor system in maintaining the status-quo (Engel, 2010).

Next to these evidences, several studies shown an enhancement of the power of beta frequency during steady contractions (Baker, 2007) as well as a reduction of the power

during voluntary movements (Sanes, 1993). Moreover, a suppression of beta power is recorded during tasks requiring motor imagery (Pfurtscheller, 1997).

In cognitive domains, oscillation in the beta frequency range are associated with the maintenance of the cognitive set and a beta power modulation could be associated with top down mechanisms able to suppress the processing of potentially novel external events (Von stein, 2000; Engel, 2010). Moreover, it could be seen as the eligible rhythm in modulating the processing of new stimuli in the somatosensory cortex (Lalo, 2007).

Related to this, recently beta oscillations involvement in executive functions (Buschman, 2012) and in working memory encoding has been proved (Siegel, 2009) as well as an externally driven synchronization of beta frequency range in the left infero-frontal gyrus seems to interfere with memory encoding (Hanslmayr, 2014).

### *Gamma rhythm*

It has been suggested that this frequency band would be related to a generic neural control operations allowing the brain to perform specific functions without implementing those functions themselves (Merker, 2013). This role of gamma oscillations accounts for the typically observed co-variation between gamma activity and cognitive tasks (Jensen, 2007). On the other hand numerous authors have suggested the role of gamma in processing information (Fries, 2001) in perception (Hanslmayr, 2007) and in the memory domain (Herrmann et al., 2004).

## **2. Electroencephalography (EEG)**

Electroencephalography (EEG) and magnetoencephalography (MEG) are the most powerful techniques to study non invasively the brain's rhythms. Electroencephalography refers to the measurement of brain electric fields via electrodes placed on the head (Teplan, 2002).

Most of the changes in the neuronal activity, during cognitive processes, occur in the range of few milliseconds. High temporal resolution techniques are well suited to capture these fast cognitive events (Cohen, 2017). EEG signal arises from fluctuations in dendritic activity of populations of neurons (Buzsáki, 2009). Each single neuron generates a small and weak electric field and electroencephalography is able to record the sum of all these electric fields passing through the skull and the scalp (Buzsáki, 2006; Cohen, 2014).

In each EEG recording we can distinguish resolution, precision and accuracy. Resolution refers to the number of data sample per unit time; precision refers to the certainty of the measurement at each time point; accuracy refers to the relationship between the timing of the EEG signal and the timing of the biophysical event that leads to the EEG signal (Cohen, 2014). Nevertheless, EEG has a low spatial resolution and accuracy, compared with other techniques such as functional magnetic resonance imaging (fMRI). In the last years, better spatial resolutions have been reached improving the number of the electrodes up to 256 (Cohen, 2014).

## **3. Oscillations in the EEG**

EEG data contain rhythmic activity reflecting brain oscillations (Cohen, 2014). Oscillations are common in nature but the mechanisms behind oscillations are still poorly

understood. Several authors argue that oscillations arise from a mechanism of interaction between inhibitory inter-neurons and excitatory pyramidal neurons (Buzsàki, 2012).

Excitation of groups of pyramidal neurons leads to an activation of inter-neurons. When the activity of inhibitory inter-neurons increases the excitatory cells are more likely to be inhibited. After this inhibition, activity of inter-neurons decreases, and the pyramidal neurons are activated again and their excitation increases (Buzsàki, 2012). This interplay between inhibitory and excitatory processes produces rhythmic activity and, consequently, oscillations (Buzsàki, 2006). Functional processes and different tasks demand lead to changes in this rhythmic activity. Such kind of changes are detected by EEG.

It has been proposed that the EEG signal reflects the summation of postsynaptic current in the dendrites of groups of pyramidal neurons perpendicularly oriented to the cortical surface (Nunez, 1981).

When thousand of neurons synchronize their activity, the sum can be measured from outside the skull by means of techniques such as EEG and MEG.

## **CHAPTER II**

### **TRANSCRANIAL ALTERNATING CURRENT STIMULATION (tACS)**

#### **Introduction and history: everything started with a fish**

The first report about transcranial electrical stimulation can be found in the Greco-Roman empire, where the organs of the fishes were used to generate electricity and to treat pain, headaches, gout and paralyses (Kellaway, 1946; Finger, 1994). Probably, the efficacy of electric fishes was already known in the ancient Egypt (Debu, 2006). Also roman, arabic and medieval population mentioned the therapeutic effect of the electric fish in diseases such as depression, epilepsy and arthritis (Zago, 2016).

Reports about the eighteen century suggest that electricity was still used to treat mental disorders, using artificial electric energy derived from electrostatic devices (Zago, 2016).

During the Victorian age devices able to deliver electricity were largely used and there was a general consensus on the feeling of euphoria generated by such a kind of stimulation. Also improvements of mental performance were documented (Kadosh, 2013; Elliot, 2014).

Despite this ancient origins, only recently there has been an effective introduction of electroconvulsive therapy, applied as a means of brain stimulation, in order to treat brain's disorders (Zago, 2016).

Nowadays, modern brain stimulation techniques are profoundly different from electroconvulsive therapy but we cannot ignore the long tradition in the use of such a kind of techniques by medical doctors and physicians in the past.



Left apart the electric fishes, electrical devices able to deliver weak currents crossing the scalp have been provided in the last decades.

The most used transcranial electrical stimulation techniques (tES) are transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and transcranial alternating current stimulation (tACS). During tES, currents are applied with intensities ranging between 0.4 and 2 mA through the human scalp (Paulus, 2016).

In this chapter we will focus on tACS, a recent technique, able to interact with cortical oscillations in a frequency-specific manner at a single given frequency.

## **1. Transcranial alternating current stimulation (tACS)**

Among tES, tACS is the newest. Similar in its electrodes' montage to the widely used tDCS, there are some important differences making this technique the best tool to interfere and to modulate brain rhythms. Typically, tACS waveform is sinusoidal, indeed, for one half of the cycle of an AC oscillation, the first electrode works as an anode and the second electrode works as a cathode, while, during the other one half of the cycle, the pattern reverses (Antal, 2016). Sinusoidal AC induced electric fields have been proved to modulate the trans-membrane potential and the biological properties of the neuronal membrane (Chan and Nicholson, 1986). It has been suggested that, during AC, neuronal polarization is directly related to the intensity of the stimulation (Deans, 2007). While DC stimulations have shown to have a stronger effect on the single neurons, networks of neurons can be more susceptible to AC stimulation (Reato, 2013). Electric fields generated by tACS can change the rate and timing of spiking neurons, affecting thereby the interactions between neurons in the same or different networks (Fröhlich and McCormick, 2010; Reato et al., 2010). Noteworthy, when applying tACS, several aspects have to be

taken into account:

### *Electrodes*

There are different shapes and sizes for the electrodes. Usually stimulation is delivered using rubber electrodes fit into sponges soaked with saline solution or gel. It is also possible to spread on the electrodes a conductive paste to directly attach the electrodes above the scalp. As for the conductive means, several possibilities are present for the electrodes' size. Previously, the most used electrodes had a squared shape and were 7x5 cm large, recently smaller round electrodes have been used and it has been suggested that smaller electrodes are more focal and have a greater current density (Neuling, 2012).

Finally, recently provided, electric field models suggest that the strongest current density is in the middle of the electrode and close to the connector (Miranda, 2006; Saturnino, 2015).

### *Montage*

Electrodes location is critical in determining the amount of current crossing through the scalp (Miranda et al., 2006). To date, there are different possible electrodes montages, indeed the two or more electrodes can be positioned at different distances, and in different brain regions or in different extra-cephalic regions (Neuling, 2012). Depending on the selected target region, the electrodes can be all placed in the scalp, determining a cephalic montage or one or more electrodes can be placed in regions such as the shoulder and the neck, allowing an extra-cephalic montage (Herrmann, 2013). A different current flow will arise as a function of different montages and consequently different brain regions will be affected by the applied electric field (Neuling, 2012). An open question is the effect of the

size and position of the *return* electrodes (Datta et al., 2009).

### *Frequency*

tACS could be set in order to reach a given number of stimulation cycles per second, these cycles reflect brain's frequencies such as delta, theta, alpha, beta, gamma that we have seen to be associated with different cognitive functions. Moreover, tACS could be set in order to reach frequencies outside the traditional range of EEG electrical activity, such as 200 kHz stimulation, used for tumour therapy (Kirson, 2007) and 5 kHz stimulation used for plasticity studies (Chaieb, 2011).

### *Current intensities*

Conventional intensities for tACS are limited to a maximum of 2 mA peak to baseline. Moreover tACS effects and after-effects seem to strongly depend on the applied intensities (Antal, 2013). Recently it has been shown that 0.2 mA intensity has no after-effects, 0.4 mA leads to inhibition in the motor cortex and 0.6 and 0.8 mA do not provide a significant online effects (Moliadze, 2012).

Taken together these results offer the opportunity to reflect on how different intensities can lead to different effects in an unpredictable manner and it suggests the need for taking into account the intensities to choose as a function of several aspects such as the target brain regions and the expected results.

## *Stimulation phase*

Stimulation cycles can be either in phase or in anti-phase (Fröhlich, 2015). Usually with two electrodes, stimulation is anti-phase meaning that when in one electrode the stimulation is in the positive site of the cycle in the other electrode it is in the negative one (Paulus, 2016). To have an in-phase montage at least three electrodes are needed, so that in two of the electrodes the polarity is the same in the same time. In phase or anti-phase electrodes seems to facilitate or disrupt the coherence and communication between different brain regions during different tasks (Helfrich, 2014; Polania, 2012).

## **2.Modulation of the activity of human brain**

Most of those studies attesting the efficacy of tACS, focus on modulation of the alpha rhythm. For instance, it has been shown during transcranial alternating current stimulation, set at 10 Hz, an enhancement of the EEG alpha amplitude in the posterior regions (Helfrich, 2014). The underlying ratio is that changes in the EEG signal can correlate with behavioural outcomes (Voss, 2014).

Noteworthy, although a growing number of researches are being conducted using tACS, the mechanisms underlying its effects are still poorly understood. This consideration implies that when tACS is applied in order to affect brain rhythms, a linear result cannot be assumed. For instance, regarding stimulation intensities, linear increases in current strength may have nonlinear effects on the stimulated brain regions and on the physiological or behavioural consequences (Moliadze, 2012). Several hypotheses have been investigated about tACS effects, most of the supposed mechanisms will be deeply discussed in the following paragraphs. Briefly, changes in neurotransmitters (Zaghi, 2010)

as well as short term synaptic plasticity effects have been proposed as possible mechanisms underlying tACS effects (Antal, 2013; Citri and Malenka, 2008). Finally, despite a day by day growing number of evidences, we cannot exclude that tACS works simply by inducing noise that summing with the system's activity, improves or worse the performance (Miniussi, 2013).

### **3. Physiological Effects of tACS**

tACS probably modulates spontaneous activity via sub-threshold membrane polarization (Reato, 2010). The periodicity of tACS currents causes an alternating hyper- and de-polarization of the membranes, this can in turn affect the firing rate and the action potential imposing a temporal structure on neuronal communication (Fröhlich, 2010).

Animal studies proved that neuronal spike activity synchronize to the external applied currents within different frequency bands (Fröhlich, 2010; Ozen, 2010), this synchronization is called *entrainment*. tACS induced effects probably can be explained in terms of entrainment (Deans, 2007) or phase alignment of endogenous neural activity to the phase of the currents delivered by tACS (Thut, 2011).

Entrainment can occur only when the stimulation frequency matches the endogenous frequency in the stimulated regions (Ali, 2013; Schmidt, 2014), therefore the effect will be in a limited range of frequencies, i.e. the stimulation frequency and its harmonics or sub-harmonics (Ali, 2013). The entrainment can be understood in terms of the underlying theory, the so called *dynamic system theory*.

#### 4. Dynamic system theory

Dynamic system theory focus on systems evolving, dedicating specific attention to the interaction between these systems and different externally applied forces (Fröhlich , 2010).

Systems able to generate rhythmic activity, by using an internal driven energy, are called *oscillators* (Glass, 2001; Pikovsky et al., 2003; Buzsaki, 2006) . When an external force is applied on the system, it can perturb the oscillator and, whether the force is periodic, the oscillator can synchronize with the applied force, this synchronization is called *entrainment* (Thut, 2011). Both the forces are characterized by their own natural frequency, phase, intensity and amplitude. All these parameters substantially affect the outcome of the rhythmic stimulation and it has been suggested that the ideal condition for entrainment occurs when the stimulation frequency matches the natural rhythmic frequency of the oscillator (Glass, 2001; Pikovsky, 2003). When the stimulation frequency does not match the frequency of the oscillator the occurrence of the entrainment seems to be dependent on the strength and the intensity of the externally applied force (Fröhlich , 2010). Therefore, the bigger the mismatch between the two forces the stronger the intensities of the stimulation needed to entrain the oscillator. Indeed, if the intensities are weak, the applied force will not counteract the divergence of frequency and phase and the system will oscillate to a certain frequency between the natural and the applied frequency (Pikovsky et al., 2003).

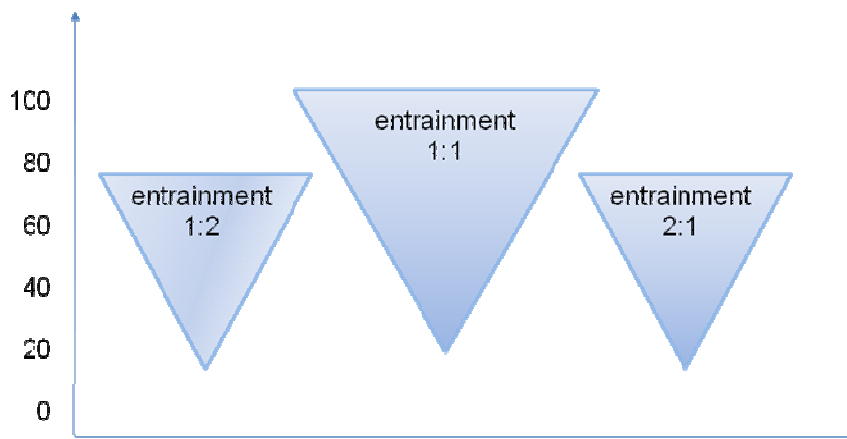
## 5. Oscillators in the brain

What we have seen about oscillators and the externally applied forces in the dynamic system theory, can be transferred in the brain, where single neurons, neuronal circuits, cortico-cortical or thalamo-cortical networks support the generation of physiological rhythms using an internal force and acting as oscillators (Buzsaki, 2006). As we have seen above, brain oscillations occur in distinct frequency bands. Acting as dynamic systems, brain oscillators are highly sensitive to the external forces (Thuth, 2011). Indeed, when an external periodic force is applied, they can start to oscillate with the same period of that force, becoming, thereby, “synchronized” (Thuth, 2011). The term *entrainment* is, consequently, used to denote synchronization of brain rhythms to an external rhythmic force (Thut, 2011). We can consider tACS such kind of a force. In this case, the external periodic force can act in a certain direction on the phase vector and its effect depends on several parameters such as the amplitude of the stimulation, the phase of the stimulation, and its frequency (Pikovsky, 2003; Thut, 2011). As we have seen above, the highest possibility for entrainment occurrence between the applied force and the underlying oscillators is reached when the stimulation frequency matches the frequency of the neural oscillations (Glass 2001, Pikovsky 2003). Entrainment, thereby, is to drive brain oscillations by applying external forces, rather than to disrupt oscillations. Whether it is true that brain rhythms play a causal role for different cognitive functions, we can argue that their entrainment has a functional impact.

Stating this, by entraining brain oscillations, it is possible to modulate the power of a given frequency in different neuronal assemblies, this modulation of the activity of a group of neurons, in turn, can affect the communication between this group and other networks in the same neuronal population (Fröhlich, 2010).

From the dynamic system theory we have seen that an oscillatory input has a stronger effect on those populations that are tuned to the input frequency (Fries, 2005; Schitzler, 2005) and that when there is a mismatch between the input frequency and the applied frequency, entrainment occurrence depend on the strength of the applied force (Fröhlich, 2010).

The effect of the interaction between the stimulation amplitude and frequency leads to the so called “Arnold tongue”, a triangle that describes the set of parameters leading to synchronization (Jensen, 1983; Ali, 2013). These parameters set can be visualized as an area in a plot with stimulation frequency on the abscissa and stimulation amplitude on the ordinate (Fröhlich, 2015). The larger the stimulation amplitude, the broader the range of stimulation frequencies entrained (Fröhlich, 2015). At lower intensities to make the entrainment occur lower frequencies mismatches are needed (Fröhlich, 2015). Thus the area takes the shape of an inverted triangle (Thut, 2011) (**Fig.2**).



**Fig.2 Entrainment (1:1) and entrainment of sub-harmonic frequencies (2:1, 1:2).** Entrainment depend on both the intensity of the applied force and the distance between the frequency of the externally applied force and the natural frequency of the oscillator. The lower the intensity the more the frequencies of the oscillator and of the applied force have to be close to make the entrainment occur. The higher the intensities the wider the frequencies that could be entrained. Sub-harmonic entrainment occurs when the frequency of the oscillator is a multiple of the frequency of the externally applied force.



## **6. Entrainment by means of brain stimulation**

The advent of non invasive electrical brain stimulation allowed the researchers to use electric currents to modulate brain oscillations (Antal, 2001).

Recently, some studies suggested the possibility to entrain brain oscillations with transcranial magnetic stimulation (Fuggetta 2008, Brignani 2008) and transcranial alternating current stimulation (Antal and Paulus, 2013).

One of the first studies reporting a clear modulation of cortical oscillations with tACS was conducted stimulating the occipital cortex at individual alpha frequency (Zahele, 2010), this first attempt was followed by several evidences on the efficacy of tACS in entrainment of brain oscillations. For instance, with regard to the entrainment of oscillations in the alpha frequency band, Neuling stimulated subjects with tACS at the individual alpha frequency (IAF) with eyes open or closed finding an increase in alpha power only for subjects who received the stimulation with eyes open, suggesting that entrainment by means of tACS could depend on the levels of the pre-stimulation alpha activity (Neuling, 2012). Additionally, Helfrich included, in the experimental procedure, a behavioural task, choosing a 10 Hz stimulation rather than a stimulation at IAF. The author found a significant enhancement of alpha activity during and after stimulation suggesting that matching the IAF with stimulation frequency may not be required (Helfrich, 2014).

These results suggest that tACS set at the alpha frequency bands appears to quite robustly enhance endogenous alpha oscillations; entrainment of other brain rhythms has been proved as well. Indeed, for instance, it seems that 20 Hz stimulation in the motor cortex has online effects on cortical activity (Wach, 2013). Some authors suggest that tACS can affect cortical excitability and that this effect is dependent on the stimulation

frequency and amplitude. Indeed, while 10 min tACS over the motor cortex at 140 Hz with an intensity of 0.63 A/m<sup>2</sup> significantly improves cortical excitability, the same frequency at 0.25 A/m<sup>2</sup> seems to decrease it (Moliadze, 2010). Moreover, evidences for tACS entrainment of given frequency bands have been provided in different cognitive domains (Laczò, 2012; Strüber, 2014; Jaušovec, 2014; Marshall, 2006; see also Fröhlich, 2016 for a review)

The results discussed above show that tACS can entrain brain rhythm. Noteworthy, tACS effects in cortical excitability depend on several aspects such as frequency, duration, intensity and not last, electrodes placement. Thereby, stimulation effects cannot be predicted as a simple function of the applied frequency.

## **7. Cognitive, perceptual and motor effects of tACS**

The effectiveness of tACS in humans has been largely proved by revealing frequency-dependent consequence in the behaviour (see Herrmann, 2013 for a review). Specifically, tACS revealed its efficacy in motor system (Wach, 2013), in both visual and auditory perception (Kanai, 2008; Neuling, 2012), in memory (Hoy, 2015), in fluid intelligence (Santarnecchi, 2013) and in decision making (Sela et al., 2012).

### *tACS in motor system*

One of the first studies using tACS was conducted placing the electrodes on the motor cortex and measuring motor evoked potential (MEP), EEG power changes and reaction times (Antal, 2008). The author found that 10 Hz AC stimulation improved implicit motor learning leaving unaltered the frequencies of EEG. Zaghi applied, in the

same brain region, 15 Hz tACS obtaining a pattern of inhibition of cortical excitability (Zaghi, 2010). Other studies replicated the effect of tACS in motor cortex by measuring MEP with single TMS pulses to the motor area or while subjects performed motor tasks (Wach, 2013). These studies confirmed the role of beta oscillations in the motor cortex, and the overall idea coming from all these evidences is that tACS in the beta range can affect MEP amplitude and slow down or speed up voluntary movements (Schitzler, 2005; Pogosyan, 2009).

Also in the motor cortex, the effect of tACS could be dependent on a great number of factors, such as the motor state of the subjects and, as seen above, the effects are not linearly dependent on the intensity of stimulation (Moliadze, 2012; Feurra, 2013).

### *tACS in perception*

In the last years numerous studies have been conducted on the visual and auditory perception. In the visual perception domain, most of the studies are focused on the manipulation of contrast perception and on perceptual stability. In an elegant recent work, Strüber and colleagues reported that tACS applied in the gamma range can affect bistable motion perception (Strüber, 2014) as well as it can improve contrast perception (Laczo, 2012) and the perception detection threshold when applied at alpha frequency band with manipulation of the oscillation phase (Neuling, 2012).

When tACS electrodes are applied in the posterior regions, stimulation in the alpha frequency range modulates flash illusions depending on the cycle of the endogenous alpha rhythm (Cecere, 2015).

In the auditory domain, the performance seems to be affected by the phase of both theta and alpha rhythm and tACS at alpha frequency affects the perception threshold

depending on the phase of the alpha rhythm (Neuling, 2012). Finally, in the somatosensory cortex, stimulation in the alpha and gamma frequency bands are able to elicit tactile sensation in the contro-lateral hand (Feurra, 2011).

### *tACS in cognitive domains*

Several studies have shown the effectiveness of tACS in modulating higher order cognitive processes as logical reasoning (Santaracchi, 2013), fluid intelligence (Pahor, 2014), working memory (Jausovec, 2014) and long and short term memory (Feurra, 2016), while tACS at 140 Hz reduces overnight forgetting if compared with sham (Ambrus, 2015).

Memory appears to be one of the most suitable cognitive processes for tACS. It has been widely shown that tACS in the theta frequency range in the prefrontal cortex improves working memory as well as gamma stimulation does (Voskuhl, 2015; Hoy, 2015). Recently a further evidence about the efficacy of tACS in enhancing memory performance has been provided by superimposing gamma bursts in the peaks of theta oscillations (Alekseichuck, 2016).

Carefulness is needed in exploring the functional role of brain oscillations in cognitive domains and their effective modulation with tACS in order to reach the best behavioural and physiological outcomes.

## **8. Electrophysiological effect of tACS**

Unluckily, due to tACS induced EEG artefacts, it is not easy, at the present, to apply tACS and EEG recording together. Nevertheless, recently Helfrich applied 10 Hz tACS to

the parieto-occipital cortex using simultaneous EEG recording to investigate neuronal entrainment during stimulation. The authors subtracted an artefact template from every artefact segment finding a stimulation related modulation of the power spectrum in the alpha band that outlasted the stimulation cessation (Helfrich, 2014).

Despite this attempt, to date, the majority of authors limited the EEG or MEG recording immediately before and after tACS. Most of these studies have shown an increase in spectral power for given frequencies immediately after tACS (Zahele, 2010; Neuling, 2012), but it is still matter of debate if tACS after-effect depend linearly on the stimulation online effect, i.e. entrainment, or, conversely, it is related to different mechanisms occurring during and after stimulation of neuronal networks (see Veniero, 2015 for a review on tACS after-effect)

Further insights into the online effects of tACS could be provided by, for instance, simultaneous recording of hemodynamic responses with functional magnetic resonance imaging.

## **9.Computed based model**

Given the lack of experimental studies and the difficulties in recording EEG during tACS, mathematical models provide an important tool to understand the observed dynamics during stimulation and to account for the inter-individual differences. Moreover, it can be useful to create some prototypes of different stimulation parameters for different brain regions and networks. Although there is no guarantee that the principles found in a simulation of neuronal frequencies can be translated to the real brain, these studies could provide a mechanistic understanding of the heterogeneity observed in human studies.

One fundamental model to conceptualize tACS effects is based on the reduction of

a cortical network, and its response to the stimulation, to a simple quasi-linear oscillator that exhibit classical entrainment as a function of stimulation amplitude and frequencies mismatch (Ali, 2013; Fröhlich., 2015). This model has been integrated taking into account the connections between the cortical networks and the interaction between endogenous network activity and externally applied stimulation (Kutchko, 2013). Also in the computational models, one of the most explored brain rhythms is alpha. Merlet and colleagues simulated EEG activity and used a set of oscillators, driven by thalamus, reproducing the typical fluctuation of rhythmic activity in the alpha band. Applying stimulation in different frequencies, the authors found that the strongest enhancement occurred at 10 Hz stimulation and that the effect did not outlast the end of the stimulation (Merlet, 2013).

Recently, Zahele simulated, in a network of spiking neurons, how tACS effects can outlast the end of the stimulation finding that spike-timing-dependent plasticity (STDP) selectively modulates synapses depending on the resonance frequencies of the neural circuits to which they belong to. The main conclusion of the authors is that tACS influences STDP that in turn results in after-effects upon neural activity (Zahele et al., 2010).

Despite results from simulated models cannot be transferred linearly to the real brain stimulation, they can provide an useful tool to optimize tACS parameters and to set the best electrodes montages and current intensities in order to affect target areas.

## **10. tACS after effect**

The first electrophysiological evidence for entrainment effects of tACS was reported by Zahele, who stimulated participants at individual alpha frequencies showing

that alpha band power was enhanced after tACS but not after sham (Zahele, 2010). Neuling, replicated these results and additionally showed that the after-effect outlasted for thirty minutes the end of tACS (Neuling, 2013).

Antal observed a weak after effect from two to five minutes after 10 Hz tACS in the motor cortex detectable with an implicit motor learning task, nevertheless any change in the frequency bands was detected in the EEG power (Antal, 2008).

Vossen found an alpha power increase, not dependent on the phase of the alpha frequency, in the occipital cortex after eight seconds trains of 10 Hz tACS . Therefore the author suggests that probably it reflects plastic changes rather than entrainment (Vossen, 2015).

Chaieb applied tACS in the motor cortex, respectively at 1, 2 and 5 kHz and tested with single pulse transcranial magnetic stimulation the corticospinal excitability, finding that all frequencies increased the amplitude of motor evoked potentials up to thirty-sixty minutes after stimulation's end (Chaieb, 2011).

When applied with a cross hemispheric electrodes montage, such as on F3- F4, during a nap, tACS can disrupt brain oscillations and, thereby, to cause a reduction in the post nap recall (Garside, 2015).

Moliadze applied tACS on the motor cortex finding an increment in motor cortex excitability lasting up to one hour after the cessation of the stimulation (Moliadze, 2010).

In light of all these results, a general hypothesis is that as well as tDCS, tACS can also induce changes in network dynamics outlasting the end of the stimulation but at the present it is not clear if tACS after effects are directly related to the entrainment or they arise from mechanisms not related to the interaction with brain oscillations *per se*; specifically long term depression (LTD) and long term potentiation (LTP) processes, already linked to tDCS after-effects (Ziemann and Siebner, 2008; Fritsch et al., 2010) have

been proposed as possible mechanisms also for tACS after-effect (see Veniero, 2015 for a review).

To understand these changes and their basic properties such as durations is, at the present, one of the most intriguing field of research for a growing number of researchers.

## **11. Clinical applications**

Many studies suggest that tACS is effective in modulating brain activity and that this modulation results in behavioural effects in human (See Herrmann, 2013 for a review). Given its efficacy in modulating brain rhythms, tACS is probably suited to treat disorders characterized by an alteration of brain oscillations, in order to restore their original functioning.

Evidences for tACS potential application in Parkinson disease (PD) are emerging. Indeed, alternating currents matched to the individual tremor frequencies, applied over the motor cortex in patients diagnosed with tremor–dominant PD, decreases tremor (Brittain, 2013). Additionally, 20 Hz tACS reduces the cortico-muscular coherence amplitude in the beta band upon isometric contraction during fast finger tapping in PD patients (Krause, 2014). These results suggest that tACS could probably entrain cortical oscillation in PD patients and open a promising strand in the therapy of movement disorders.

Moreover, epilepsy could be another eligible disorder treatable with tACS, indeed in light of those studies suggesting that in epileptic patients shortly before a seizure an alteration of brain rhythms can be found, as well as increased synchronization of gamma band oscillations (Herrmann, 2004), tACS could be applied to restore normal oscillations in epileptic patients.



## **12. Safety**

Several studies explored the safety of applied transcranial electric stimulation. There are no reports of severe adverse effects in the current literature. The applied intensities are at least two order of magnitude less than the intensities needed to induce seizures and thus, are considered safe. The only common effects are limited to unpleasant skin sensations during stimulation and rarely pain under some of the electrodes (see Antal, 2017 for a review).

## **CHAPTER III**

### **SELECTIVE EFFECTS OF TACS IN WORKING MEMORY BUT NOT IN PERCEPTUAL TASKS**

#### **1. Do oscillations play a causal role in working memory?**

Working memory (WM) can be defined as a “limited capacity system for retaining information over short interval of time in order to perform mental operation on them” (Gazzanica, 2002). The classical model for working memory highlights its dependency on the interaction between an attentional control system and a sensorial buffer for short-term storage (Baddeley, 1974). These information, having sensorial origin or coming out from the long term memory, have to be retained even after the input disappears, and the performance is a function of the number of items that have to be retained as well as of the difficulty of the manipulation to perform (Baddeley, 1992). It is straightforward that such a complex system requires the involvement of different brain regions and networks and that in the oscillations domain, it is not possible to select a unique rhythm devoted to implement such a kind of process.

Evidences coming from imaging studies investigating the anatomical correlates of working memory, have shown that involved regions are typically prefrontal (Courtney et al. 1997), perisylvian cortex, medial temporal and parietal regions (Stern, 2001). On the other hand electrophysiological correlates of memory performance have been investigated in order to understand the role of different rhythms in different features of working memory processes (Gevins, 1997).

Several studies about working memory converged on the crucial role played by theta oscillations. Specifically, theoretical works suggest that theta band oscillations are involved in active maintenance and recall of working memory representations and, specifically, the power of theta oscillations increases parametrically with the number of items retained in memory (Jensen, 2002). Studies using Sternberg tasks, in which a series of stimuli are presented one at a time, followed by a probe stimulus, proved that during this task, theta oscillations increase at the start of each trial and return to baseline when subjects provide a response (Raghavachari, 2001). During a working memory task, hippocampal theta activity appears to be phase-locked to stimuli (Givens, 1996), probably reflecting the sensory encoding (Hasselmo, 2002).

The role of hippocampal theta rhythm has been shown also for long term potentiation (LTP), probably related to the phase of this hippocampal activity (Staubli, 1987). Synaptic plasticity is thought to be enhanced during the peaks of theta and depressed during the troughs (Holscher, 1997).

Another candidate for an electrophysiological signature of working memory load is activity in the gamma band (30-60 Hz). It has been hypothesized that gamma rhythm is a marker of feature binding and of maintenance of detailed item representations over a delay (Tallon-Baudry, 1999). These evidences indicate a role for gamma in working memory as well as in perception (Demirlap, 2007). Specifically, some authors suggest that gamma power increases with memory load over the course of a list presentation and it remains constant during retention interval (Herrmann, 2004). Gamma power, it has been hypothesized, reflects the amount of information held in working memory. Indeed, while the gamma power increases during memory delay, after the information is no longer needed the power of gamma returns to the baseline level (Howard, 2003).

The preeminent role absolved by theta and gamma oscillations and the evidences

about the occurrence of synchronization between different brain rhythms during different tasks, pushed some researchers to explore the role of coupling between the two band rhythms. Specifically, recently evidences have been provided about cross frequency coupling (CFC) in the hippocampal circuits (Belluscio, 2012) and in other brain structures (Van der Meij, 2012) occurring between theta and gamma oscillations. This coupling is thought to represent cycles of gamma band oscillations coordinated through an underlying theta rhythm, codifying thereby, different and sequentially ordered working memory items (Lisman, 2013).

Working memory models assume that items have not just to be retained but they have also to be maintained and, consequently, protected from interferences and non relevant information (Bunge, 2001) . In this line of reasoning the role of alpha oscillations in working memory is introduced. First of all, next to theta-gamma coupling, during retention in a working memory task, an alpha-gamma coupling has been found (Roux, 2014). It seems that when sequentially ordered items have to be retained in memory a coupling occurs between theta and gamma oscillations; on the contrary, if the content of WM is constituted of discrete visual or spatial information, theta activity is replaced by alpha rhythm (Fries, 2001). This cross-frequency coupling occurs as a phase-amplitude coupling (PAC) and an important issue is that while PAC in theta-gamma occurs preferentially in fronto-temporal regions during non visual tasks, alpha-gamma PAC is observed in parietal occipital networks during visual information processing (Voytek, 2010). In addition, activity in 9-12 Hz has been found in a modified Sternberg task, during the retention interval (Jensen et al., 2002). This activity have been observed in several sensory modalities during WM maintenance (Haegens, 2010).

Contrarily to theta oscillations, the interpretation of the role of alpha in WM is matter of debate. Some authors consider alpha activity during the delay as a functional inhibition

of irrelevant brain regions (Tuladhar, 2007), while others have linked alpha band activity directly to the processing of the items that have to be retained in memory (Sauseng, 2005).

In the next paragraphs the role of alpha in working memory performance will be deeply discussed and the evidences from an experimental study involving the use of tACS to modulate visual working memory performance will be reported and discussed.

## **2.Alpha in memory and working memory**

Alpha rhythm arises from inhibitory and excitatory post-synaptic potentials in the dendrites of pyramidal neurons. These potentials are influenced from near and distant cortical pyramidal neurons (Nunez, 2001) as well as from the interactions between excitatory cortico-thalamo-cortical relay fibers and inhibitory thalamic fibers (Lopes da Silva, 1980). This interaction leads to a condition so that in the resting state, the higher the number of synchronized neurons, the higher the amplitude of the alpha rhythm and the slower the frequency of the alpha peaks (Singer, 1993; Pfurtscheller, 1999). Moreover, some authors suggested that thalamus originated alpha oscillations induce neural synchronization in the cortex (Steriade, 1990; Basar, 1992).

Additionally, also in long term memory alpha is thought to play a functional role. Indeed, on one hand, alpha in the lower frequency bands, i.e. 8-10 Hz, could be related to attentional processes and on the other hand, alpha in the higher bands, i.e. 10-12 Hz, is particularly involved in semantic memory performances (Klimesch, 1994). Therefore, a lack in long term memory performance is reflected by an insufficient desynchronization of the upper alpha band (Klimesch, 1997). Probably, engagement and disengagement of specific brain regions in both attention and memory tasks could be reached by means of modulation of the power in the alpha frequency band (Meeuwissen, 2011; Poch, 2014).

Specifically, successful long term memory encoding is reflected by alpha power decrease in the sensory regions related to the processing of the to-be-remembered stimuli as well as an alpha power increase in the regions that could be involved in the distracters processing (Jiang, 2015).

Traditionally considered as an “idling” rhythm (Pfurtscheller, 1996), in the last years, alpha rhythm has been investigated in several works and its active role in cognition has been widely proved (Palva, 2007).

### **3.Introduction to the experimental study**

Alpha rhythm (8–14 Hz) is the prominent rhythm in the posterior scalp regions, where it probably reflects the spontaneous endogenous rhythm (Hari, 1997) and it is modulated by visual perception (Capotosto, 2009; Romei, 2010). Alpha rhythm seems to play a role in top-down processes carried out over posterior brain regions by prefrontal cortex, as part of a general inhibitory mechanism of task irrelevant brain regions (Klimesch, 2012). Related to this, in occipito-parietal areas alpha phase influences visual attention, such that stimuli appearing during specific alpha phases are less likely to be processed (Busch, 2009; Mathewson, 2009).

It has been suggested that the excitability of the visual cortex can be influenced by the power of alpha as confirmed by recent studies using transcranial magnetic stimulation (TMS) over the occipital lobe (Romei, 2008). Consequently, the alpha power seems to be predictive of the following accuracy in the perceptual tasks (Ergenoglu, 2004; Hanslmayr, 2007; van Dijk, 2008). Taken together these results highlight the role of alpha rhythm in processing the incoming perceptual information. Several studies have demonstrated functional similarities between visual perception and visual mental imagery so that similar

cortical regions appear to be activated during both these processes (Dijkstra, 2017).

Consistent with its role in visual imagery, power increases of alpha rhythm have been observed during the retention interval in working memory tasks (Heinz and Johnson, 2017). It has been suggested that alpha frequency oscillations are involved in the active storage of information in visual WM (Anderson, 2014; Foster, 2017). An interesting hypothesis is that alpha oscillations modulate working memory through inhibition of task-irrelevant representations, i.e. facilitating activation of task-relevant representations (de Vries et al., 2017).

Traditionally associated with processing of visual stimuli (Malach, 1995), more recently, occipital lobes have been proved to be strongly activated by distracters presentation under condition of high working memory demand (de Fockert, 2001).

Moreover some authors suggest that, during items maintenance in memory, occipital cortex could be recruited as a storage for the to-be-remembered stimuli (Jonides, 1993).

Additionally, in an elegant work about visual mental imagery and perception, Kosslyn shown a similar pattern of activation, involving primarily the occipital cortex, in both perceptual and mental imagery tasks. The author argued that during tasks requiring to create a mental image of a visually presented stimulus, in order to manipulate it, the same areas, involved during simple perceptual task, are activated (Kosslyn, 1997).

In the presented work we tested the role of the occipital cortex in working memory, by driving an alpha power enhancement using tACS, in both a perceptual and a working memory task.

The effectiveness of transcranial alternating current stimulation (tACS) in modulating brain oscillations in different frequencies bands has been largely proved (Antal and Paulus, 2013; Engel, 2001; Feurra, 2013). Recently, evidences of a load-dependent enhancement of the performance in a working memory task after tACS set at gamma

frequency have been also provided (Hoy et al., 2015).

Here, we propose that tACS at alpha frequency may also significantly improve visuo-spatial working memory. At this aim, we applied  $\alpha$ -tACS in the occipital cortex of subjects performing a visuo-spatial working memory task and a basic visual perception task.

## **4. Material and methods**

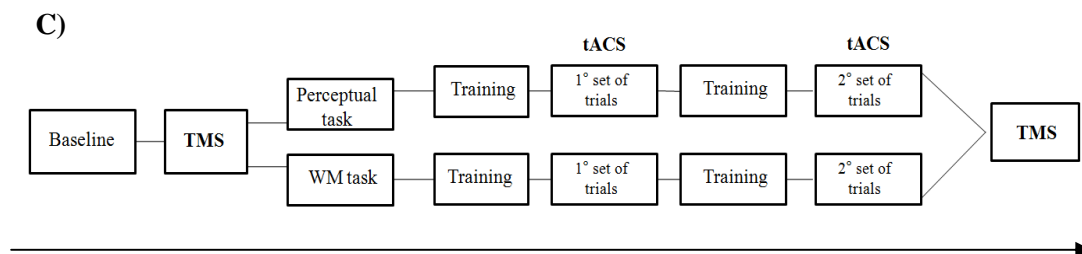
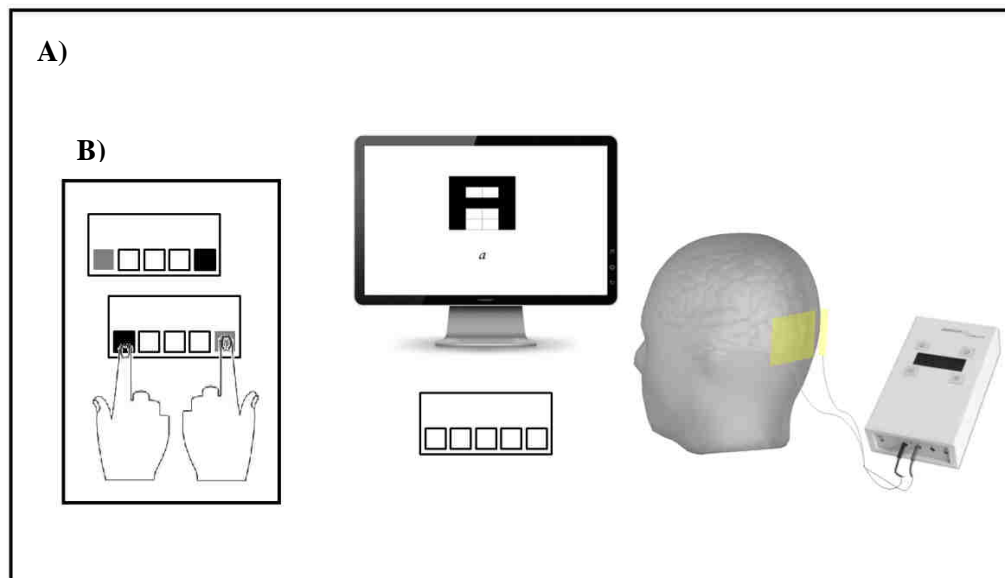
### *Participants*

Sixteen adult volunteers (mean age= 24.1 years;  $\pm$  1.14 years) were recruited for the study after giving written informed consent. All participants were in good health and had no previous history of neurological or psychiatric illness. The experiment was conducted in two different sessions.

### *Experimental procedure*

Task is derived from a task developed by Podgorny and Shepard (1978). We adapted the task in order to have two different conditions: one perception condition and one working memory condition. Before starting the experiment, subjects performed a training session both for the perceptual and the working memory conditions. The order of the sessions and the versions of the task were randomized across subjects (**Fig. 3**). In all the different tasks and conditions, all stimuli appeared in a 5x5 matrix subtending 2.6 (horizontal) by 3.4 (vertical) degrees of visual angle from the subject's viewpoint, at a distance of 50 cm.





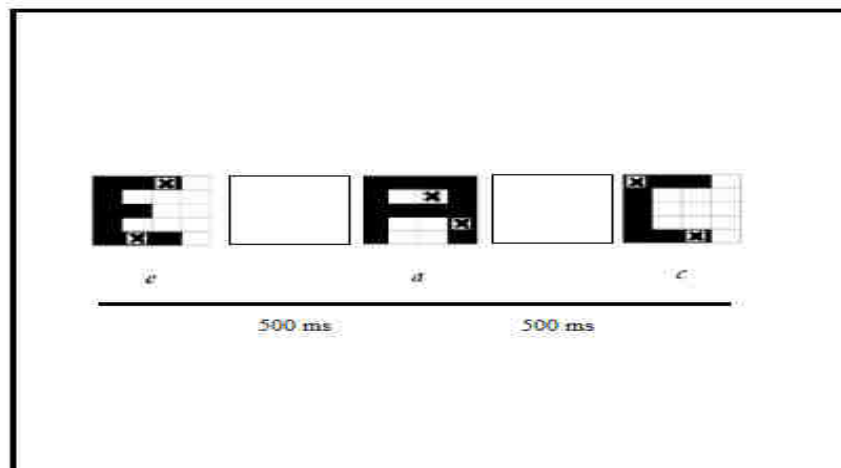
**Fig.3 Experimental procedure.** A) subjects performed both a visual perceptual and a visual working memory task while underwent to a tACS stimulation in the occipital cortex at alpha frequency. Subjects were sit at 50 cm from the computer monitor and were instructed to provide an answer by pressing a button on the button box (B). Subjects had to press the right key with the right hand if the Xs were both inside the letter, and the left key with the left hand if they were not. After completing the first set of trials subjects were asked to reverse the answer keys. C) the entire experimental procedure for each subject in all the conditions.

### *Perceptual task*

Task was implemented using E-prime software. Sixteen uppercase letters (A, B, C, E, F, G, H, J, L, O, P, R, S, T, U, Y) and four numbers (1, 3, 4, 7) were used as stimuli and were equally distributed in the trials. In each trial, one uppercase letter was displayed by filling specific cells of one 5x5 matrix. Immediately after the letter was displayed, two Xs appeared in two different positions of the matrix. The volunteers were asked to judge whether one or both Xs occupied a spatial position corresponding to the letter. In one-half

of the trials (i.e. 36) both Xs occupied spatial positions corresponding to the cell where the letter was presented. In the other half of the trials (i.e. 36), one of the two Xs occupied a spatial position where the letter was presented. The two conditions were randomly presented in each experiment.

There were two sets of trials requiring a different pattern of response. In a first set of 36 trials subjects were instructed and practiced to press the right key of a button box when one X fell into the letter and to press the left key of the button box when both Xs fell into the letter, and vice-versa in a second consecutive set of 36 trials. In both the sets of trials, probes (i.e. letters and Xs) were displayed on the screen until subjects' response (**Fig.4**).



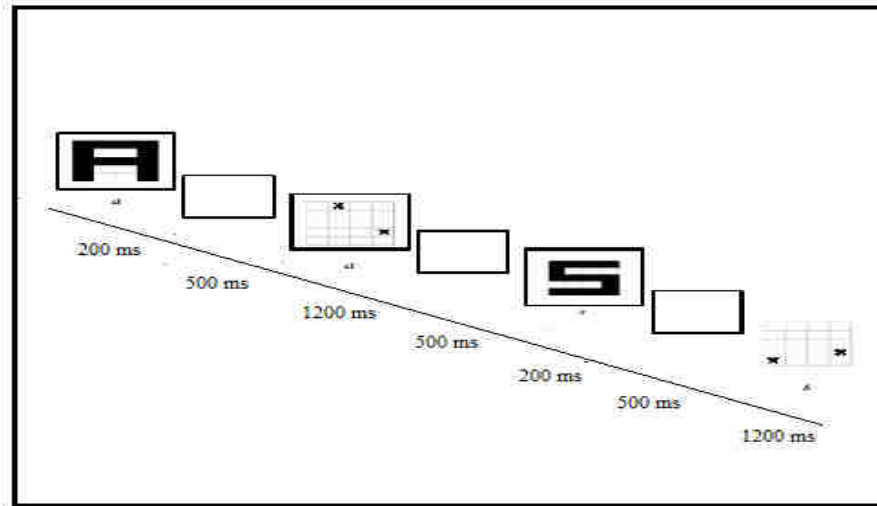
**Fig.4. Sample trial for the perceptual task.** A letter was displayed in a matrix, filled with two Xs, lasting until the subject responded. Subjects were instructed to provide an answer as soon as possible by pressing a button on the button box. Between each trial a white screen was presented lasting 500 ms. In the first set of trials subject had to press the right key with the right hand if both the Xs fell inside the letter, the left key with the left hand if not. After completing the first set of trials, subjects were instructed and practiced to reverse the response key.

### *Working memory task*

Subjects viewed in the display a 5x5 matrix filled in specific cells so that a letter was displayed for 250ms. Subjects were instructed to maintain in memory the letter before its disappearance. Immediately after letter disappearance, there was a white screen of 500 ms duration. Immediately after this delay, an empty 5x5 matrix was presented and two Xs were displayed inside the empty grid cells. Subjects, keeping in mind the previously presented letter, had to judge whether both Xs or only one X occupied a spatial position matching with spatial positions of the previously presented letter. Subjects were instructed to respond as soon as possible. The Xs lasted on the screen for 1200 ms and, if no answer was given, they disappeared. After completion of each trial, a new white screen appeared, lasting as long as volunteers decided to start a new trial by pressing a random key of the button box (**Fig.5**).

As in the perceptual condition, in a first set of 36 trials, subjects were instructed and practiced to press the right key of the button box when they judged that both Xs fell into positions occupied by the previously presented letter and the left key of the button box when they judged that only one of the Xs fell into the letter, and vice-versa on a second consecutive set of 36 trials.

Before starting the experiment, subjects performed a training session both for the perceptual and the working memory conditions. The order of the sessions and the versions of the task were randomized across subjects.



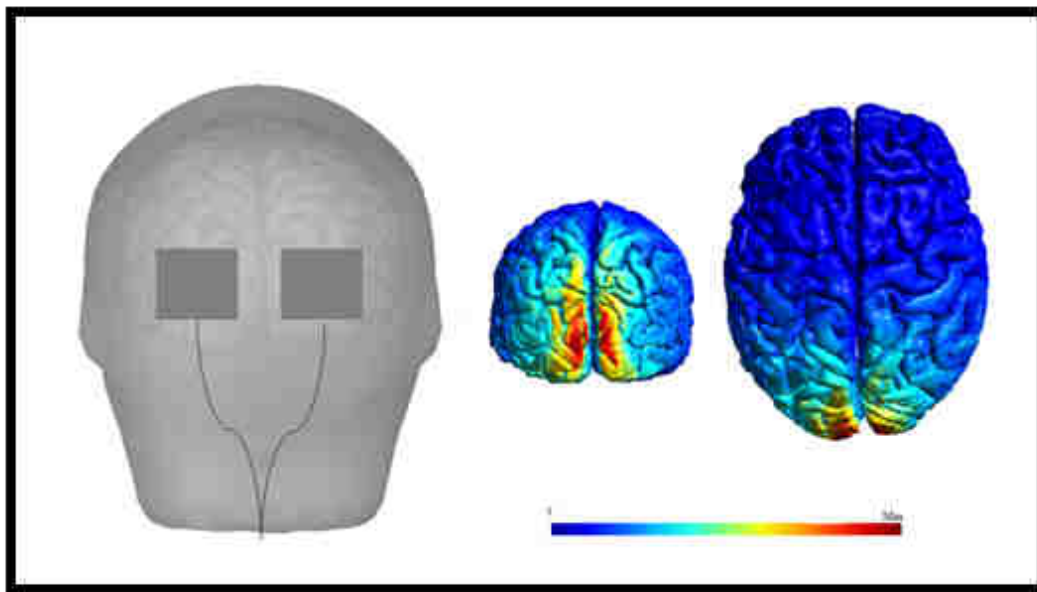
**Fig.5. Sample trial for the working memory task.** A white matrix was filled with the upper case version of a letter, displayed for 200 ms. Immediately after, the matrix disappeared and an empty matrix filled with two Xs appears, lasting 1200 ms. In the first set of trials subjects had to press the right key with the right hand if both the Xs fell inside the letter and the left button with the left hand if not. In the second set of trials subjects had to press the left button with the left hand if both the Xs fell inside the letter and the right key if not.

### *tACS montage*

tACS was delivered using a DC stimulator (Brainstim, EMS) through a pair of saline-soaked sponge electrodes of 5x5 cm size. Electrodes were placed over the left and right occipital areas (O1 and O2 sites according to the International 10–20 EEG placement system). Electrodes positions were chosen in order to affect V1 bilaterally.

tACS was applied at a frequency of 10 Hz during both perceptual and working memory tasks, with a current intensity of 1 mA. Stimulation was applied without DC offset. The current was ramped up over the first 30 s of stimulation. The control condition was sham stimulation, when tACS was terminated after 15 sec in order to elicit the typical tingling sensation under the electrodes at the beginning of stimulation. This procedure it has been shown to not impact the underlying brain tissue. Stimulation was in compliance with established safety protocols regarding AC stimulation. Subjects were blind to which

session was real or sham. All subjects well tolerated tACS and none of them reported phosphenes during tACS. For the real stimulation, the electrodes position was established by simulating the applied electric field. The realistic, finite element model was generated using SimNIBS 2 (Saturnino, 2015). Visualization of the mesh file was ran with Gmsh. The resulting electric field confirmed the target region as the occipital cortex (**Fig.6**).



**Fig. 6. Simulation of the applied electric field.** The realistic finite element head model included five compartments: scalp, bone, cerebrospinal fluid, gray matter and white matter. The maximum strength of the electric field is colour coded from 0 to 0.46 mV/mm.

### *Phosphenes threshold*

To test changes in phosphenes threshold, single-pulses of TMS were delivered in the occipital cortex immediately before and after tACS. The exact position of the tACS electrodes was previously marked in order to keep constant the position of the TMS coil across conditions. The phosphenes thresholds were measured decreasing the stimulation intensity when the subjects reported to see the phosphenes and increasing the stimulation

intensity when the subjects reported their absence. The session started with a single-pulse of TMS delivered at 80% of the maximum stimulator output. When subjects claimed to see the phosphenes, the intensity was reduced of 3% every time the phosphenes sight was confirmed; once that the phosphenes were no longer perceived the intensity was increased of 3% until subjected perceived the phosphenes. Then the intensity was respectively reduced and increased in steps of 2%. Finally the procedure was repeated in steps of 1% of the maximum stimulator output. Threshold was defined as the last stimulation intensity at which phosphenes were clearly perceived from the subjects.

## **5.Statistical analyses**

In both perceptual and working memory tasks, perceptual and memory performance were estimated as follows: sensitivity index  $d' = Z(\text{"hit rate"}) - Z(\text{"false alarm rate"})$  (Mcmillian, 2005). Higher  $d'$  indicate a better detection of the signal. The impact of the stimulation on perceptual and memory performance was analyzed using the generalized linear model. Hit rates and reaction times (RTs) were also measured.  $D'$  values were then analyzed using ANOVA for repeated measures.

In addition, ANOVA was run on hit rates for both tasks. A subsequent non parametric bootstrap t test ( $p \leq 0.05$ ) was used for pairwise comparisons between the conditions of the working memory task. For this test the null hypothesis distribution of the T scores was estimated for every comparison using the bootstrapping approach (2,000 iterations).

## 6.Signal detection theory

Signal detection theory (STD) can be applied in all the conditions in which two possible stimulus types must be discriminated, i.e. yes/no tasks (Macmillan, 2002). STD provides a framework to understand the processes in which subjects carry out a choice in the presence of uncertainty. Subjects' choice depends on both objective information and subjective bias (Stanislaw, 1999).

Indeed, the choice is based on the value that a decision variable achieves during each trial. A "yes" answer will be provided if the value of this decision variable is high, otherwise "no" will be the provided answer. This value is called *criterion* (Nevin, 1969).

Based on the possible subjects' answer we can have different rates. When the signal is present, "yes" response are correct and constitute the *hits*, while when signal is not present, namely in the noise trials, "yes" response are incorrect and constitute the *false alarms*, conversely when the signal is absent "no" responses are correct and constitute the "*correct rejection*" while, when the signal is present, "no" response are incorrect and constitute the "*missed rates*" (Stanislaw, 1999) (**Fig.7a**).

The decision variable can vary across the trials, determining a distribution of values. These values, distributed across the signal present trials create the *signal distribution*, whereas from the distribution under noise trials, the *noise distribution* arises (Stanislaw, 1999).

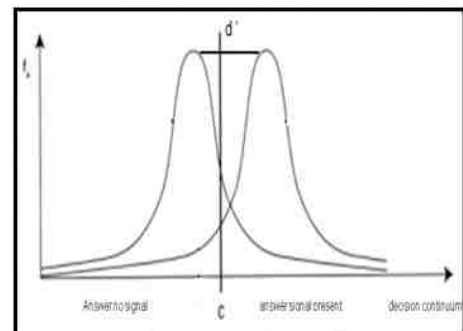
The false alarm and hit rates depend on both the subjects response bias and the degree of overlap between the signal and the noise distribution. This overlap is called *sensitivity*, meaning that when the signal is present, an higher level of hit rates will be reached from subjects with higher level of sensitivity to the changes. Sensitivity ( $d'$ ) is measured on the distance between the mean of the signal distribution and the mean of the noise distribution (Macmillan, 2002). The less the overlap the more the distance. Intuitively, the more the

distance between the means the higher the  $d'$  (Stanislaw, 1999) (**Fig.7b**). Indeed, a value of  $d' = 0$  indicate no distinction between signal and noise. Generally,  $d'$  have not negative values, however, when present, a negative value indicate sampling error or confusion in providing the answer. Finally,  $d'$  have two assumption: both the signal and the noise are normally distributed and have the same standard deviation (Stanislaw, 1999).

A)

	Answer "absent"	Answer "present"
Noise	Correct rejection	False alarm
Signal	Missed Rate	Hit rate

B)



**Fig.7. Signal detection theory** A) Based on the signal and the noise presence, subjects' answers can be *yes* or *not*. Four different possible answers arises from both the signal and the noise distributions. B) Distribution of the decision variable across noise and signal trials, showing  $d'$  and  $c$ .

## 7. Results

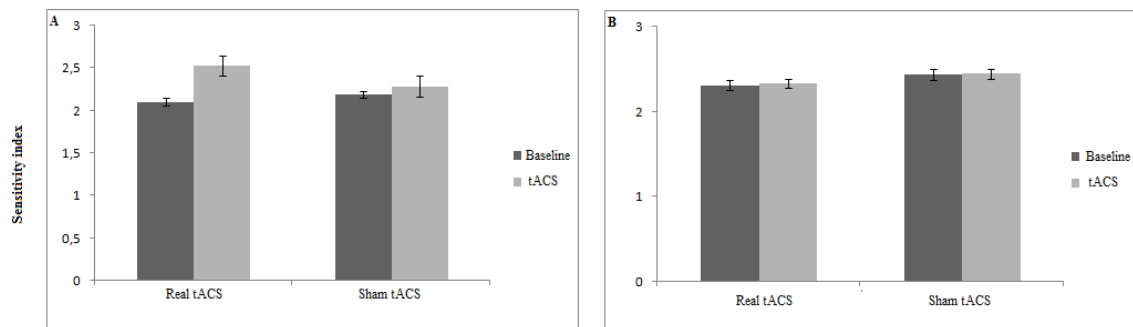
### *Experiment 1- Perceptual task*

#### *Sensitivity index*

ANOVA on  $d'$  values with the factors Stimulation (real vs. sham tACS), Session (baseline vs. tACS), Trial (first set vs. second set of trials) did not show any significant effect for the factors Stimulation [ $F = (1,15) = 0.56$ ,  $p = 0.46$ ], Session [ $F = (1,15) = 2$ ,  $p = 0.17$ ] and Trial [ $F = (1,15) = 0.01$ ,  $p = 0.90$ ]. The interactions Stimulation X Session [ $F = (1,15) = 3.4$



$p = 0.08$ ], Stimulation X Trial [ $F = (1,15) = 1.01$ ,  $p = 0.33$ ], Session X Trial [ $F = (1,15) = 4.1$ ,  $p = 0.06$ ], Stimulation X Session X Trial [ $F = (1,15) = 0.80$ ,  $p = 0.38$ ] were also not significant (**Fig.8**).



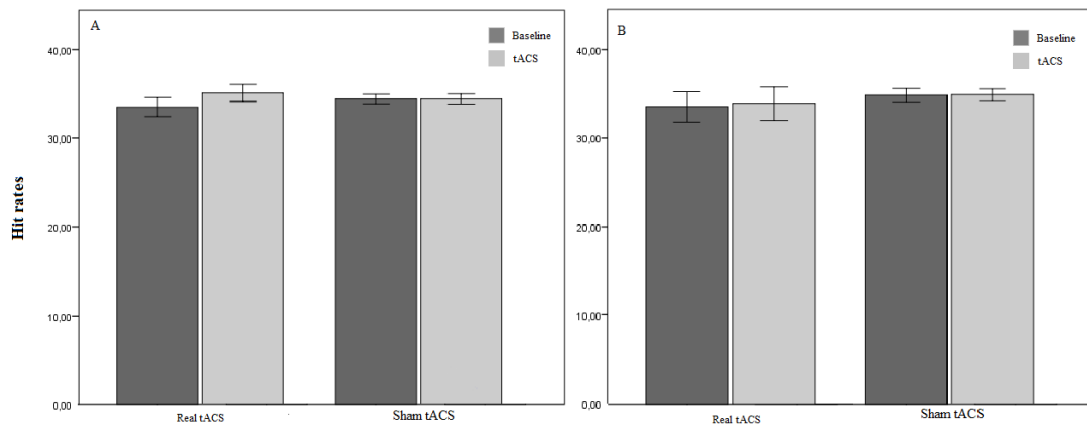
**Fig. 8** Sensitivity index ( $d'$ ) values in the perceptual task.  $D'$  prime was calculated for both real and sham tACS respectively for the first (**A**) and the second (**B**) set of trials.

### *Hit rates*

ANOVA on hit rates with the factors Stimulation (real vs. sham tACS), Session (baseline vs. tACS), Trial (first set vs. second set of trials) as within-subjects did not show any significant effect for the factors Stimulation [ $F = (1,15) = 1.75$ ,  $p = 0.20$ ,  $\eta^2 = .10$ ], Session [ $F = (1,15) = 1.64$ ,  $p = 0.21$ ,  $\eta^2 = .09$ ] and Trial [ $F = (1,15) = 0.02$ ,  $p = 0.88$ ,  $\eta^2 = .001$ ]. The interactions Stimulation X Session [ $F = (1,15) = 1.73$ ,  $p = 0.20$ ,  $\eta^2 = .10$ ], Stimulation X Trial [ $F = (1,15) = 2.47$ ,  $p = 0.13$ ,  $\eta^2 = .14$ ], Session X Trial [ $F = (1,15) = 1.06$ ,  $p = 0.31$ ,  $\eta^2 = .06$ ], Stimulation X Session X Trial [ $F = (1,15) = 0.60$ ,  $p = 0.45$ ,  $\eta^2 = .03$ ] were also not significant (**Fig.9**). False alarms and missed rates were few and did not show any significant main effects or interactions across conditions (**Table 1**).

Error rates	tACS		Sham	
	Baseline	Stimulation	Baseline	stimulation
A	1	0.40	0.62	0.68
B	1.68	0.43	0.93	0.81
C	1.31	1.06	0.65	1.06
D	1.12	1	0.56	0.44

**Tab.1 Mean error rates in perceptual task.** **A)** False alarm rates for the first set of trials; **B)** Missed rates for the first set of trials; **C)** False alarm rates for the second set of trials; **D)** Missed rates for the second set of trials. Error rates were small and no significant differences between the two conditions were found.



**Fig. 9. Mean hit rates in the perceptual task.** The graphs show the mean hit rates in the perceptual task during baseline (dark gray) and during stimulation (light gray) in both real tACS and sham tACS for the first (A) and the second (B) set of trials. Statistical analyses did not reveal any significant effect or interaction between conditions ( $p > .05$ )

### *Reaction times*

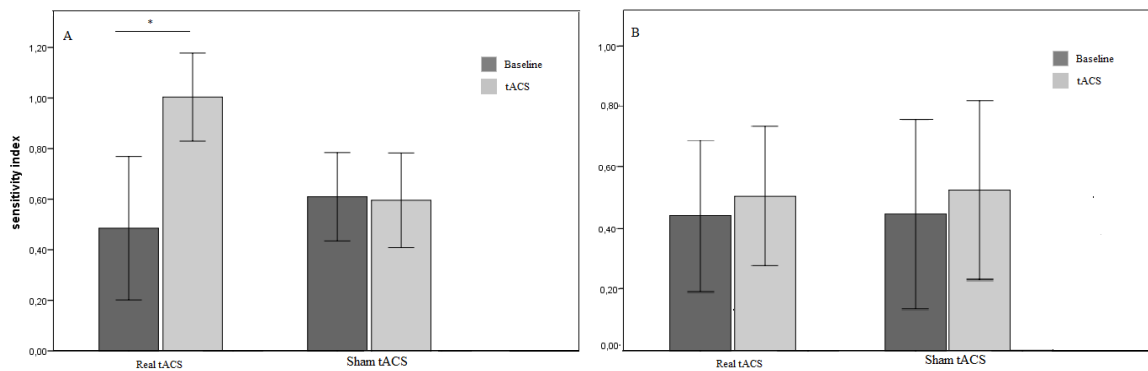
ANOVA on reaction times with the factors Stimulation (real vs. sham tACS), Session (baseline vs. tACS), Trial (first set vs. second set of trials) as within-subjects factors showed a significant main effect for the factors Trial [ $F = (1,15) = 13,765$ ,  $p = 0.002$ ] and Session [ $F = (1,15) = 20.95$ ,  $p = 0.0003$ ,  $\eta^2 = .58$ ] but not for the Stimulation factor [ $F = (1,15) = 0.48$ ,  $p = 0.49$ ,  $\eta^2 = .03$ ]. The interaction Stimulation X Session X Trial was not

significant [ $F = (1,15) = 0.000$ ,  $p = 0.98$ ,  $\eta^2 = .00$ ]. The interactions Session X Trial [ $F = (1,15) = 0.009$ ,  $p = 0.92$ ,  $\eta^2 = .00$ ] and Stimulation X Trial [ $F = (1,15) = 0.216$ ,  $p = 0.64$ ,  $\eta^2 = .01$ ] were also not significant. Interaction of Stimulation X Session was significant [ $F = (1,15) = 7.67$ ,  $p = 0.01$ ,  $\eta^2 = .33$ ]. An exploratory post-hoc Bonferroni's test was conducted and it showed that real tACS reduced reaction times for both the first ( $p = 0.004$ ) and the second set of trials ( $p = 0.003$ ). In the sham condition, difference between baseline and stimulation was not significant for both the first ( $p > 0.5$ ) and the second ( $p > 0.5$ ) set of trials (**Fig.10a-b**). No significant differences between baselines were found ( $p > 0.5$ ).

## *Experiment 2- Working memory task*

### *Sensitivity index*

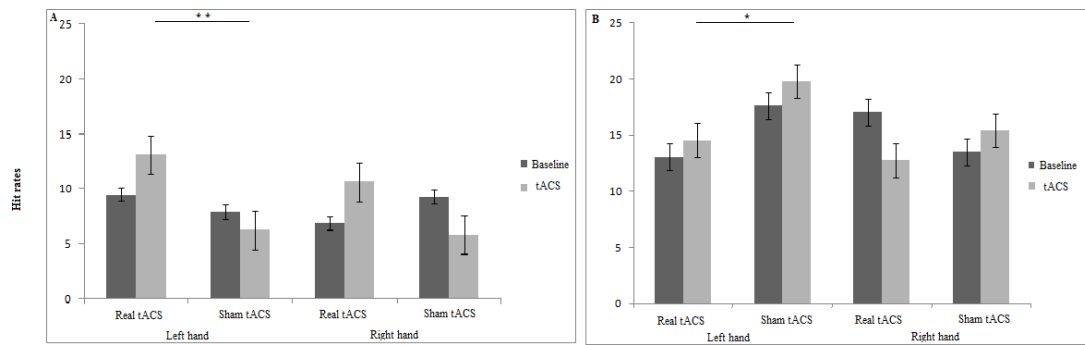
ANOVA on  $d'$  values with the factors Stimulation (real vs. sham tACS), Session (baseline vs. tACS), Trial (first set vs. second set of trials) as within-subjects showed a significant effect of the factors Session [ $F = (1,15) = 7.15$ ,  $p = 0.01$ ] and Trial [ $F = (1,15) = 1.22$ ,  $p = 0.02$ ] and a significant interaction of Stimulation X Session X Trial [ $F = (1,15) = 9.92$ ,  $p = 0.01$ ] but not of Stimulation X Session [ $F = (1,15) = 2.40$ ,  $p = 0.14$ ]. Post-hoc Bonferroni's test showed a significant improvement of performance following real tACS for the first set of trials ( $p < 0.01$ ) but not for the second set of trials ( $p = 1.000$ ). The following pairwise bootstrap t-test (2,000 iterations,  $p < 0.01$ ) confirmed that alpha stimulation improved memory performance (**Fig.11**).



**Fig. 11. Sensitivity index ( $d'$ ) for all the different conditions during working memory tasks.** The graphs show the results respectively during the baseline (dark grey) and the stimulation (light grey), for both the first (**A**) and the second (**B**) set of trials. Statistical analyses revealed a significant effect of tACS stimulation on performance while subjects executed the first set of trials ( $p = .01$ ).

### *Hit rates*

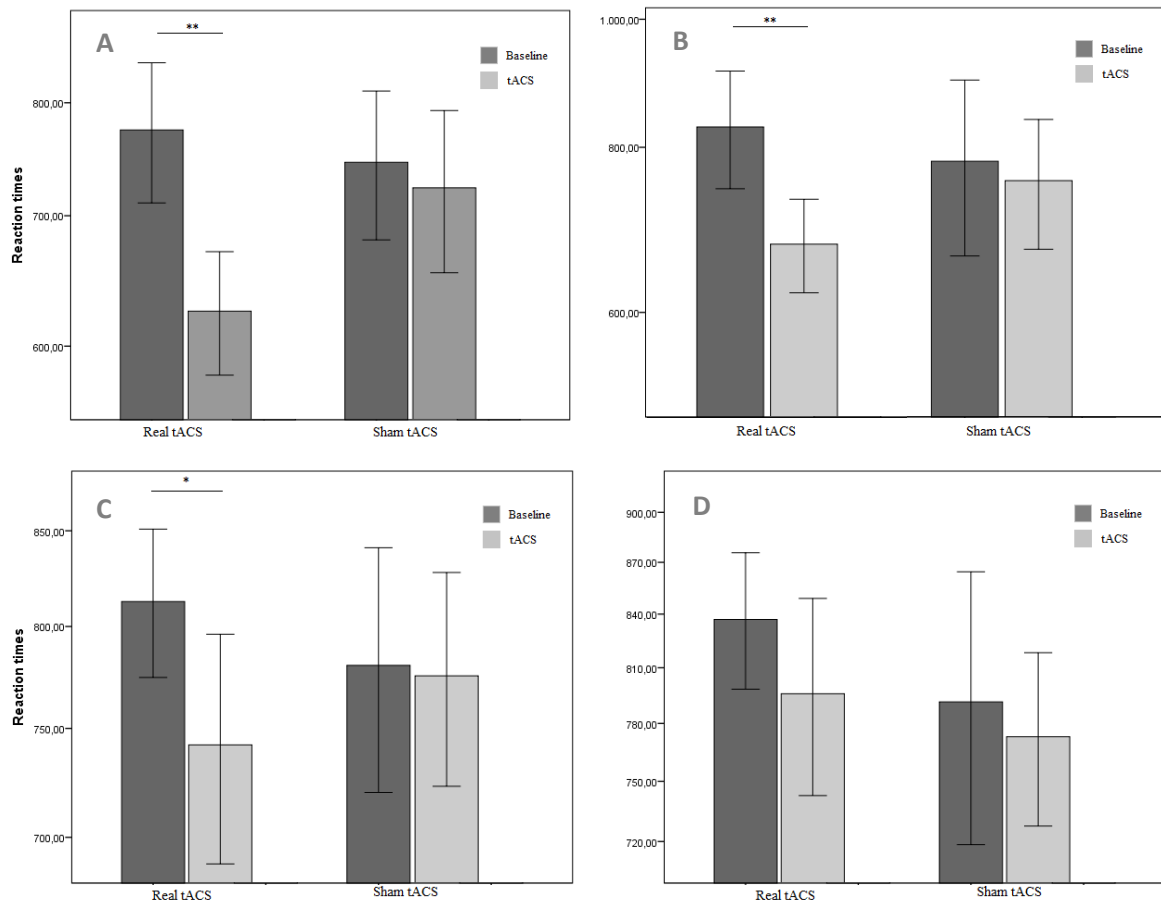
ANOVA on hit rates with the factors Stimulation (sham vs. real tACS), Session (baseline vs. stimulation), Trial (2 probes vs. 1 probe), Hand (right vs. left) as within-subjects factors showed a significant effect of the factors Trial [ $F(1,15)=80.03$ ;  $p < 0.001$ ], Hand [ $F(1,15)= 16.62$ ;  $p < 0.001$ ] and a significant interaction of Stimulation x Trial [ $F(1,15)=9.96$ ;  $p < 0.01$ ], Stimulation x Session x Trial [ $F(1,15)=18.82$ ;  $p < 0.001$ ], Stimulation x Trial x Hand [ $F(1,15)= 13.80$ ;  $p < 0.01$ ], Stimulation x Session x Trial x Hand [ $F(1,15)= 5.85$ ;  $p < 0.05$ ]. Working memory task was more difficult when subjects had to decide that one vs. two probes matched with previously presented stimulus ( $p < 0.01$ ). Real tACS vs. sham significantly improved the performance in trials with 1 probe ( $p = 0.001$ ), and significantly worsened the performance in trials with 2 probes ( $p = 0.02$ ), when using the left hand (**Fig. 12**).



**Fig 12. Hit rates in the working memory task.** (A) Trials with one probe matching a spatial position of the previously presented letter. (B) Trials with both probes matching a spatial position of the previously presented letter.

### *Reaction times*

ANOVA showed a significant effect of the factors Session [ $F = (1,15) = 7.806$ ,  $p = 0.01$ ,  $\eta^2 = .34$ ] and Trials [ $F = (1,15) = 4.66$ ,  $p = .04$ ,  $\eta^2 = .23$ ] but not of the factor Condition [ $F = (1,15) = 0.297$ ,  $p = .59$ ,  $\eta^2 = .01$ ]. Interactions Condition X Session [ $F = (1,15) = 2.290$ ,  $p = .15$ ,  $\eta^2 = .13$ ], Condition X Trials [ $F = (1,15) = 2.81$ ,  $p = .11$ ,  $\eta^2 = .15$ ], Session X Trials [ $F = (1,15) = 0.137$ ,  $p = .71$ ,  $\eta^2 = .00$ ] and Condition X Session X Trials [ $F = (1,15) = 2.957$ ,  $p = .10$ ,  $\eta^2 = .16$ ] were not significant. (**Fig.10-c-d**).

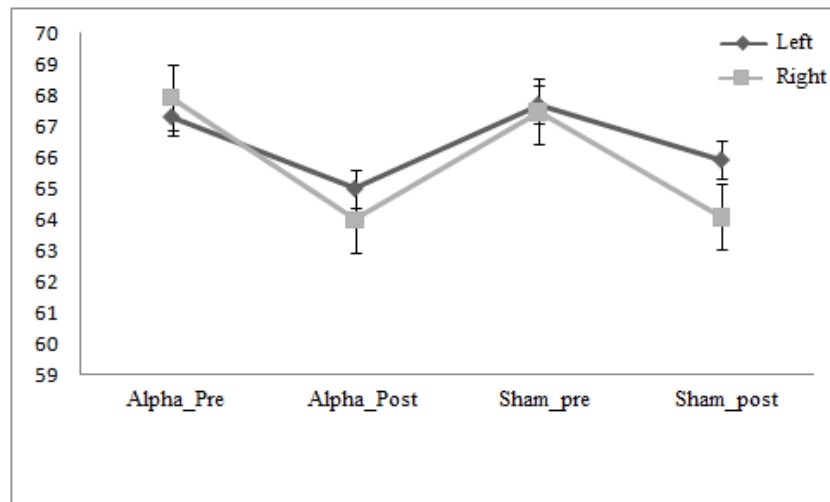


**Fig. 10. Mean reaction times (RT)** for both the perceptual (A-B) and the working memory tasks (C-D) during baseline (dark grey) and stimulation (light grey) in both real tACS and sham tACS in the first (A-C) and the second (B-D) set of trials. Statistical analyses revealed a significant reduction in RT for both the first and the second set of trials in the perceptual task ( $p = .003$  vs.  $p = .004$ ) and only for the first set of trials in the working memory task ( $p < .05$ ).

### *Phosphenes threshold*

The baseline TMS-phosphenes threshold was  $67.69 \pm 9.28\%$  (range 58-85%) when subjects were stimulated in the left occipital cortex and  $67.46 \pm 10.75\%$  (range 55-85%) when stimulated in the right occipital cortex. Despite the phosphenes threshold tends to decrease after stimulation, ANOVA showed no significant effect of stimulation neither in

the right ( $p > .05$ ) nor in the left hemisphere ( $p > .05$ ). These results show that tACS effects in the visual cortex did not extend beyond the end of the stimulation (**Fig.13**).



**Fig. 13. Phosphenes threshold.** Mean phosphenes threshold before and after alpha- tACS and before and after sham-tACS. No significant effects or interaction were found neither in the left nor in the right hemisphere ( $p > .05$ )

## 8. Discussion

The main result of this study is the improvement in visual working memory performance after 10 Hz tACS in the occipital cortex. A large body of recent studies confirms an enhancement of the alpha power during internal tasks, such as mental calculation and mental imagery (Palva, 2005; Vanni, 1997; Cooper, 2006) as well as during short-term memory and working memory (Jensen, 2002; Conway, 2002). Moreover during working memory tasks, a strong occipital alpha power increase and a synchronization between prefrontal and occipital cortices has been reported (Sauseng, 2007). In line with these results, we found that alpha enhancement using tACS in the occipital cortex improves working memory for visual stimuli. Interestingly, the facilitatory

effect of tACS at alpha frequency is selectively observed in the most difficult condition, i.e. when subjects are asked to judge whether one probe matches with spatial positions of the previously presented target. This finding suggests that alpha tACS selectively facilitates working memory performance under trials with higher cognitive demand. Since the right hemisphere should be preferentially engaged in the visual spatial working memory task, especially in posterior brain areas (Koch, 2005), one could speculate that increasing alpha power in the occipital cortex boosts performance in trials with higher cognitive demand where the right rather than the left hemisphere is activated to respond (i.e. when responding with the left hand; see also Vermeij et al., 2014 for a discussion on hemispheric asymmetries during spatial working memory tasks).

A possible explanation of the facilitatory effects of alpha tACS on visuospatial working memory performance is that enhancing the alpha power allows a stronger coupling between anterior (i.e. premotor or prefrontal) and posterior brain regions. In this way, the occipital cortex could be used as a blackboard to store the previously encoded visual images. It has been shown that during retention of items in memory, an alpha synchronization from posterior to anterior regions occurs (Sauseng, 2007; Halgren, 2002; Bonnefond, 2012). Alpha-tACS could have modulated this synchronization, thereby improving memory performance and acting as a gate for perceptual information processing. In the present experiment, alpha power increase induced by tACS could have facilitated inhibition of non-relevant information in trials where subjects recognized that one of the two probes did not occupy spatial position corresponding to the previously presented stimulus letter. Consistent with this interpretation, in the easier trials when it was not necessary to inhibit non-relevant information (i.e. non matching probes) from working memory, increasing alpha power disrupted, rather than facilitating, working memory performance.



The apparent discrepancy between the analyses with sensitivity index (i.e. showing increased performance in the first set of trials, where subjects used the right hand to indicate that one probe did not occupy a spatial position corresponding to the previously presented stimulus letter) and the analyses on hit rates (i.e. showing increased performance in trials where subjects used the left hand to indicate that one probe did not occupy a spatial position corresponding to the previously presented stimulus letter) could be ascribed to the different factors taken into account by the two analyses, indeed sensitivity index is used as a measure able to take into account not only the errors rates but also the subjects' criterion in providing the answer.

This result is in line with some studies suggesting that alpha rhythm in the occipital cortex acts as a gate, and that, inhibiting the processing of those visual informations that are non-relevant for the ongoing task, it may protect items in working memory from possible visual interferences (Bonnefond, 2012). In other words, alpha synchronization could close the gate of perception in order to focus on internal images and to allow the brain to carry out the processing of the encoded stimuli (Klimesch, 2007; Jensen and Mazaheri, 2010). On the other hand, whether it is true that during alpha activity brain regions are less excitable so that only few processes survive to inhibition, we would have expected a worsening of performance by alpha tACS in the perceptual task. Indeed, visual perceptual task was not affected by alpha tACS in the present study. A possible reason could be a methodological one, i.e. the perceptual task being too easy to be modulated by brain stimulation. Moreover, although numerous studies highlighted the importance of 10 Hz oscillatory phase in visual perception (Busch, 2009; Mathewson, 2009; Busch and VanRullen, 2010), a growing number of evidences shows that the alpha role in perception depends also on the phase of prestimulus alpha oscillation. Moreover, perception is also

affected by higher frequencies such as beta and gamma oscillations in the occipital cortex (Hanslmayr, 2007).

Some other methodological details could also explain the lack of significant modulation of the perceptual task by alpha tACS. We applied a continuous  $\alpha$ -tACS that could not be the most suitable stimulation setting to affect perception. In fact, enhancing alpha power just before the stimulus presentation could have improved performance (Klimesch, 1999), while enhancing alpha power exactly during stimulus presentation could have worsened it (Romei, 2010). An intermittent paradigm or short-triggered tACS trains could have been more efficacious to impact visual perception. Moreover, since alpha oscillations reflect different states of excitability and being perceptual performance dependent on the alpha phase during stimulus presentation, the absence of synchronization between visual stimulus onset and alpha phase could be one of the reasons for the lack of significant results in our perceptual task. Although tACS did not affect perceptual performance, we found a significant reduction of the reaction times during tACS either in the perceptual and in the working memory task. It can be hypothesized that reaction times reduction is related to a significant correlation between alpha activity and the speed in information processing (Callaway, 1960; Klimesch, 1996). Moreover, alpha modulation has been linked to both changes in reaction times and accuracy in visual perception (Surwillo, 1961; Dustman, 1965; Samaha, 2015; van Dijk, 2008). Being our perceptual task probably too easy to be modulated by tACS, we cannot clarify exactly if our stimulation led to a better performance together with a reduction in reaction times or if it affected the speed of information processing leaving unaltered the accuracy. In light of this, the results we found during our working memory task state in favour of an improvement in memory performance during alpha tACS together with a reduction in reaction times, indeed, the

reduction in reaction times is present only in those trials in which also an improvement in memory performance is reached.

Another explanation for the results of the present study is that alpha occipital tACS has modulated allocation of attentional focus to relevant stimuli, thereby improving the subsequent memory for those stimuli. For example, high alpha frequency band (10-14 Hz) reduces reaction times for stimuli presented in attended position and coordinates processes underlying visuospatial attention (Lobier, 2017). Directing attention to a location results in an alpha power modulation (Rajagovinda and Ding, 2011). In tasks requiring attention shift to one visual hemifield, there is an alpha power enhancement ipsilateral to the hemifield in which the stimuli are presented and an alpha desynchronization in the contralateral hemisphere (Romei, 2008). The alpha power lateralization has been hypothesized to regulate excitability levels in specific regions, so that it is possible to focus on processing of information at attended locations (Foxye, 1998; Worden 2000; Jensen, 2010). Therefore, allocating attention to regions involved in processing the relevant items could lead to an alpha modulation, when subjects are executing working memory task (Poch, 2014). Recent studies using cues and retro-cues during working memory tasks highlighted the role of two different alpha band activities. Alpha band lateralization after a pre-cue is probably related to anticipatory attention, while alpha modulation after a retro-cue may reflect the controlled access to recently encoded visual information (Myers, 2014). In the present study, by using a continuous tACS, we probably affected alpha power both during the anticipatory attention and during the access to the encoded visual information, especially in light of the evidences showing that when attending to both a visual stimulus or to an imagined visual stimulus, the same areas are activated and alpha band activity plays a role in both processes (Nobre, 2004; Chun, 2011).

We found that our tACS stimulation does not affect phosphenes threshold, as assessed by single-pulse TMS, immediately after the end of the stimulation. This negative result is in line with previous studies showing that tACS can modulate cortical excitability and reduce phosphenes threshold when applied at 20 Hz but not at 10 Hz frequency (Kanai, 2010). Moreover, our phosphenes threshold assessment was conducted after the end of the stimulation and, although a growing number of studies highlight the presence of tACS after-effect when tACS is applied at alpha frequency in the occipital cortex (Vossen, 2015; Zahele, 2010), all these studies suggest that this after-effect is dependent on the brain state.

Moreover, tACS after-effect has been generally assessed for tACS applied at individual alpha frequency rather than at a general alpha frequencies as in the present study (Neuling, 2013). Moreover, although several evidences state in favour of entrainment as the mechanism of action during on-line tACS, to date, entrainment have not been directly linked to the processes underlying tACS after-effect, and the existence of a tACS after-effect *per se* is still matter of debate (see Veniero, 2015 for a review).

In conclusion, we provide evidence of working memory modulation by tACS at alpha frequency over the occipital cortex. Further studies will further explore the eventual clinical significance of these findings and their interpretation in terms of neuronal connectivity between posterior and anterior brain sites.



## **CHAPTER IV**

### **Alpha-tACS EFFECTS IN WORKING MEMORY PERFORMANCE DEPEND ON BOTH THE NUMBER OF RELEVANT AND NON RELEVANT ITEMS.**

#### **Prelude: the gate of the inhibition**

One of the most common questions about the brain is “how information are gated between different regions during a cognitive process?” a possible answer is that information are gated, in part, by inhibiting task irrelevant regions and this inhibition allows to transfer information towards the relevant regions (Jensens, 2010). It has been shown that this functional inhibition occurs with an alpha synchronization in the mammalian brain (Klimesch, 2007). From a physiological point of view this activity reduces the capacity of processing in a given area. GABAergic feedbacks from interneurons has been strongly implicated in the physiological mechanism that generate alpha (Jensen, 2010). After being generated, the alpha rhythm is probably modulated by thalamic rhythm generators (da Silva 1973; Huges 2005; Jones 2009; Lorincz 2009).

## **1.Introduction**

Working memory implies the ability to maintain and manipulate information over short periods of time. It consists of the encoding of the information, maintenance and retrieval (Baddeley, 2001). These three components could not work as good as they do, without a mechanism able to protect items in memory from interferences.

As discussed in the previous chapter, in the oscillations domain, while theta and gamma rhythms seem to be involved in the successful maintenance of the relevant items, alpha activity seems to be the elective rhythm in protecting memoranda from interferences caused by irrelevant informations (Jensen, 2002; Bonnefond, 2012; Roux, 2014). It has been shown that alpha rhythm plays the same role in protecting information from distracters also in perceptual processes (Haegens, 2012). Moreover, next to an alpha enhancement in the task irrelevant regions, an alpha suppression has been found in task requiring spatial attention or anticipation of the target (Thut et al., 2006; Tallon-Baudrey, 2012). In the attention domain, directing attention externally, as in a perceptual task, requires an alpha suppression (Ward, 2003; Benedek, 2011), conversely, directing attention internally, as in a working memory task, requires an alpha enhancement (Cooper, 2003; Cooper, 2006; Benedek, 2014).

Working memory could be conceptualized as a process based on an internal direction of the attention that needs the sensory intake rejection (Lacey, 1963). The rejection is related to the hypothesis that to carry out activities with internally directed attention, subjects have to inhibit incoming sensory information, therefore an alpha power enhancement is needed (Cooper, 2003).

A recent study, presenting relevant and not relevant visual items distributed in the two visual hemifields, has found, during the encoding phase, that the active maintenance

of memoranda is reflected by a contralateral alpha suppression, while the active inhibition of the irrelevant items is reflected by an ipsilateral alpha enhancement (Sauseng, 2009).

Moreover, applying rTMS at alpha frequency band in the parietal cortex, contralateral to the hemifield in which the to-be-remembered items are presented, detracts the memory capacity during a visuo-spatial working memory task (Sauseng, 2009).

Next to an alpha enhancement during distracters presentation, many authors found an alpha enhancement with increasing memory load, regardless of the presence of distracters (Jensen, 2002; Klimesch 1999). Probably, the more the demands to the working memory system, the stronger the need for task-irrelevant regions' disengagement and thus the stronger the alpha rhythm. Taken together these evidences suggest that alpha plays a role in either distracter suppression (Tuladhar, 2007) and memoranda maintenance (Kolev, 2001; Maltseva, 2000).

Another strand of research is trying to shed further light in the differences between different alpha frequencies in the different phases of the memory processes. At increasing memory load, during the retention interval, an alpha enhancement in the posterior regions has been found (Klimesch,1999; Shack, 2005), while during the retrieval, alpha power seems to decrease as characterized by an event-related desynchronization (Klimesch, 1988; Shack, 2005).

In light of all these evidences, in the present work we aimed to modulate alpha activity, using tACS, in a visuo-spatial working memory task including either relevant and irrelevant items.

In line with a previous reported study using TMS (Sauseng, 2009), we assume that entrainment of posterior alpha frequency improves visual working memory performance and that this improvement is dependent on the number of distracters rather than on the



number of relevant items. Moreover, to avoid an effect of alpha modulation in memory performance due to a continuous stimulation, our tACS stimulation started before the encoding phase and lasted eight seconds with a ramping down until zero of the current immediately before the recognition phase. Indeed we propose that, despite several evidences have been provided about the effectiveness of tACS in affecting behavioural outcomes, being changes in brain oscillations fast and immediate, more flexible stimulation paradigms need to be explored.

## **2. Materials and methods**

### *Participant*

Twenty-seven right-handed healthy volunteers [mean age= 25.46 years;  $\pm$  4.09 years] with normal or corrected to normal vision were recruited for the study after giving written informed consent. None of the participants reported history of neurological or psychiatric syndromes, brain injury or other chronic conditions. All participants were naïve about the cognitive task.

Seventeen subjects completed the first experiment, ten subjects completed the control experiment, both the experiments counted three sessions. In the first experiment two volunteers did not show up for two of the three sessions and their data were excluded from further analyses.

After each session a questionnaire about stimulation related effects was administered, none of the subjects reported any discomfort or effect during or after the sessions. All the experiments were conducted in accordance with the declaration of Helsinki and with the approval of the ethics committee of the Georg-August-Universität, Göttingen, Germany.

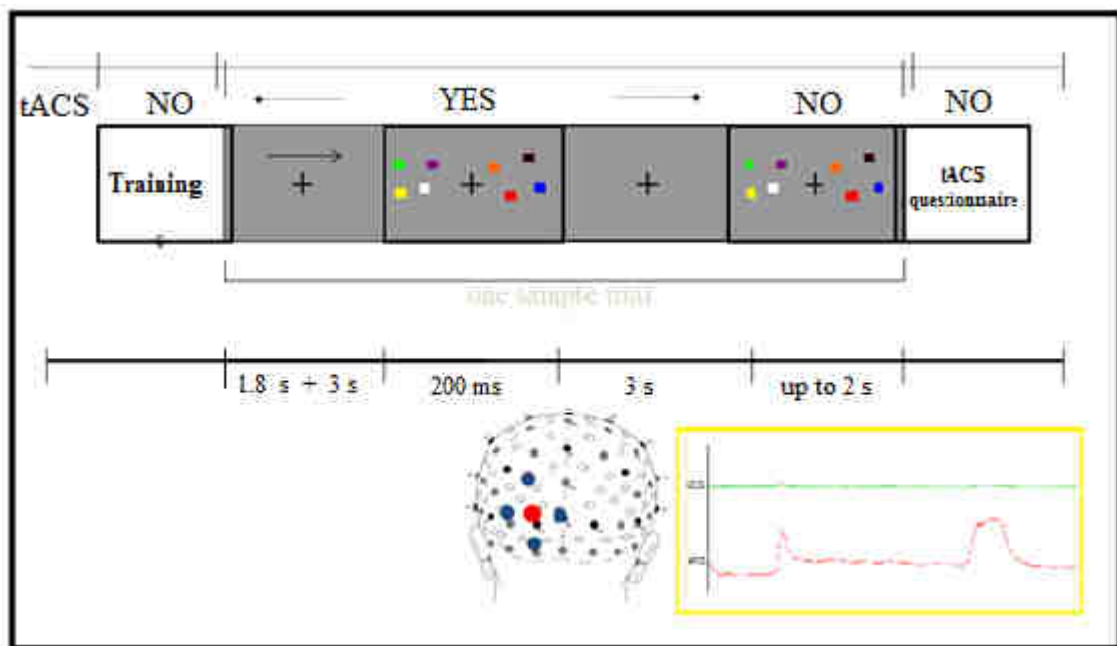
## *Experimental procedure*

Two experiments were conducted successively. All subjects were first of all familiarized with the laboratory and the procedure. Both the experiments included three sessions in a randomized counterbalanced order, respectively the first group underwent to a 10 Hz stimulation and the second group to a 23 Hz stimulation. The three conditions were left-tACS stimulation, right-tACS stimulation, sham-tACS stimulation. At least 48 hours were waited between each session.

Subjects were subdivided into two groups, the first group participated only in the first experiment; the second group took part only in the second experiment designed as control.

In both the experiment subjects performed a visuo-spatial working memory task while underwent to a tACS stimulation (**Fig.14**).

Each session consisted of a brief task practice and a visuo-spatial working memory task during tACS stimulation, followed by a post stimulation questionnaire, administered to investigate subjective feeling during stimulation and tACS related discomfort.

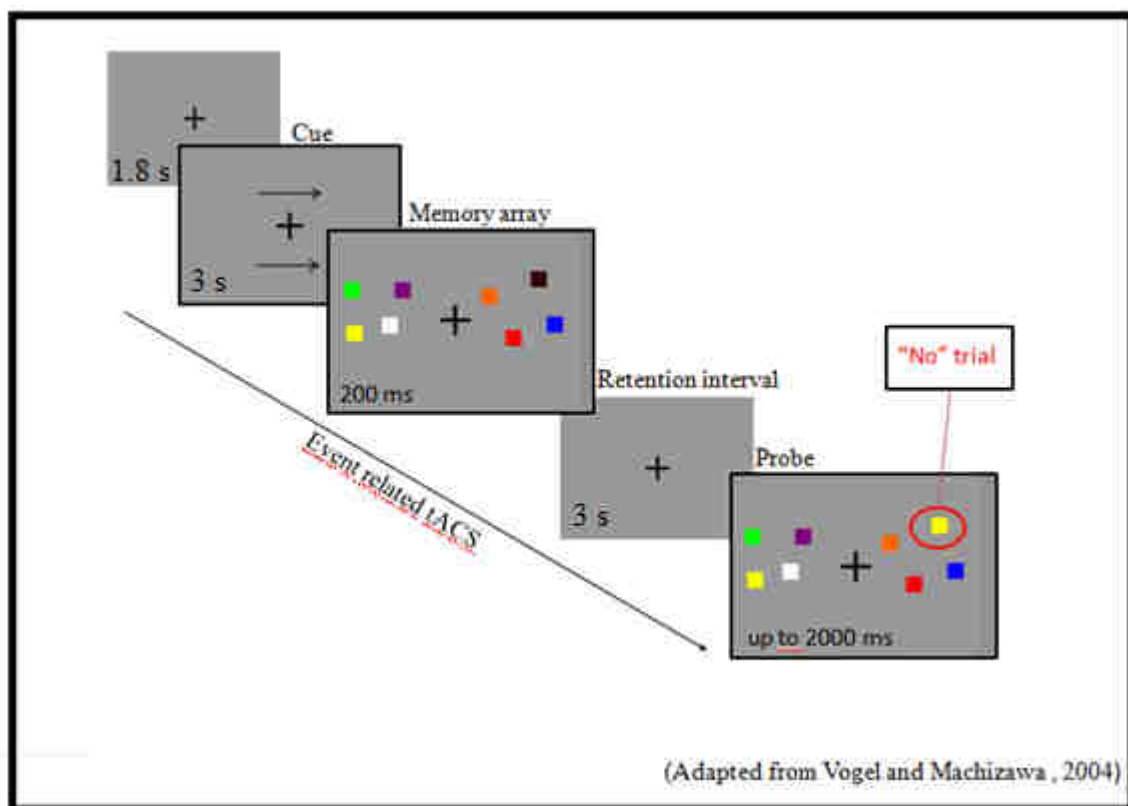


**Fig.14. Experimental procedure.** During triggered tACS subjects completed the visual working memory task. Horizontal and vertical eye movement were registered using two additional bipolar electrodes. Left, right and sham tACS were randomized and counter-balanced across subjects for both the experiments.

### *Working memory task*

A visuo-spatial working memory task as used by Vogel and Machizawa (Vogel and Machizawa, 2004) was performed by each volunteer. A fixation cross was presented throughout the whole trials. Subjects were instructed to stare the centre of the screen. 1800 ms after the fixation cross appeared, an arrow pointing to the left or to the right was presented for 2000 ms. Immediately after, the memory array was presented for 200 ms. The stimulus array consisted of respectively 4 or 6 coloured squares ( $0.65^{\circ} \times 0.65^{\circ}$ ) and 4 or 6 distracters in each hemifield. Each square was randomly coloured of one highly discriminable colour and each colour cannot appear more than twice in an array. Stimulus positions were randomized in each trial with a constant distance between squares in each hemifield of at least  $2^{\circ}$ . All these stimuli were presented inside two  $4^{\circ} \times 7.3^{\circ}$  rectangular regions, centered  $3^{\circ}$  to the left and right of the central fixation cross on a grey background.

Subjects were instructed to pay attention and memorize only the squares presented in the hemifield previously cued by the arrow and only the squares in that hemisphere had to be retained for the following retention interval of 3000 ms. All the other squares had to be ignored. After the retention interval, in the 50% of trials the colour of one square in the test array was different from the corresponding item in the memory array. In the remaining 50%, all the squares in the probe were identical to the squares presented in the memory array (Fig.15).



**Fig.15. One sample trial with memory array size four.** Subjects were instructed to attend to the hemifield previously cued from the arrow and to ignore the items presented in the un-cued hemifield. After a retention interval subject had to press the left key if all the squares were the same as in the memory array and to press the right key if at least one square changed in colour.

### *Transcranial alternating current stimulation*

Each session was conducted in an electrically shielded, sound attenuated laboratory. Electrical stimulation was delivered by a battery-driven constant-current stimulator (NeuroConn GmbH, Ilmenau, Germany) through a set of five 2 cm<sup>2</sup> rubber-round electrodes with Ten20 paste as conductivity means. Both the groups received 1.5 mA peak-to-baseline triggered tACS applied for 8 s during both the encoding and delay phases, with stimulation off set immediately before the probe presentation (**Fig. 16-b**). Specifically, in the first experiment subjects received a 10 Hz tACS and in the second experiment (i.e. the second group) the stimulation frequency was 23 Hz, sets as a control frequency. Both the groups underwent to three different conditions: left tACS, right tACS and sham tACS. Sham stimulation was randomly applied to the left or to the right hemisphere. Impedance was kept below 5 kOhm as measured from the device.

### *Montage*

The position of the electrodes was kept constant across all the sessions and experiments, with the plugs and cable always turned in a medial-to-lateral direction. The electrodes montage was a Laplacian multi-electrodes montage. It consisted of a central electrode positioned on respectively PO3 or PO4 and four surrounding return electrodes equally placed with a minimum distance of 6 cm (**Fig.16-a**). Additionally, vertical and the horizontal electro-oculogram (vEOG, hEOG) were recorded from two bipolar channels to control for eyes movements and blinks.

### **3. Statistical and data analyses**

#### *Behavioural data analysis*

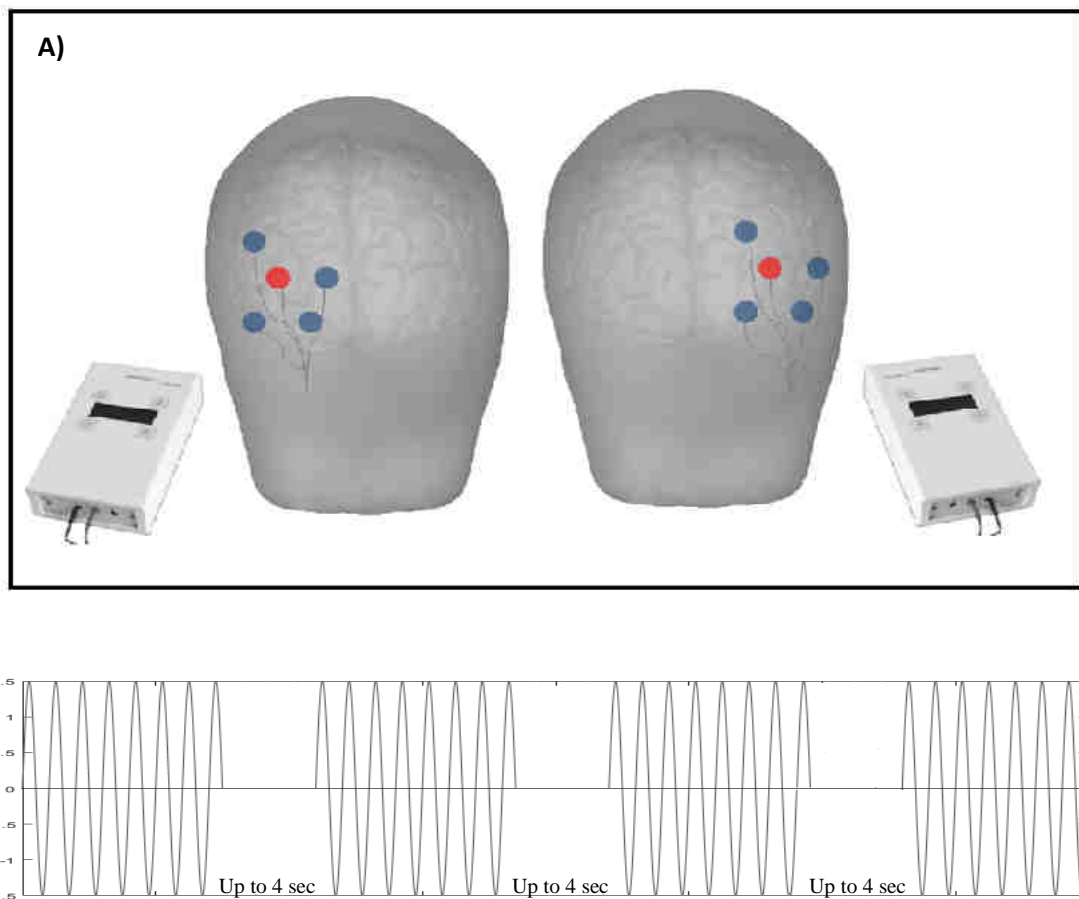
Data were first corrected for eyes movements, trials contaminated by eyes movements were removed from further analyses.

For the remaining trials, sensitivity index ( $d'$ ) was calculated for each single subject taking into account the hits and the false alarm rate and the number of relevant and irrelevant items in the memory array.  $D'$  as a measure of memory effectiveness in a given condition is a dimensionless statistic (see pag. 37 for a detailed discussion) calculated as follow:  $d' = Z(\text{hit rates}) - Z(\text{false alarm})$  (Macmillan, 2002). A higher  $d'$  indicates that the signal can be more readily detected. Signal and noise can be represented under two normal distributions (Stanislaw, 1999). Sensitivity index represents the distance between the means of both the distributions, that is, respectively, signal and signal plus noise distribution. The mean of the noise distribution is zero and both distributions' standard deviation is one (see Chapter 3 for a detailed description). In cognitive science, this index measures the sensitivity in task in which responses have to be detected (Macmillan, 2002).

All the statistical comparisons were computed in IBM SPSS Statistics, version 20, IBM Corp, Armonk/US.

The impact of the stimulation on the performance was analyzed using the generalized linear mixed-effect model, with a subsequent ANOVA, with STIMULATION (left tACS vs. right tACS vs. Sham tACS), HEMIFIELD (left. vs. right), MEMORY LOAD (four vs. six) and DISTRACTERS (four vs. six) as within subjects factors and GROUP as a between-subjects factor. Post-hoc Tukey HSD tests were applied when needed. The normal distribution was tested using the Kolmogorov-Smirnov test.

Mauchly's sphericity test was conducted and when needed, effects were corrected using Greenhouse-Geisser criteria.



**Fig.16 tACS Laplacian Montage for left and right tACS condition. A)** Five rubber round electrodes were attached to the scalp using a conductive paste. the first electrode was placed respectively in PO3 and PO4 with four equally spaced return electrodes. Stimulation frequency was 10 Hz with an intensity of 1.5 mA peak-to-baseline. The same montages were randomly used for sham stimulation.

**B)** Event-related tACS. Schematic representation of the 8 s trains tACS driven at alpha frequency.

## 4.Results

Subject-specific effects of the stimulation on  $d'$  were modeled using the generalized linear approach.

ANOVA did not show any significant effect of the factors Group [ $F = (1,23) = 0,74$ ,  $p = .39$ ,  $\eta^2 = .03$ ] and Stimulation [ $F = (2,46) = 0,07$ ,  $p = .92$ ,  $\eta^2 = .00$ ] and of the number of Distracters [ $F = (1,23) = 1,36$ ,  $p = .25$ ,  $\eta^2 = .05$ ], while the factor Hemifield [ $F = (1,23) = 8,76$ ,  $p = .007$ ,  $\eta^2 = .27$ ] and Memory load [ $F = (1,23) = 108,97$ ,  $p = .00$ ,  $\eta^2 = .82$ ] were significant. The interaction Stimulation X Hemifield [ $F = (2,46) = 4,12$ ,  $p = .02$ ,  $\eta^2 = .15$ ] was significant while the interaction Stimulation X Memory Load [ $F = (2,46) = 0,65$ ,  $p = .52$ ,  $\eta^2 = .02$ ], Memory Load X Distracters [ $F = (1,23) = 0,86$ ,  $p = .36$ ,  $\eta^2 = .03$ ] and Stimulation X Distracters [ $F = (2,46) = 1,59$ ,  $p = .21$ ,  $\eta^2 = .06$ ] were not significant. The interactions Stimulation X Hemifield X Distracters [ $F = (2,46) = 5,13$ ,  $p = .009$ ,  $\eta^2 = .18$ ] and Stimulation X Memory Load X Distracters [ $F = (2,46) = 5,25$ ,  $p = .008$ ,  $\eta^2 = .18$ ] were both significant as well as the interaction Stimulation X Hemifield X Group [ $F = (2,46) = 3,36$ ,  $p = .04$ ,  $\eta^2 = .12$ ].

Interaction Hemifield X Memory Load X Distracters [ $F = (1,23) = 0,00$ ,  $p = .96$ ,  $\eta^2 = .00$ ] was not significant, while interaction Stimulation X Hemifield X Memory Load [ $F = (2,46) = 3,00$ ,  $p = 0.059$ ,  $\eta^2 = .11$ ] tended towards significance.

Interaction Stimulation X Memory Load X Group [ $F = (2,46) = 1,45$ ,  $p = .24$ ,  $\eta^2 = .05$ ], Hemifield X Memory Load X Group [ $F = (1,23) = 0,24$ ,  $p = .62$ ,  $\eta^2 = .01$ ], Stimulation X Distracters X Group [ $F = (2,46) = 0,78$ ,  $p = .46$ ,  $\eta^2 = .03$ ] Hemifield X Distracters X Group [ $F = (1,23) = 0,43$ ,  $p = .51$ ,  $\eta^2 = .01$ ], Memory Load X Distracters X Group [ $F = (1,23) = 0,21$ ,  $p = .64$ ,  $\eta^2 = .00$ ] were not significant.

Although the main factor for Stimulation was not significant, we conducted a Tukey HSD post-hoc test as an explorative analysis of the interaction between the stimulation and



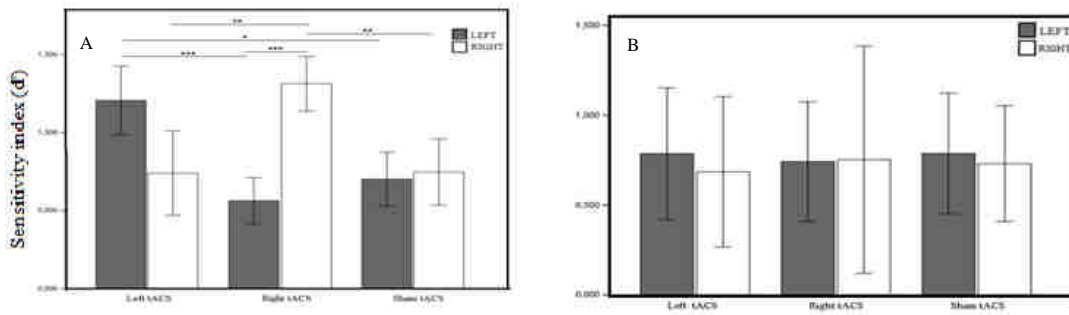
the hemifield. Indeed, this interaction appears to be different in the two different groups, suggesting a different effect of the stimulation dependent on the hemifield and on the frequency of the stimulation (10 Hz vs. 23 Hz).

The Tukey HSD post-hoc test, exploratively conducted on the main significant interactions, showed that the main effects of the stimulation were present when six relevant items and six distracters were presented together.

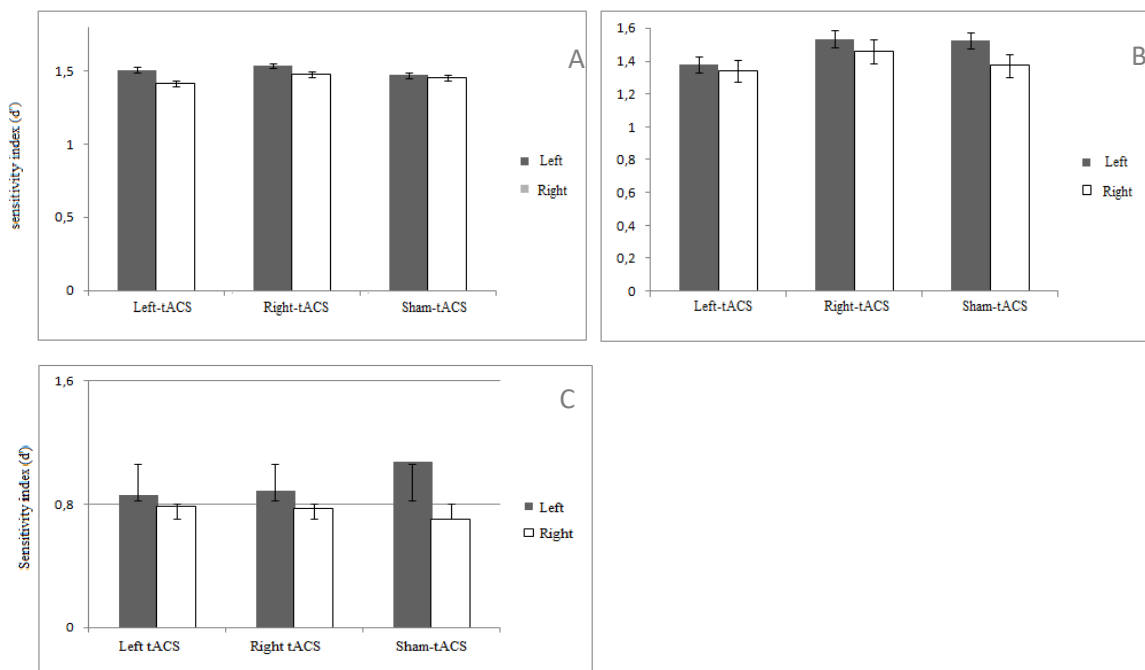
When items were presented in the right hemifield, tACS applied in the left hemisphere disrupted memory performance if compared with right stimulation (.739 vs. 1.313,  $p = .003$ ) but not if compared with sham (.563 vs. .701,  $p = 1.000$ ), while if compared with relevant items presented in the right hemifield it tended toward significance (.739 vs. 1.205,  $p = .05$ ). Conversely, right tACS improved memory performance if compared with relevant items presented in the left hemifield (1.313 vs. .563  $p = .0001$ ) and if compared with sham (1.313 vs. .746.  $p = .003$ ).

When items were presented in the left hemifield, left tACS improved memory performance if compared with right stimulation (1.205 vs. .563  $p = .0005$ ) and if compared with sham (1.205 vs. .701,  $p = .02$ ).

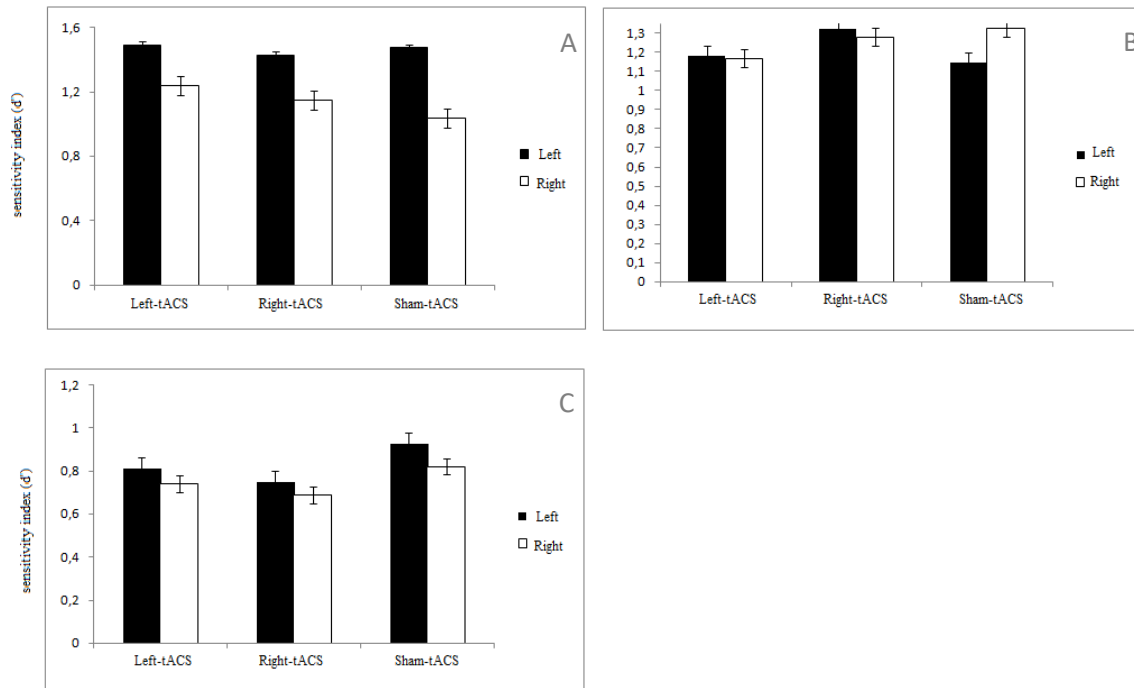
Right tACS disrupted memory performance if compared with left stimulation (.563 vs. 1.205  $p = .0005$ ) and if compared with condition in which items were presented in the right hemisphere (.563 vs. 1.313  $p = .0001$ ), but not if compared with sham (.563 vs. .701  $p > .05$ ) (**Fig. 17**). Finally, no significant effects were found neither when four relevant items and four distracters were presented ( $p > .05$ ) nor when six relevant items or four relevant items were presented together with four or six distracters ( $p > .05$ ). The results of these explorative analyses are plotted in **Fig. 18 and Fig.19**.



**Fig.16. Sensitivity index ( $d'$ )** for condition with six relevant items and six distracters during working memory task. The graphs show the results respectively for items presented in the left (dark grey bar) and in the right hemisphere (white bar), for all the different stimulation conditions (Left, Right, Sham) for the first (A) and the second (B) group. Statistical analyses revealed a significant effect of 10 Hz tACS in memory performance Left tACS improves memory for items presented in the left hemifield if compared with sham ( $p = .02$ ). Right tACS improves memory performance for items presented in the right hemisphere if compared with sham ( $p = .003$ ). Neither left tACS nor right tACS have a significant impact in memory disruption when applied contro-laterally, if compared with sham ( $p > .05$ ). No effects were found when tACS was applied at a frequency of 23 Hz.



**Fig.18. Sensitivity index ( $d'$ )** Respectively for condition with four relevant items and four distracters (A), four relevant items and 6 distracters (B), six relevant items and four distracters (C). The graphs show the results respectively for items presented in the left (dark grey bar) and in the right hemisphere (white bar), for all the different stimulation conditions (Left, Right, Sham) during the first experiment. Statistical analyses revealed no significant effect of the stimulation in none of the conditions ( $p > .05$ ).



**Fig.19. Sensitivity index (d')** Respectively for condition with four relevant items and four distractors (A), four relevant items and 6 distractors (B), six relevant items and four distractors (C). The graphs show the results respectively for items presented in the left (dark grey bar) and in the right hemisphere (white bar), for all the different stimulation conditions (Left, Right, Sham) for the third experiment (23 Hz stimulation). Statistical analyses revealed no significant effect of the stimulation ( $p > .05$ ).

## 5. Discussion

This study tested the role of a novel intermittent tACS paradigm in a working memory task. The main result is a significant improvement of the memory performance following  $\alpha$ -tACS trains of the parieto-occipital cortex. The improvement is frequency-dependent and, contrarily to our hypothesis, it does not depend on the number of presented distractors, but it depends on both the number of relevant and not relevant items presented together.

Animal studies, have shown that rhythms in the brain are subjected to rapid changes from one moment to the next (Braging, 1995; Womelsdorf, 2007; Atallah, 2009). In light of these evidences we applied an intermittent tACS protocol in order to enhance alpha

power during both encoding and retention interval, avoiding tACS online effect during the probe presentation. Our stimulation paradigm resulted, thereby, in several 8 seconds tACS trains. Evidences for entrainment effects during 8 second trains of tACS have been recently provided (Vossen, 2015), while shorter tACS trains seem to not affect brain oscillations (Vossen, 2015; Braun, 2017).

As we stated above, one of the main results of this study is that 8 seconds tACS trains improve working memory performance when applied ipsilaterally to the to-be-remembered items, on the same time, contrarily to our hypothesis, when applied controlaterally, alpha tACS did not significantly disrupt memory performance.

In other words we found that when subjects were stimulated in the right hemisphere there was a significant improvement in the memory performance when six items were presented in the right hemifield while the disruption for items presented in the controlateral hemifield was not significant if compared with sham stimulation.

Conversely, when subjects were stimulated in the left hemisphere, there was a significant improvement when relevant item were presented in the left hemifield, while the disruption for relevant items presented in the contro-lateral hemifield was again not significant if compared with sham stimulation.

These results are only partially consistent with the body of existing research on the role of occipito-parietal alpha enhancement during working memory tasks.

For instance, in a recent study, Sauseng shown that alpha activity in the parietal cortex during the retention interval increases with increasing the amount of irrelevant information and this increase did not depend on the amount of relevant information (Sauseng, 2009).

Following this line of reasoning one would have expected that, regardless of the memory load, enhancing controlateral alpha power when the highest number of distracters

is presented should have brought to the best memory performance. Whether on one hand, we found an improvement in memory performance when the highest number of distracters was displayed (i.e. six), on the other hand, when less than six relevant items were presented (i.e. four) no effect was observed.

This result states in favour of a dependency of the effect of  $\alpha$ -tACS on both the memory load and the number of presented distracters, and it is in line with previously reported works, in which a detriment of performance with increasing memory load when distracters are presented has been found (De Fockert, 2001). This memory disruption could be related to the top-down control exerted from the prefrontal cortex to the posterior cortices, indeed, distracters would be more processed when the memory load increases (Posner, 1990; Shallice, 1991; De Fockert, 2001). This, in turn, could explain why, in our study, regardless of the stimulation, subjects' accuracy was only partially affected from the number of the non relevant items or memory load *per se* but performance was worsened when the highest memory load and the highest number of distracters were presented together. Following this line of reasoning, if the control exerted from prefrontal cortex to the posterior cortices increases with increasing memory load in order to inhibit the processing of not relevant items (Posner, 1990; Shallice, 1991; De Fockert, 2001), the more the number of visual distracters to inhibit or the brain areas to disengage the more the need for an inhibition in the posterior cortices.

In the mammalian brain, such a kind of inhibition occurs in the alpha frequency band (Klimesch, 2007; Jensen, 2010) thereby we can argue that our stimulation at alpha frequency enhanced working memory when an higher memory load required a stronger inhibition in visual areas to avoid the processing of contralaterally presented distracters.

In line with this hypothesis, a recent study found an increase during working memory task in the parieto-occipital areas related to the need of closing the dorsal information flow

from visual areas. Specifically, the more the memory load, the higher the posterior alpha activity, especially when the distracters and the relevant items are perceptually similar (Shimi, 2013).

This is the first study using  $\alpha$ -tACS in the parieto-occipital cortex to improve working memory performance, previously, a similar result was reported by Sauseng and colleagues, who have shown that enhancing alpha power with 10 Hz rTMS, increases memory capacity when applied ipsi-laterally to the hemifield with the relevant items, while decreases memory capacity when applied contro-laterally (Sauseng, 2009).

Inserting themselves in this strand of research, our results expand this previously reported works, highlighting that alpha enhancement in the parieto-occipital cortex plays a selective role in working memory depending on both the memory load and the presented distracters.

At higher visual memory loads a higher parieto-occipital disengagement is needed, that means that an enhancement of the alpha power have to be provided. We can argue that tACS was effective only when an alpha entrainment was really needed in order to overcome the memory limit and to suppress the higher risk of processing the distracters.

From another point of view, subjects with poor memory performances could allocate attentional resources also to irrelevant stimuli, reflected, during the delay period, as an increased memory load (Zanto, 2009). Specifically, an alpha power increase suppresses visual inputs in order to devote resources to the brain regions involved in the active maintenance of relevant stimuli, avoiding the incoming of non relevant items and allowing to maintain an internally directed focus of the attention (Zanto, 2009).

A florid strand of research have been provided about the role of alpha oscillations in attentional processes and it is widely accepted that appropriate top-down allocation of attentional resources is critical for successful WM (Luck and Vogel, 1997; Hasher et al.,

2006). An alpha enhancement has been found in anticipating visual distracters during an externally directed attention task (Fu, 2001; Ruff, 2006) as well as during the internally directed attention in the retention interval of a working memory task (Cowan, 1988).

These evidences found a further confirm in neuro-imaging studies showing a mechanistic overlap between attention and working memory (LaBar, 1999; Awh and Jonide, 2001). One can argue, therefore, that, due to our stimulation protocol, we cannot elucidate exactly if our effects are due to an improvement of attention processes, (i.e. allowing a better allocation of the limited available resources and a more effective suppression of the contralateral visually presented distracters) or due to a more direct effect on memory phases such as the retention interval. Effectively, these two interval of times are characterized by two different locus of attention, external the former while more internal the latter. Unfortunately, in our paradigm we cannot rule out clearly the effect of the stimulation at alpha frequency in attention, being the stimulation carried out since the cue presentation until the end of the retention interval, to address this issue a shorter stimulation paradigm would be useful, unlikely we cannot administer shorter tACS trains due to its proved inefficacy (Vossen 2015; Braun 2017).

On the other hand, to address this point a general issue needs to be discussed: previous studies reported that during attention processes, the phase of alpha oscillations before stimulus presentation modulates synaptic spiking, maximising stimulus detection and subsequently memory processes (Cross, 2017). Likewise, in the memory domain, an increased alpha synchronization during encoding, predicts enhanced performance on recognition memory tasks (Jensens, 2002). Similarly, in an elegant recent work using cue and retrocue during memory tasks, Meyers and colleagues did not found any differences in alpha power neither in the cue (attentional stage) nor in the retro-cue presentation (memory stage), suggesting a similar pattern of alpha activity underlying the two different

processes in the different phases of a memory task (Meyers, 2015).

Therefore, probably, with our stimulation paradigm we affected either attentional-pre-encoding processes and memory mechanisms, both depending on alpha enhancement, reaching thereby a memory improvement.

Moreover, as several studies have shown, items that can be retained in memory at once are about four (Luck, 1997; Alvarez, 2004; Cowan, 2005), and a decline in recognition memory performance can be observed with increasing the numbers of items even at small set sizes. It is likely that limited visual memory resources must be shared between presented items, such that, increasing the number of the items, these are stored with decreased precision (Bays, 2008).

Looking at the neuronal levels, information is encoded by means of the simultaneous activity of a large number of neurons, a neuron encodes informations about one stimulus, thereby, when multiple items have to be retained, the total number of neurons have to be shared between the different items (Bays, 2008). Because of the presence of a certain amount of noise, reducing the number of neurons representing an item will increase variability in the population estimate, and, consequently, the precision with which the item is represented will be reduced. (Bays, 2008).

Set size related neuronal activity has been found in the posterior parietal cortex and it can predict visual short term memory capacity (Todd and Marois, 2004), the proved role of parietal cortex in maintaining attention directed to the relevant items is accompanied by the evidences of this cortex as a limited capacity store, indeed, representations are limited by a fixed number of objects at different spatial locations during both encoding and maintenance of visual short term memories (Todd and Marois, 2004).

Following this line of reasoning, we can argue that our parietal stimulation at alpha frequency, inhibiting non relevant information processes, could have allowed the release



of several neuronal population that have been allocated in the processing of the relevant items, expanding, thereby, memory capacity.

One of the fundamental results of this study is the frequency specificity of tACS effects, indeed we administered two different frequencies of stimulation together with a sham stimulation in two different groups of subjects. We found a positive result, reflected as a memory improvement only in the group that underwent to 10 Hz tACS.

Finally, next to the improvement in memory performance for ipsilaterally presented items, we did not find the expected impairment for contralaterally presented items. This lack of results can be a consequence of our task's structure. Indeed, in our task, to avoid higher charges on the memory system (Zanto, 2009), stimuli positions were maintained constants and subjects were instructed to pay attention to the colour of the squares, while the position did not change.

Maintaining fixed the position and changing the colours, probably, charged more the ventral stream, involved in the processing of the visual features of the objects, than the dorsal pathway, devoted mostly to the spatial features of the objects (James, 2002). In line with this reasoning higher levels of alpha activity have been found in the parieto-occipital cortex during the retention of face identities (engaging more the ventral stream), compared with retention of face position and orientations (engaging more the dorsal pathway) (Jensen, 2007). Specifically, the authors suggest that the inhibition of the dorsal stream together with the engagement of the ventral pathway is reflected by a parieto-occipital alpha synchronization followed by a gamma synchronization in the occipital lobe (Jensen, 2007). Thereby, probably the engagement of the ventral stream can account for the absence of a disruption in memory for colours as well as for an improvement in memory performance when the dorsal pathway is disengaged by means of an alpha power enhancement.

Finally, this study places itself inside a stream of recent evidences suggesting a new role for alpha oscillations, overcoming the previously suggested idea of alpha as an idling rhythm (Pfurtscheller, 1996). We suggest that alpha activity serves as a gating mechanism, modulating memory encoding within thalamo-neocortical-hippocampal network and its role in distractors suppression as well as in disengagement of task irrelevant regions is one time more confirmed.



## CONCLUSION

Despite the first brain rhythm was discovered in the second decade of the XIX century, only in the last years, a wide consensus has been provided on the functional role of brain oscillations in cognitive functions. The exciting possibility to link behaviour to oscillations attracts day by day a growing number of scientists. As a consequence, in the last years, electroencephalography has been rediscovered as a flexible tool to obtain a direct measurement of the changes in the rhythms of the brain during behavioural tasks. In the same time, several researches have been dedicated to the modulation of the recorded brain oscillations by means of tES.

Allowing stimulation with alternating currents, tACS is the most suitable tool for this purpose.

The present work reports the effect of tACS in memory performance in healthy subjects. We found that when applied at alpha frequency in the posterior regions tACS affects memory performance in a frequency dependent manner.

These studies insert themselves in a growing number of evidences showing tACS effects on both behavioural performance and brain neuronal activity, as recorded using EEG. Unluckily, next to this body of researches, in the last few years, several studies reporting negative results of tACS have been provided.

Mixed and controversial results are rather normal in research, especially in a new area such as tACS application, characterized by a wide number of parameters and large degrees of freedom in application's choice.

To realize tACS potentiality, reliable parameters and safe protocols are needed. To date there is no consensus in the scientific community about the best tACS montages to reach given behavioural or physiological outcomes. Moreover, tACS have been often defined as a promising

tool, indeed, offering the possibility to externally manipulate brain oscillations, it can be used for therapeutic aims.

Probably, in the future, tACS will be applied to treat oscillation-related disorders, but to reach such a kind of result, further investigation about mechanisms underlying stimulation are needed. Aware of the distance from a complete knowledge of tACS mechanisms, the present work provides some insights about the stimulation protocol to affect working memory performance, as well as it highlights the need for converging of evidences from different methods. Indeed, whether on one hand, the final aim is the behavioural change, on the other hand, to investigate tACS effects juxtaposing other techniques such as electroencephalography and transcranial magnetic stimulation, as well as evidences coming from computational models and in vivo studies, is the main requirement for these initial approaches to the technique.

Additionally, our results insert themselves in a strand of research that, overcoming the traditional theories of alpha as an idling rhythm, suggests a new active role for alpha oscillations in cognition and, specifically, in memory processes. Indeed, all the reported experimental results state in favour of those theories that, overcoming the traditional idea of alpha as an idling rhythm, recognize alpha as an active rhythm, able to play a crucial role in the interplay between different brain regions in order to reach optimal cognitive performances. Despite its old story, this brain rhythm seems to reserve still a large number of surprises to the scientific community, revealing, day by day, new different and surprising roles in the brain functioning.

Finally, going back to tACS, the present work, using one of the newest brain stimulation techniques to modulate one of the oldest brain rhythms, does not move the balance needle towards the effectiveness of tACS in impacting brain rhythm but it is a grain of sand going towards the research of reliable parameters in the use of brain stimulation, in order to shade further light in the shadow of tES and last, but not least, in order to pull out from the background noise the functional importance of the rhythms of the brain.

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