
13 Transcranial Magnetic and Electric Stimulation in Perception and Cognition Research

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13.1 INTRODUCTION

In recent years, we have witnessed the emergence of new techniques for studying the mechanisms that underlie perceptual and cognitive function in the human brain. An important contribution has come from the introduction of non-invasive brain stimulation (NIBS). The development of NIBS techniques to study perception and cognition constitutes a significant breakthrough in our understanding of the changes in the brain that may account for behavioral plasticity. NIBS approaches aim to induce changes in the activity of the brain, which can lead to alterations in the performance of a wide range of behavioral tasks (Sandrini et al. 2011). NIBS techniques that are used to modulate cortical activity include transcranial magnetic stimulation (TMS)

(see Chapter 1) and transcranial electric stimulation (tES) (see Chapter 4). TMS and tES can transiently influence behavior by altering neuronal activity through different mechanisms, which may have facilitative or inhibitory effects. The relevance that NIBS has recently gained in the field of cognitive neuroscience is mainly derived from its ability to transiently probe the functions of the stimulated cortical area/network by changing behavior. These behavioral changes can sometimes be related to its effects on modulating cortical excitability, but the explanatory route is not always direct. This opportunity to probe and modulate functional brain mechanisms opens up new possibilities for basic cognitive neuroscience and in the field of cognitive rehabilitation in directing adaptive cognitive plasticity in pathological conditions.

13.2 TRANSCRANIAL MAGNETIC STIMULATION

AQ1 TMS is a technique that can be used to investigate brain-behavior relationships and to explore the state of different regions of the brain (see Chapter 1 for an overview on technical aspects). Since its discovery (Barker et al. 1985), TMS has been used to investigate the state of cortical excitability, and the excitability of cortico-cortical and cortico-spinal pathways (Rothwell et al. 1987). Moreover, this technique has been used in cognitive neuroscience to investigate the role of a given brain region in a particular cognitive function (Robertson et al. 2003) and to examine the timing of its activity (Walsh and Cowey 1998, 2000). TMS is a tool that involves the induction of a brief electric current in the cortical surface under a coil, which causes a depolarization of a population of cortical neurons. The spatial and temporal resolution of this technique enables the investigation of two important questions in cognitive neuroscience: what information is processed in a given brain structure, and when this processing occurs (Sandrini et al. 2011, Walsh and Cowey 2000, Walsh et al. 1998). Accordingly, TMS has been used in many different cognitive domains to establish causality in brain-behavior relationships.

The results of functional neuroimaging (PET, fMRI) and high-resolution electroencephalography (EEG, MEG) experiments have revealed important correlative evidence for the involvement of a number of brain regions in perception and cognition. Neuroimaging and EEG techniques based on *in vivo* measurements of local changes in activity provide the best spatial and temporal resolution available. Functional neuroimaging is helpful in identifying brain regions involved in a given task; however, it cannot distinguish between the areas that play a critical role in the task (Price and Friston 1999).

Numerous lesion studies have reported a putative role in brain areas dedicated to the execution of cognitive tasks, and this approach is still very productive. Neuropsychology is, of course, a valuable bedrock of information about brain organization and function. Nevertheless, studies that attempt to infer normal function from a single patient with brain damage are susceptible to criticism because, among other issues, such cases provide evidence about the brain organization of a single individual and may not be generalizable to the population as a whole. A second, more important criticism leveled at these studies is that chronic brain lesions can often lead to plastic changes that affect the damaged region and may cause undamaged subsystems to be used in new ways. Therefore, the behavioral changes that are

observed could reflect the functional reorganization of the intact systems rather than the loss of the damaged system. Thus, results from single cases, while extremely valuable, must always be interpreted with some caution, and it is important to obtain converging evidence using a variety of methods.

The use of TMS has the advantage of combining lesion and neuroimaging approaches, which allows for more information to be obtained in functionally relevant areas. Therefore, TMS is an excellent tool for directly investigating the functional participation of a brain area in an ongoing cognitive process (Walsh and Cowey 1998). This approach does not depend on the measurement of electrophysiological or hemodynamic responses to cognitive challenges; therefore, it complements traditional neuroimaging techniques by offering the unique opportunity to directly interfere with and investigate cortical area functions and the related neuronal circuitry during the execution of a task.

13.3 GENERAL ASPECTS IN THE USE OF TMS

We now know more about some of the basic properties of TMS effects. These properties depend on several technical parameters, the intensity (% of maximum stimulator output or % of motor threshold determined by the stimulation intensity necessary to produce a response of at least 50 μ V in amplitude in a relaxed muscle in at least 5 out of 10 consecutive stimulations [Rossi et al. 2009]), the number of stimulator discharges (frequency), the coil orientation, coil shape and dimension (focality, with a circular coil being less focal than a figure-eight-shaped coil), and the depth of stimulation as well as the possible interactions between these factors. The effects also depend on a number of variables related to the stimulated subject, including age, gender, eventual pharmacological treatments, and the activity state of the subject (Landi and Rossini 2010, Miniussi et al. 2010, Silvanto et al. 2008). This basic knowledge and selection of opportune parameters are essential when planning TMS studies.

A direct demonstration of the intimate mechanisms of TMS in the field of cognitive neuroscience is still lacking, although it is reasonable to believe that two possible mechanisms are at play. One mechanism implies the interruption of neural processes (a reduction in signal strength (Harris et al. 2008b). This might reflect an alteration in membrane permeability directly induced by TMS or an enhancement of inhibitory GABAergic activity, which is more likely the case (Mantovani et al. 2006, Moliadze et al. 2003). The other mechanism that may explain the TMS effect on cognition has been attributed to an introduction of random activity into the system (neural noise) (Harris et al. 2008b, Miniussi et al. 2010, Ruzzoli et al. 2010, 2011). Both of these mechanisms are consistent with the impact of TMS on depolarizing neurons.

In the field of cognitive neuroscience, TMS has been mainly used for the stimulation of cortical areas with the aim of interfering with cognitive processing at a precise time during task execution (Sack and Linden 2003). This type of application is called online TMS, and the functional impact is due to the ability to impinge on neuronal function temporarily, which modifying information processing that is dependent on the activity of the involved neurons (Ruzzoli et al. 2010, Silvanto et al. 2007).

In this respect, the specificity of TMS is remarkable in space and time. TMS combines good spatial and temporal resolution, and the rapid rise-time and short duration of the magnetic pulses offer millisecond precision. It is difficult to determine the exact spatial extent of TMS but some strong inferences can be made. For example, one can produce phosphenes in different regions of the visual field with an accuracy of 1° – 2° of visual angle. In the motor cortex, one can selectively activate cortical representations of finger muscles without affecting other finger muscles or facial representations. The distinction between these areas is of the order of 1–2 cm across the cortex. This does not mean that the induced field only affects that 1–2 cm of cortex. Rather, it is a functional way of determining the physiological efficacy of the spread of the stimulation. When one induces a phosphene in a given part of the visual space the extent of that phosphene is a good measure of the amount of stimulation that is above the threshold for neuronal activation.

Temporal resolution is related to the duration of a single TMS pulse and its physiological effects over the area. The physical duration of the TMS pulse is very brief and is on the order of microseconds (less than 1 ms), whereas physiologically induced effects are more complex and last for approximately several hundred milliseconds (Moliadze et al. 2005). It is clear, however, that not all of these physiological effects are functionally effective. This is a temporal analogue of the spatial resolution issue. Although there are measurable effects of a TMS pulse that last for several hundred milliseconds, it is evident that single pulses can have effects with a resolution of tens or even 1 or 2 ms (Amassian et al. 1989, Corthout et al. 2003, Pascual-Leone and Walsh 2001), which means that the excess, recordable activity is not functionally effective. In this respect, TMS can be applied at different time points during the execution of a perceptual or cognitive task to provide valuable information about when a brain region is involved in that task.

The initial application of TMS involved the delivery of single magnetic pulses. More recent technological advances allow for the delivery of rhythmic trains of magnetic pulses in sequences with a repetition rate as fast as 100 Hz, a technique that is called repetitive TMS (rTMS). rTMS can be used to map the flow of information across different brain regions during the execution of a task with a large temporal window. For example, Harris (2008) investigated whether neural activity in the parietal cortex is essential for successful mental rotation by observing the effects of disrupting this activity during the execution of a mental rotation task. rTMS was applied at 200–400, 400–600, or 600–800 ms after the onset of a mental rotation trial on the left or right parietal cortex. Only stimulation of the left parietal cortex at 400–600 ms affected the performance reliably, which provided information on the brain area involved and when it functioned during the task.

In summary, rTMS delivered during the execution of a cognitive task triggers synchronous activity in a subpopulation of neurons located under the stimulating coil, which results in a disruption in the pattern of activity that occurs at the same time as the stimulation (Jahanshahi and Rothwell 2000) and enables the adequate execution of the task. This allows information to be obtained about the timing of the contribution of a given cortical region to a specific behavior, which enables the study of the mental chronometry of a cognitive process, using TMS with high temporal resolution (Pascual-Leone et al. 2000, Sack 2006).

AQ3

There are two distinct approaches to the application of rTMS. Manipulating cognitive processing when rTMS is applied during the performance of a task, as just described, is called online TMS. In contrast, rTMS may be applied several minutes before the subject is tested on the task, which is defined as offline stimulation (see Rossi et al. [2009] for a classification of the TMS approaches).

Presumably, in the online application, the faster the rTMS frequency, the greater the disruption of the activity of the targeted brain region, and the greater the final behavioral effects will be. However, the potential risks are that greater and more prominent nonspecific behavioral and attentional effects will be observed, which can make the results more difficult to interpret (Rossi et al. 2009). Moreover, the effects induced by online stimulation are generally short-lived, lasting approximately a few hundred milliseconds to a few seconds.

The alternative offline approach, which has achieved some popularity over the last few years, is to stimulate the site of interest for several seconds, using theta burst stimulation (TBS) (Huang et al. 2005, Vallesi et al. 2007) or for minutes (5–30 min) at a given frequency (low or high) “before” beginning a cognitive task. In this case, rTMS affects the modulation of cortical excitability (increased vs. decreased) beyond the duration of the application itself, and the aim of rTMS is to alter cognitive performance. The division between high and low frequency is not arbitrary. The cut-off is empirically based on direct and indirect measurements of brain activity as well as on behavioral outputs. Therefore, treating low- and high-frequency rTMS as separate phenomena is essential because the application of these two types of stimulation for several minutes might produce distinct effects on brain activity. Converging evidence has indicated that continuous rTMS below 1 Hz (low frequency) causes a reduction in neuronal firing and decreases cortical excitability locally and in functionally related regions. By contrast, intermittent rTMS above 5 Hz (high frequency), which leads to increased neuronal firing, appears to have the opposite effect (Chen et al. 1997, Maeda et al. 2000, Pascual-Leone et al. 1994). However, studies have not always confirmed the strict and unequivocal association between behavioral improvement and excitation or between behavioral disruption and inhibition (Andoh et al. 2006, Drager et al. 2004, Hilgetag et al. 2001, Kim et al. 2005, Waterston and Pack 2010). Therefore, we need to separate the physiological effects from the behavioral effects (Miniussi et al. 2010).

Some evidence has suggested that the effects induced by different offline rTMS approaches were site specific; however, they were not site limited (Bestmann et al. 2008). Thus, the long-term consequences induced by sustained and repetitive brain stimulation were most likely due to activity changes in a given network of cortical and subcortical areas rather than local inhibition or excitation of an individual brain area (Selimbeyoglu and Parvizi 2010). This means that brain stimulation can modulate the ongoing properties of a neuronal network by amplifying or reducing its activity. Moreover, the stimulated area cannot be considered to be isolated from its own functions or the functional status induced by the state of the subject (Harris et al. 2008b, Pasley et al. 2009, Ruzzoli et al. 2010, Silvanto et al. 2008). These aspects suggest that the functional effects induced in one area could be co-opted into different functions in other areas depending on the mode of activation or which of its interconnected networks was activated (Harris et al. 2008b, Selimbeyoglu and Parvizi 2010, Silvanto et al. 2005).

Moreover, the effects of offline rTMS using specific protocols have been shown to outlast the stimulation period itself, and synaptic long-term potentiation and depression (LTP and LTD, respectively) have been suggested to account for these modifications (Cooke and Bliss 2006, Thickbroom 2007, Ziemann and Siebner 2008). In general, one of the advantages of TMS is that it can be used on a larger population of subjects, and the location of the coil can be precisely controlled using a neuronavigation approach. Manipulation with rTMS can be meaningful if the coil position can be accurately localized on an individual basis, especially in situations where inter-individual differences are particularly relevant (Manenti et al. 2010). Therefore, in some cases, it is very important to guide the positioning of the coil over the target area using a neuronavigation system with single subject functional magnetic resonance imaging (Sack et al. 2009). Nevertheless, it should also be mentioned that even though the location of the stimulation can be precisely controlled, the spatial resolution of the induced effects has not been completely determined (Bestmann et al. 2008). Therefore, sometimes the spatial resolution of rTMS effects hinders a precise interpretation of the observed functional effects in terms of anatomical localization. For example, the discharging coil produces a clicking sound that may induce arousal and disrupt task performance irrespective of the exact demands of the experimental design. While this issue may be addressed by giving the subject earplugs, this approach is not practical in all cases, such as in language experiments that require the subject to listen to voices or sounds. Therefore, a control condition must be used to try to ensure that changes in performance are specifically attributable to the effects of TMS on the brain. One of these controls is a sham (placebo) stimulation, which should be used to obtain a baseline measurement. In the sham condition, one should ensure that no effective magnetic stimulation reaches the brain (Rossi et al. 2007) while all other experimental parameters are identical. Another approach is the stimulation of contralateral homologous areas (homotopic) or vertex areas while the subject performs the same task under identical auditory and somatosensory perceptions. This allows for the comparison of the effects of rTMS at different sites where only one site has functional relevance. Finally, it is also possible to observe subject's behavior across a number of distinct tasks following stimulation at one site. Consequently, many studies have also taken the approach of observing behavior across several distinct tasks following stimulation at one site (Sandrini et al. 2011). Following stimulation at one site, only one task is functionally related to the stimulated site.

All of these technical controls are critically important in experiments that involve cognition because the functional effects that can be induced after stimulation of a cortical area can have different manifestations depending on which of the interconnected networks are engaged in a given task (Sack and Linden 2003).

13.4 TMS AND COGNITIVE NEUROSCIENCE

The use of TMS as an investigative tool in the study of specific cognitive functions has been previously established (Walsh and Cowey 2000). In the last few years, many TMS studies have significantly contributed to our understanding of the role of different cortical sites in various perceptual and cognitive functions. For example,

the application of TMS over prefrontal sites (for a review, see Guse et al. 2010) has allowed for understanding the role of these sites in cognitive tasks involving working memory (Pascual-Leone and Hallett 1994), episodic memory (Rossi et al. 2001, 2004, Sandrini et al. 2003), and implicit learning (Pascual-Leone et al. 1996). Moreover, spatial attention (Ashbridge et al. 1997, Thut et al. 2005), somatosensation (Seyal et al. 1995), object recognition (Harris et al. 2008a), and numerical processing (Rusconi et al. 2005, Sandrini et al. 2004) are a subset of the functions that have been investigated through stimulation of the parietal cortex. TMS over the occipital cortex has been used to examine a number of aspects of visual processing as well as visual motion (Ruzzoli et al. 2010) and color perception (Maccabee et al. 1991). Additional studies have applied TMS over the temporal cortex to understand the functions related to language and semantic cognition (Pobric et al. 2010).

Although it is impossible to summarize all the studies that have used TMS in the field of cognitive neuroscience in an exhaustive manner, it is possible to report the principal questions that may be addressed with TMS in cognitive function studies. As highlighted by Jahanshahi and Rothwell (2000), TMS may be used as a tool to investigate and understand the role and timing of the involvement of a target area during a specific performance, the contribution of different sites to different aspects of a task, the relative timing of the contribution of two or more areas to task performance and the function of intracortical and transcallosal connectivity. In general, the possibility of understanding the location, timing and functional relevance of the neuronal activity underlying cortical functions makes TMS an essential technique in perception and cognitive research.

13.5 TRANSCRANIAL ELECTRIC STIMULATION

tES, like TMS, is a technique that can be used to investigate brain-behavior relationships and explore the state of different regions of the brain. The tES technique (see Chapter 4 for an overview of the technical aspects) involves applying weak electrical currents directly to the head for several minutes. These currents generate an electrical field that modulates neuronal activity according to the modality of the application, which can be direct (transcranial direct current stimulation, tDCS), alternating current (transcranial alternating current stimulation, tACS), or random noise (transcranial random noise stimulation, tRNS).

tDCS applied through the skull was shown to directly modulate the excitability of motor (Nitsche and Paulus 2000, 2001) and visual (Antal and Paulus 2008) cortices in human subjects. tDCS is applied for a much longer duration than TMS, and has been shown to modulate the resting membrane potential and related cortical activity and induces transient functional changes in the human brain (Nitsche and Paulus 2000, 2001).

From a methodological prospective, most of the general points made for TMS are valid for tES in cognitive neuroscience research; however, there are a few exceptions. There is a reduction in spatial and temporal resolution (Dmochowski et al. 2011), although there is an advantage in terms of applicability. tES does not produce the noise and discomfort produced by TMS; therefore, changes in performance are not attributable to nonspecific effects (tactile or auditory).

With regard to the mechanism and efficacy of tDCS, the vast majority of evidence comes from stimulation of the primary motor cortex (M1). It is still not clear to what extent these findings are transferable to other areas of the cortex, although it is likely that some of the mechanisms of action are similar. Cognitive neuroscience using tES can still be considered a nascent field; therefore, in this chapter, we describe the current knowledge of the physiological and behavioral effects of tES on perception and cognition.

13.6 tDCS AND VISUAL PERCEPTION

Several studies have investigated the effect of anodal and cathodal tDCS over the occipital cortex (for an overview, see Antal and Paulus 2008). In a study using large Gabor patch stimuli with a spatial frequency of 4 cycles/degree, only cathodal stimulation significantly decreased static and dynamic contrast sensitivity (Antal et al. 2001). However, a recent study (Kraft et al. 2010) demonstrated that anodal tDCS of the visual cortex could also cause a transient increase in contrast sensitivity for central positions at eccentricities smaller than 2°. In this study, cathodal stimulation of the visual cortex did not affect contrast sensitivity. This might result from the different stimulation durations used in the two studies; however, it also may be due to the specific visual stimuli used.

When applied over the visual cortex, tDCS is capable of modifying the perception threshold of phosphenes. Induction of phosphenes can be evoked by single pulses or by repetitive TMS of the visual cortex (V1). These phosphenes are commonly described as spots of light or stars that tend to persist during the time of the stimulation and disappear with its cessation. Cathodal stimulation increases, whereas anodal stimulation decreases phosphene thresholds (PT) (Antal et al. 2003a,b). Compared to PT measurements, the measurement of visual evoked potential (VEP), which characterizes occipital activation in response to visual activation, is a more objective and widely accepted method for evaluating visual-cortical function in humans. Using montages obtained from a number of stimulating electrode positions, only the occipital (Oz)-vertex (Cz) electrode position was effective in inducing after-effects, which shows that the stimulation efficacy of tDCS highly depends on the direction of the current flow (Antal et al. 2004a). This finding is similar to what is observed using tDCS in M1 (Nitsche and Paulus 2000). Cathodal tDCS over V1 decreased the amplitude of a negative waveform at 70 ms, the N70 component of the VEP, whereas anodal tDCS increased N70 amplitude. However, significant effects can only be observed when low-contrast visual stimuli were shown. High-contrast stimuli most likely activate the appropriate visual-cortical pathways and areas optimally; therefore, subthreshold excitability modulation induced by tDCS could not produce a clear change in the VEP amplitude. With regard to stimulation polarity, the opposite effect was also observed in another study, and anodal stimulation resulted in a reduction in the P100 amplitude, whereas cathodal stimulation increased the P100 amplitude (Accornero et al. 2007). This apparent discrepancy may be due to the different VEP modalities used. The first study used a sinusoidal onset pattern, whereas the second study used a checkerboard pattern-reversal stimulation. Furthermore, the position of the reference electrode (Cz in the first study, and the neck in the second study) could have a strong influence on DC-induced after-effects.

Results from several studies provide evidence that external modulation of visual neural excitability using tDCS goes beyond V1 and could influence complex, visual adaptation-related processes. Neural cells in the MT and medial-superior temporal (MST) areas (the human analogue is called V5 or MT+) are particularly sensitive to motion, and many cells in these areas selectively react to optical flow (Lappe et al. 1996). Direct current stimulation over MT+/V5 using tDCS affected the strength of the perceived motion after-effect (MAE), which supports the involvement of MT+/V5 in motion adaptation processes (Antal et al. 2004d). Interestingly, both cathodal and anodal stimulation over this area resulted in a significant reduction in the MAE duration. One possible explanation of this effect is that tDCS affects the interaction between the neural representations of different motion directions in MT+/V5. It has been suggested that adaptation results in an imbalance of mutual inhibition processes between different motion directions, which will lead to an illusory perception of motion. Modulation of neural excitability with anodal and cathodal tDCS might result in attenuated expression of the adaptation-induced imbalance in both cases, and consequently, weakened motion after-effects.

In addition, cathodal stimulation to the right temporo-parietal cortex reduced the magnitude of facial adaptation, whereas stimulation over V1 did not have a significant effect (Varga et al. 2007). These data imply that lateral temporo-parietal cortical areas play a major role in facial adaptation and in facial gender discrimination, which supports the idea that the observed after-effects are the result of high-level, configurational adaptation mechanisms. In agreement with previous studies, the inhibitory effect of cathodal tDCS on adaptation may be related to the focal diminishment of cortical excitability due to membrane hyperpolarization.

Recent results also demonstrated that anodal tDCS applied over the posterior parietal cortex (PPC) is a promising technique for enhancing visuo-spatial abilities when combined with a visual field exploration training task. When anodal tDCS was applied to the right PPC, it increased the training-induced behavioral improvement of visual exploration when compared to sham tDCS (Bolognini et al. 2010). In addition, stimulation of the right PPC enhanced covert visual orientation and stimulation of this area by itself, even without associated training or enhanced visual exploration. Unilateral stimulation of the PPC bidirectionally modulated the performance of healthy subjects in a visual dot-detection task depending on the side of stimulation and current polarity (Schweid et al. 2008, Sparing et al. 2009). Anodal tDCS improved the detection of contralateral stimuli, whereas cathodal tDCS ameliorated the detection of ipsilateral stimuli and worsened the detection of contralateral stimuli using bilateral stimulation conditions with an extinction-like pattern. These findings are encouraging for future interventions in brain-damaged patients with visuo-spatial disabilities.

In summary, the results from the studies mentioned above show that the effects of anodal and cathodal stimulation highly depend on the task and on the activity state of the visual system. To date, the definition of relevant stimulation parameters, such as task type, strength and duration of stimulation, size of electrodes, and position of electrodes, have been elaborated thoroughly for the motor system (for a review, see Nitsche et al. 2008); however, this still needs to be established for the visual system (Jacobson et al. 2011).

13.7 tDCS AND MOTOR/VISUO-MOTOR LEARNING

As learning requires functional changes in the cortical construction that involves modifications of excitability, the induction of neuroplastic changes using tDCS is an interesting tool with which to modulate these processes. tDCS has been investigated as a means of modulating visual perception and as a tool that can modulate cortical excitability to reveal causal relationships between brain regions, cognitive functions and facilitate skill acquisition and learning. Generally, combining tDCS with behavioral interventions could be a powerful method to enhance the response of the target system and increase behavioral performance. However, the effects of tDCS on learning and cognitive processing not only depend on the stimulation parameters applied, but also on the stimulated area and task used. For example, it has been shown that anodal stimulation of M1 specifically improves implicit motor learning in its acquisition phase, whereas stimulation of other motor-related areas, such as the premotor and prefrontal cortices, had no effect (Nitsche et al. 2003). However, studying the functional effects of tDCS over the visual areas revealed that the percentage of correct tracking movements in a visuo-motor task significantly increased during and immediately after cathodal tDCS of V5. In contrast, anodal stimulation had no effect when a previously learned manual visuo-motor tracking task was applied (Antal et al. 2004c). Indeed, the effect of cathodal tDCS is highly specific in reducing excitability in V5 and enhancing performance in this visually guided tracking task. This effect is most likely explained by the complexity of the perceptual information processing needed for the task. This task most likely produces a noisy activation state in its neuronal patterns in response to different directions of movement. In this activation state, cathodal stimulation may have a focusing effect by decreasing global excitation levels and diminishing the amount of activation of concurrent patterns below the threshold for eliciting a (Antal et al. 2004c). Therefore, cathodal stimulation increases the signal-to-noise ratio and improves performance. However, when tDCS was applied during the learning phase of the same visuo-motor coordination task in a different subject group, performance was significantly increased 5–10 min after the beginning of anodal stimulation of V5 or M1, whereas cathodal stimulation had no significant effect (Antal et al. 2004b). The positive effect of anodal tDCS was restricted to the learning phase, which suggests a highly specific temporal effect of stimulation (Stagg et al. 2011).

However, tDCS can also influence long-term motor skill learning. Reis et al. (2009) used a computerized motor skill task to evaluate the effects of anodal tDCS during the course of learning. Speed and accuracy were measured on the training day and on the days before and after training. The experimental training group received five sessions of anodal tDCS for 20 min over the left M1 region, whereas the two control groups received either sham or cathodal tDCS. Anodal tDCS showed greater effects on learning over the entire training period when compared to cathodal or sham stimulation. These effects were maintained in follow-up sessions, and the anodal group still performed better than the two control groups.

Interestingly, in some tasks, such as the Jebsen-Taylor hand function task that mimics daily activities and is often used in stroke research, the increase in performance was only observed when the brain area of the non-dominant hand was stimulated, which suggests a ceiling effect of the stimulation (Boggio et al. 2006).

Generally, compared to the M1, the after-effects are relatively short lasting in the visual areas using the same stimulation durations. However, visual and motor cortices vary with regard to factors influencing neuroplasticity and in their excitatory/inhibitory circuitry. Differences in cortical connections and neuronal membrane properties, including receptor expression, between primary motor and visual cortices may also account for the contrasting responses to the application of tDCS. Furthermore, the results indicate that gender differences exist within the visual cortex of humans and may be subject to the influences of modulatory neurotransmitters or gonadal hormones, which induce short-term neuroplasticity (Chaieb et al. 2008). Alternatively, it is possible that the threshold for stimulating M1 is lower than the visual areas.

13.8 tDCS AND COGNITION

tDCS can modulate many aspects of cognition. However, studies investigating the influence of tDCS on cognitive function show facilitatory as well as inhibitory effects. In general, considering the bipolar nature of tDCS, it would be too simplistic to assume that anodal stimulation has a beneficial effect and cathodal stimulation has a disrupting effect on cognition. For example, Kincses et al. (2004) demonstrated that anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) improved implicit classification learning, whereas cathodal tDCS had no effect. Anodal stimulation of the left DLPFC also improved the accuracy of performance during a sequential letter working-memory task in healthy subjects (Fregni et al. 2005). More recently, Zaehle et al. (2011) observed that 15 min of anodal tDCS to the left DLPFC resulted in significantly greater working memory performance on a 2-back task in healthy controls when compared with sham and cathodal tDCS stimulation. In another study (Ambrus et al. 2011), the effects of tDCS over the DLPFC on categorization using the *A-not-A* dot-pattern version of a prototype distortion task was investigated. Contrary to the expectations of the authors, it was determined that anodal tDCS of the DLPFC (linked to categorization processes in previous studies) did not improve categorization performance. Rather, the prototype effect present in the sham stimulation condition disappeared in all stimulation conditions (anodal tDCS of the right and left DLPFC, cathodal tDCS of the right DLPFC). In another study, Ferrucci et al. (2008) showed that anodal and cathodal tDCS over the cerebellum disrupted practice-dependent improvements during a modified Sternberg verbal working-memory task. In addition, intermittent frontal bilateral tDCS during a modified Sternberg task impaired response selection and preparation in this task (Marshall et al. 2005). The opposing results in these studies might be due to task characteristics, for example, the Sternberg paradigm demands more complex information processing than the three-back letter task; however, the results may have been caused by the different stimulation protocols that were employed.

The state of the cortex during stimulation might also be an important factor regarding the effect of tDCS. In a study by Andrews et al. (2011), the execution of a working memory task during anodal tDCS stimulation of the DLPFC increased performance on the digit span task compared to either stimulation without the digit span task or sham tDCS with this secondary task.

To date, there are very few studies showing that tDCS over temporal areas can modulate cognitive function in healthy subjects. Language learning and visual picture naming can be improved by anodal stimulation of the left perisylvian area (Fertonani et al. 2010, Sparing et al. 2008). A more recent study demonstrated that visual memory can be enhanced in healthy people using tDCS (Chi et al. 2010). In this study, 13 min of bilateral tDCS was applied to the anterior temporal lobes. Only participants who received left cathodal stimulation along with right anodal stimulation showed an improvement in visual memory. This 110% improvement was similar to the performance of individuals with autism (who are known to be more literal) compared to normal subjects in an identical visual task. Participants receiving stimulation of the opposite polarity (left anodal with right cathodal stimulation) failed to show any change in memory performance. The authors argued that this was the first brain stimulation study to employ an identical task that had been previously used in testing subjects with autism, which suggests a possible technique for temporarily inducing an autistic-like performance in healthy people.

A recent study explored whether tDCS could also be effective in modulating multisensory audiovisual interactions in the human brain (Bolognini et al. 2010). In different sessions, healthy participants performed the sound-induced flash illusion task (Shams et al. 2000) while receiving anodal, cathodal, or sham stimulation with an intensity of 2 mA for 8 min to the occipital, temporal, or posterior parietal cortices. The perception of a single flash combined with two beeps was enhanced after anodal tDCS of the temporal cortex and decreased after anodal stimulation of the occipital cortex. A reversal of these effects was induced by cathodal tDCS. However, the perceptual fusion of multiple flashes combined with a single beep was unaffected by tDCS. This result might open new possibilities for modulating multisensory perception in humans.

13.9 tACS AND VISUAL PERCEPTION

In a recent study, it was demonstrated that tACS could induce phosphenes and interact with ongoing rhythmic activities in V1 in a frequency-specific manner (Kanai et al. 2008). In this study, an oscillatory current was applied over V1 using different frequencies to observe interactions with ongoing cortical rhythms, and the effects of delivering tACS under conditions of light or darkness were compared. Stimulation induced phosphenes most effectively when the beta frequency range was applied in an illuminated room, whereas the most effective stimulation frequency shifted to the alpha frequency range during testing in darkness. Stimulation with theta or gamma frequencies did not produce any visual phenomena. These results show that tACS can induce perceptions more effectively if it is used to strengthen spontaneously occurring oscillations. These findings might lead to new implementations of rhythmic stimulation as tools in therapy and neurorehabilitation. Nevertheless it has been suggested that current spread from the occipital electrode might evoke phosphenes in the retina (Schwiedrzik 2009).

Several recent studies, in line with tACS results, have indicated that manipulating cortical activity using rhythmic TMS can positively influence cognitive performance in normal subjects (Thut et al. 2011) and in patients affected by neural disorders,

such as unilateral neglect or dementia (Thut and Miniussi 2009). The modification of cortical activity with rhythmic electrical stimulation might regulate maladaptive patterns of brain oscillations and provide the possibility of inducing a new balance within an affected functional network. It is likely that by restoring sufficient synchronization, improvements in sensory function can be achieved.

13.10 tRNS AND LEARNING

tRNS consists of the application of a random electrical oscillation spectrum over the cortex. tRNS can be applied at different frequency band ranges over the entire spectrum from 0.1 to 640 Hz. Terney et al. (2008) have demonstrated that 10 min of tRNS at high frequency (101–640 Hz) on the motor cortex is able to modulate cortical excitability (an increase in averaged motor-evoked potential [MEP] amplitude) that persists after cessation of the stimulation. Moreover, the potential of tRNS at high frequency was also demonstrated by Fertoni et al. (2011). They applied tRNS to the visual cortices of healthy subjects and observed a significant improvement in the performance of healthy subjects in a visual perceptual learning task. This improvement was significantly higher than the improvement obtained with anodal tDCS or with low frequency (0.1–100 Hz) tRNS. Therefore, tRNS might potentiate the activity of neural populations involved in tasks that facilitate brain plasticity by strengthening synaptic transmission between neurons (Fertoni et al. 2011, Terney et al. 2008). Modulation of the efficacy of synaptic transmission can result in excitability and activity changes in specific cortical networks that are activated by the execution of the task, and these changes correlate with cognitive plasticity at the behavioral level. These data show the great potential of tRNS, especially considering the substantially reduced cutaneous sensations elicited by tRNS, which makes verum tRNS indistinguishable from placebo tRNS (Ambrus et al. 2010).

13.11 PROSPECTS FOR COGNITIVE REHABILITATION BY NIBS

TMS and tES can transiently influence behavior by producing an alteration of the stimulated cortical areas. Generally, this alteration interferes with task execution. Nevertheless, TMS and tES as reported in this chapter may also lead to enhanced performance (Antal et al. 2004a, Cappa et al. 2002, Cohen Kadosh et al. 2010, Harris et al. 2008b, Vallar and Bolognini 2011, Walsh et al. 1998).

For TMS, the facilitation effects could be due to nonspecific factors, such as general arousal due to stimulation. These effects can be directly controlled, and there are cases where TMS-induced improvements in accuracy or reaction times are not due to nonspecific factors but clearly depend on the site of stimulation or the type of task given to the participants (Miniussi et al. 2008). tES does not produce this type of nonspecific effect because the induced activation of esteroceptive somatosensory receptors is minimal, and there is no activation of the auditory system. In addition, framing the experimental hypothesis in a signal-to-noise context should also predict performance facilitation, although a reduction of signal strength would predict a performance decrease. In non-linear systems, such as the nervous system, noise can even enhance performance through a phenomenon called “stochastic resonance,”

which produces an “optimal” level of noise (Antal et al. 2004b, Miniussi et al. 2010, Ruzzoli et al. 2010, 2011, Stein et al. 2005).

These mechanisms have important implications for neurorehabilitation because, in principle, they may begin to allow for the specific enhancement of impaired functions as a component of therapeutic interventions. Most of these effects are transient (in the order of minutes) but their application, in concert with learning and plasticity processes, can perpetuate facilitatory effects beyond the end of the stimulation period, which provides important opportunities for progress.

In clinical populations, tES over the visual cortex is a promising technique for modulating residual visual capacities. In motor cognition and rehabilitation, tES has already shown its clinical usefulness, e.g., anodal tDCS improved motor performance in stroke patients with hemiparesis (Hummel et al. 2005, Tanaka et al. 2011). To our knowledge, there have been a limited number of studies where the excitability of the occipital cortex was modified for clinical rehabilitation. In vision rehabilitation, the idea of a visual prosthesis (Brindley and Lewin 1968) for blind subjects or patients with cortical visual field defects may be rejuvenated with tDCS. In cases where the excitability of the occipital cortex should be changed, such as in photosensitive epilepsy, stroke or migraine (Antal et al. 2011) the application of tES/rTMS could also be therapeutically beneficial. These are just a few examples of many recent studies that have been reported to improve cognitive abilities in patients with unilateral spatial neglect (Hesse et al. 2011), aphasia (Cotelli et al. 2011b) or memory problems (Boggio et al. 2011, Cotelli et al. 2011a).

In summary, NIBS methods are able to induce cortical plasticity modifications, which may outlast the stimulation period itself. Given this potential, there is currently a growing interest in therapeutically applying these methodologies to reduce cognitive deficits in patients with stroke or chronic neurodegenerative diseases. Although in its infancy, this approach is poised to deliver novel insight into the fundamental aspects of cognitive rehabilitation (Stuss 2011), thereby paving the way for more effective neuromodulatory therapeutic interventions (Miniussi and Rossini 2011, Miniussi and Vallar 2011, Miniussi et al. 2008, Paulus 2011).

13.12 CONCLUSIONS

There are a number of exciting prospects for the use of tES and TMS as tools to promote changes in brain activity that are paralleled by behavioral improvements. There is emerging evidence that multiple sessions may increase the duration of these behavioral effects to several weeks in healthy controls (Reis et al. 2009). According to previous studies and results from our own laboratories, tES and TMS appear to be promising methods for inducing acute, as well as prolonged, cortical excitability and activity modulation. Recently, significant efforts have been made to combine tDCS and TMS with other techniques, such as fMRI, EEG (see Chapter 12; Antal et al. 2011, Baudewig et al. 2001, Miniussi and Thut 2010, Miniussi et al. 2012, Siebner et al. 2004, 2009, Taylor et al. 2008). The combination of these techniques appears to be a very important approach in learning more about the location, time course and functional specifications of brain areas involved in visual and visuo-cognitive tasks. To make this tool relevant for basic research purposes and for clinical application, additional studies are necessary.

It is interesting to note that the effects of NIBS are proportional to the level of neuronal activation during the application of the stimulus (Epstein and Rothwell 2003). In the motor system, an increase in the amplitude of MEPs can be achieved by voluntary contraction of the target muscle (Rothwell et al. 1987). A similar effect was observed by Silvanto et al. (2007) using a neural adaptation paradigm over the visual area. These authors systematically manipulated the activity of distinct neural populations within V1 through perceptual adaptation induced before TMS application, which enabled them to study the interaction between the state of activation of the stimulated area (adapted vs. not adapted) and the neural activity induced by TMS. When TMS was applied over V1, the induced perceived phosphenes, which are generally colorless, were the same color as the adapting stimulus. Moreover, it has been showed by Antal et al. (2007) that the effect of tDCS differs if it is applied to an active, rested or fatigued cortical area (Antal et al. 2007). For example, also the induction of a phosphene by TMS is strictly related to the amount of alpha activity present in the occipital cortex (Romei et al. 2008). These findings suggest that NIBS effects are sensitive to changes in the cortical state and open the intriguing possibility that administration of NIBS while a subject is in a given condition, or as the subject performs a behavioral task, may permit the targeting of specific circuitry.

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AUTHOR QUERIES

- [AQ1] Please check if edits to the sentence starting “Since its discovery...” are ok.
- [AQ2] Please check the Running head is edited from the chapter title.
- [AQ3] The following references Harris (2008), Nitsche et al. (2008), and Thut et al. (2011) are cited in the text but not provided in the reference list. Please check.
- [AQ4] Please check the page range of Brindley and Lewin (1968) for correctness.
- [AQ5] Please provide volume number and page range for the reference Cotelli et al. (2011a).
- [AQ6] Please update the reference Miniussi et al. (2012).