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Non-invasive brain stimulation techniques can modulate cognitive processing

Abstract:

Recent methods that allow a non-invasive modulation of brain activity are able to modulate human cognitive behavior. Among these methods are transcranial electric stimulation and transcranial magnetic stimulation which both come in multiple variants. A property of both types of brain stimulation is that they modulate brain activity and, in turn, modulate cognitive behavior. Here, we describe the methods with their assumed neural mechanisms for readers from the economic and social sciences and little prior knowledge of these techniques. Our emphasis is on available protocols and experimental parameters to choose from when designing a study. We also review a selection of recent studies that have successfully applied them in the respective field. We provide short pointers to limitations that need to be considered and refer to the relevant papers where appropriate.

Keywords:

Repetitive transcranial magnetic stimulation (TMS), single-pulse TMS, repetitive TMS, transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS).

Non-invasive Brain Stimulation (NIBS) techniques

Non-invasive brain stimulation (NIBS) methods which include transcranial electric stimulation (tES) and Transcranial Magnetic Stimulation (TMS) are used to transiently interfere with or modulate cortical activity.

tES is the superordinate term for various non-invasive brain stimulation techniques that use a stimulator delivering weak electrical currents of approximately 1-2 mA between two or more electrodes attached to the scalp (Paulus, 2011, Fig. 1). According to whether direct current (DC) or alternating current (AC) is applied to the brain, the method is referred to as either transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS). If the alternating current is superimposed onto a direct current, this combination results in so-called oscillatory tDCS (oTDCS, Groppa et al., 2010). Whereas the current stays constant over time if applied via tDCS, it alternates at a certain frequency (or any combination of different frequencies) if applied via tACS or otDCS. Stimulation with a random electrical frequency spectrum is known as transcranial random noise stimulation (tRNS, Terney, Chaieb, Moliadze, Antal, & Paulus, 2008).

[Insert figure 1 here]

In TMS, a stimulating coil is positioned over the participants' head to deliver a strong and transient magnetic pulse to induce an electric current at the cortical surface (Fig. 2A). TMS can be delivered as a single pulse (spTMS) at a precise time point or as a series of stimuli in conventional or patterned protocols (also called repetitive TMS/ rTMS).

[Insert figure 2 here]

Common to all these NIBS methods is their ability to modify brain activity and in turn to influence cognitive processes (Cohen Kadosh, 2015; Kuo & Nitsche, 2012; Luber & Lisanby, 2014). In general, these techniques are well tolerated and, for tES, low-cost, and easy to apply. Together, these features make NIBS an interesting tool for noninvasive brain stimulation in basic neuroscience and clinical applications.

Why should we apply NIBS?

Causal vs. correlative evidence

The popularity of NIBS as a mapping tool for studying perceptual, motor and cognitive functions in the human brain is due to the unique possibility it offers to investigate the causal implication of an area in a specific task. Before the introduction of NIBS the causal involvement of an area could only be inferred by studying patients with brain damage. However, after an injury the brain undergoes complex reorganization so that the behavioural changes also reflect compensatory strategies and plasticity phenomena. Moreover, brain damages are rarely restricted to a specific region so that any close relation between an area and a cognitive function is hard to infer (Robertson, Theoret, & Pascual-Leone, 2003; Walsh & Cowey, 1998).

Other neuroimaging techniques such as electroencephalography (EEG) or functional magnetic resonance imaging (fMRI), on the other hand, represent purely correlational methods. In a typical neurocognitive experiment, brain activity is measured by EEG or fMRI while the participants are engaged in a specific cognitive task. In this approach, the cognitive processes serve as independent variables; whereas the physiological measures (e.g., brain oscillations or the BOLD signal) serve as dependent variables and the observed results have to be interpreted as a correlation between variations in cognition and brain activity. However, for drawing the conclusion that an area is crucially involved in a specific brain function, it is not sufficient to demonstrate neural activation during performance of a specific task. It needs to be shown that manipulation of that area also induces changes in the subjects' performance associated with the task.

NIBS techniques provide the opportunity to interfere with brain activity. Hence, the usual dependent variables (any measure of brain activity) are externally manipulated and the resulting variation in cognitive processes can be studied directly. Thus, the observed changes in brain activity and/or cognition are unequivocally related to the external manipulation (i.e., tES or TMS), providing causal evidence that a cognitive process of interest is related to a specific brain area (in case of using tDCS or rTMS) or a specific brain oscillation (in case of using tACS, otDCS or patterned TMS (Herrmann, Struber, Helfrich, & Engel, 2015; Romei, Gross, & Thut, 2010). In sum, NIBS applications offer the possibility to evaluate well-known correlations between certain measures of brain activity and cognitive processes in terms of causality.

In the following, we will describe these methods in more detail and illustrate their potential relevance for organizational research.

Transcranial Magnetic Stimulation

Brief history

The idea of stimulating the cerebral cortex to gain fundamental information about brain organization and function as well as to modulate cortical activity to treat clinical conditions has a long history. It is not surprising that following this idea, already in the mid-1700s, Caldani and Fontana (1757) applied electrical current on the brain surface of conscious men during surgical procedures; and that later on, in the attempt to discredit anti-localizationist theories, Fritsch and Hitzig (1870) were able to locate and successfully stimulate the motor cortex by inducing generalized muscle twitch in the part of the body opposite to the stimulated hemisphere. Some years later, Ferrier (1875) reported a complete functional map of the motor cortex by stimulating the exposed brain of anaesthetized animals. Interestingly he also accurately localized many brain functions by selectively stimulating sensory and prefrontal areas.

For many years, electrical stimulation has been the main available tool to investigate brain functions and structures. In most of these experiments, however, the skull was removed and electric stimulation given through a small probe directly to the surface of the cerebral cortex (Adrian & Moruzzi, 1939; Patton & Amassian, 1954). Indeed, a strong limitation of electrical stimulation is due to the high resistance imposed by the scalp and bone structures. As a consequence of these biological properties, to discharge neurons non-invasively by electrical stimulation through the scalp, and hence to find applications in human participants (Merton & Morton, 1980), it is necessary to apply high voltage stimuli to penetrate the skull and reach the cortical surface. Else much of the applied current flows along the skin and subcutaneous tissues, causing contractions of scalp muscles. The associated leakage of current makes the electrical stimulation a rather uncomfortable and not well tolerated technique (Di Lazzaro et al., 2004; Rothwell et al., 1999). Note that tES as described in this chapter uses much lower currents as it does not aim to discharge neurons (see in tES section).

A different approach to brain stimulation originated in 1896, when inspired by recent discoveries reported by Michael Faraday (see following section, Faraday, 1839), Arséne D’Arsonval put forth that it should be possible to stimulate the intact human brain by means of a strong magnetic field (d’Arsonval, 1896). Following his idea, he built a big coil of wires to generate an alternating magnetic field and asked volunteers to place their heads inside this apparatus. The volunteers experienced light sensations but also reported vertigo and dizziness. These were the first reports of physiological effects due to a magnetic field.

In the following years, these findings were replicated. In 1910, Thompson (1910) ascribed the flickering visual sensations - that he called magneto-phosphenes - to direct stimulation of the visual cortex. However, given the low effectiveness of these earlier stimulators and the particular coil shapes, these early investigators were likely stimulating the retina rather than the brain directly (Barker, 2002; Cowey, 2005). Further development of magnetic stimulation was made possible by technological advance allowing to make stimulation coils compact enough while still able to generate a magnetic field of an effective field strength. Most of the following work aimed at testing whether it was possible to go beyond retinal stimulation and to reach different part of the nervous system by changing the characteristics of the applied magnetic field. This helped to establish the importance of the magnetic field strength, as D’Arsonval and Thompson thought, and of pulsed stimulation in the order of μs (Walsh & Pascual-Leone, 2003).

Based on these findings, Bickford and Freeming (1965) successfully stimulated human and animal peripheral nerves using a pulsed magnetic field of 2 tesla lasting for 300 μs, but failed to measure the physiological responses, because of the magnetic field interfering with the recording equipment (Barker, 2002). From 1974 to 1985, Barker and colleagues started to test different kinds of stimulators, producing different types of magnetic pulses based on the idea that a rapidly-changing magnetic field is effective in stimulating not only peripheral nerves but also the intact human brain. Thanks to technical developments, they were able in 1985 to stimulate the motor cortex and elicit contralateral hand movements with no discomfort (Barker, Jalinous, & Freeston, 1985). This afforded the opportunity to overcome problems of discomfort caused by electrical stimulation.

Since then, TMS has been applied also over sensory and to higher-order areas with the aim to interfere with its associated functions (for reviews see Amassian et al., 1993; Miniussi, Ruzzoli, & Walsh, 2009; Walsh & Cowey, 1998; Walsh & Pascual-Leone, 2003). With the introduction of rapid rate stimulators in 1988 able to deliver trains of stimuli, TMS applications have been further extended also to cognitive enhancement and rehabilitation purposes (for a review see Miniussi et al., 2008).

Basic principles of TMS

The physical foundation underlying TMS is the principle of electromagnetic induction, discovered by Faraday in 1831 (published in 1839; Faraday, 1839). In his pioneering experiment, a coil of wire called primary coil was directly connected to a current source, whereas a secondary coil was connected to a galvanometer. When the current was briefly passed through the primary coil, an electric current was detected in the nearby secondary coil. This was explained by the current flowing through the primary coil generating a magnetic field which in turn induces a secondary current in any nearby conductor, in this case the secondary coil. The induced current is proportional to the rate of change of the magnetic field over time, which in turn depends on the rate of change of the electric current flowing in the primary coil.

The TMS machine takes advantage of this principle and contains two main parts (Fig. 2), one or more capacitors where the energy is stored connecting to a stimulation coil through which the electrical currents are driven. In analogy with Faraday's experiment, the primary circuit is the stimulation coil held against the participant‘s head (Fig. 2A). When the stimulus is delivered, the discharging of the capacitors produces a high peak amplitude current (up to 10000 A) which flows into the coil in a very short time span (typically 100-200 μs). This will generate a perpendicular magnetic field which goes through bone structures without deformations and induces an electric field in the secondary circuit, in this case the brain (Barker, 2002).

The current intensity and the rate of change (duration of the electric pulse) determine the intensity of the magnetic field and the strength of the induced electric filed in the brain, which is parallel, but opposite in direction, to the electric field generated in the stimulating coil, as described by Lenz's law (Ruohonen & Ilmoniemi, 2002; Sack & Linden, 2003). The main advantage of TMS is that the skull and scalp present almost no impendence to the passage of a magnetic field, which penetrates human tissue painlessly since it has little excitatory effects on skin receptors and pain fibers (Rossini et al., 2015).

The electric field induced by the pulse affects the transmembrane potentials and when delivered with adequate parameters leads to a depolarization of nerve cells and the generation of action potentials. The magnetic field is therefore not able to stimulate the brain tissue by itself, but will rather serve as a means to induce an electric field which is responsible for brain stimulation.

An important feature of TMS is that the magnetic field falls off rapidly with distance from the coil, being inversely proportional to the square of the distance between the coil and cortex (Ilmoniemi, Ruohonen, & Karhu, 1999). As a consequence, TMS will easily stimulate superficial areas of the brain, but is mostly unable to reach deeper cortical structures, at least directly (note that deeper structures may be reached through spreading of activity along stimulated anatomical pathways). Although the depth of stimulation depends on the intensity and the type of TMS coil (see *Stimulation coil* section), it has been estimated that with a sufficiently strong intensity, the effective magnetic field for stimulation can reach a depth of about 4 cm (Terao & Ugawa, 2002). Note that this limitation may be overcome by new coil designs for targeting deep brain structure (Roth, Amir, Levkovitz, & Zangen, 2007).

Another important TMS feature is its focality which is in the order of 1-2 square centimeters, depending on the intensity and the stimulation coil (Deng, Lisanby, & Peterchev, 2013). Focality and depth are not independent features so increasing the intensity of the stimulation will increase the depth but also recruit a larger volume of tissue (Deng et al., 2013; Siebner, Hartwigsen, Kassuba, & Rothwell, 2009).

Despite a lack of knowledge about how TMS actually affects the neural tissue, there is general agreement that the electric field (which is maximum underneath the stimulating coil) is primarily affecting the surface of gyri and that it mainly excites the cortical gray matter which is closer to the scalp rather than subcortical white matter (Bijsterbosch, Barker, Lee, & Woodruff, 2012; Thielscher, Opitz, & Windhoff, 2011). At a smaller scale, it has been suggested that the magnetic stimulation acts by depolarizing axons more than cell bodies (Di Lazzaro et al., 2004; Siebner et al., 2009). The specific characteristics of neural populations such as the orientation of the neurons and the size of axonal diameter will determine the strength of TMS effects. Cells with a large-diameter myelinated axon and a dendritic tree located at the opposite site of the soma to the axon (such as the pyramidal neurons in primary motor cortex) have been shown to be highly responsive to the stimulation (Siebner et al., 2009). As for neuronal orientation, the maximal effect is thought to be achieved when the induced currents are perpendicular to the orientation of the underlying gyrus (Thielscher et al., 2011).

How to design a TMS experiment

TMS can be applied to localize brain functions in time and space by briefly interfering with a relatively restricted cortical region or as it will be discussed in the following sections, with the aim to obtain persistent effects that outlast stimulation. Selecting the right TMS protocols and parameters such as intensity, frequency and duration is therefore important to harness the outcome.

Stimulation coils

Several types of TMS coils are available. Since most of them are modified versions of two basic coil designs, we will limit the description to these two coils (for a complete description of coil types see Deng et al., 2013).

The circular coil was the first configuration to be used (Fig. 2B). It usually has an outer diameter of about 8-15 cm and induces currents that are maximal just underneath the course of its outer edge (with a reverse direction). Although it can be used to simultaneously stimulate both hemispheres (e.g. targeting motor cortex), the stimulated area coincides with its circumference so it's not particularly suited for cognitive studies which usually aim at stimulating more restricted brain areas (Epstein, 2008; Terao & Ugawa, 2002).

To improve the focality of stimulation, TMS is usually applied through the so called figure-of-eight coil (Fig. 2B), which is composed of two small round coils placed side by side (Ueno, Tashiro, & Harada, 1988). The maximal magnetic field is produced at the coil centre, i.e. at the junction between the two round coils. This coil design allows a more precise targeting of delimited brain areas, as the maximal electric field is induced just beneath the point of contact between the centre of coil and the scalp, whereas electric fields induced at the edge of the loops can be largely ignored (Epstein, 2008; Terao & Ugawa, 2002).

TMS intensity

The stimulation intensity is defined as percentage of the maximum stimulator output. Ideally, this is adjusted to individual excitability of the brain, which can be assessed in several ways. One approach is based on the stimulation of brain areas where TMS can induce a quantifiable response, such as after motor cortex or visual cortex stimulation. With TMS over the primary motor cortex of one hemisphere, the corticospinal tract is activated which in turn produces a measurable muscle twitch evoking motor evoked potential (MEP) that can be recorded using electromyogram (EMG) in the contralateral hand (Rossini et al., 2015). This allows determining the individual motor threshold (MT).

Following the most used approach (relative frequency method), the stimulation intensity is progressively reduced by 2-5% of the machine output until MEPs of certain amplitude are evoked in 5 out of 10 stimuli (Rossini et al., 2015). However, when the target of a TMS experiment is a non-motor area, a more feasible way of defining the MT is to determine the lowest machine output able to generate a visible twitch in the contralateral hand, not requiring the use of EMG (Sandrini, Umilta, & Rusconi, 2011). The MT approach allows the experimenter to take into account individual differences in excitability and intensity can by normalized by using multiples of the MT. An alternative, but yet similar approach, to the MT determination is the determination of the phosphene threshold (PT). In this case, the threshold is defined as the lowest stimulator output able to induce visual sensations (phosphenes) in half of the trials when the TMS pulse is applied over the visual cortex (Abrahamyan, Clifford, Ruzzoli, et al., 2011).

The individual threshold approach relies on the assumption that the motor or phosphene thresholds represent a reliable estimate of excitability across the whole brain, i.e. even when the stimulation has to be applied to other (non-motor, non-visual) brain regions. However many factors influence TMS effects over different areas, such as the scalp/cortex distance or different neuronal orientations or the presence of different cell types across different regions. For this reason, the intensity of stimulation has been increasingly set at a fixed intensity across participants in cognitive studies. The advantage of this approach is that it reduces the experimental duration and the total number of applied stimuli. However, further research on this issue is needed as it is possible that using this approach, stimulation will not be sufficient to interfere with performance for some participants (Robertson et al., 2003; Sandrini et al., 2011).

An alternative approach to target areas that do not produce a direct measurable output, such as MEPs or phosphenes is the so called “hunting” procedure (for a comparison of different threshold procedures sees Groppa et al., 2012). In this case TMS target can be initially defined based on probabilistic location using an MRI scan (Grosbars&Paus, 2002) or the scalp coordinates of EEG electrode system (Oliver et al., 2009), whereas the initial stimulation intensity is defined as percentage of each individual resting MT using the relative frequency method. However, in this procedure, the TMS coil is systematically moved around the initial spot and stimulation efficacy is tested in terms of behavioural modulations over a certain number of trials. As examples, Grosbars and Paus (2002) defined the individual MT according to the relative rate method and then tested its effectiveness over the frontal eye field (FEF) which was defined as the scalp location where single pulse TMS significantly increased the latency of saccades generated towards the contralateral hemifield.

TMS protocols

TMS protocols can be roughly categorized according to how pulses are spaced in time or when the pulses are applied. Accordingly, it has been categorized as single pulse (spTMS) versus repetitive TMS (rTMS) (pulse spacing), or as online versus offline (time of delivery relative to task performance).

In spTMS (Fig 3A), TMS pulses are applied with an inter-pulse interval long enough to prevent any summation of the effects induced by each pulse. Despite that no guidelines are available as to the minimum interval, spTMS is usually applied with a 5-7 seconds interpulse interval (Robertson et al., 2003; Sandrini et al., 2011). Since the magnetic pulse is short lasting, spTMS has a good temporal resolution and is therefore suited to address the question of when the activation of a region is crucial during performance of a cognitive task (Sack & Linden, 2003; Walsh & Cowey, 2000). As an example, Mottaghy et al (2003) used spTMS to investigate the chronometry of parietal and prefrontal activations during a verbal working memory task, by applying a pulse at different time points after stimulus onset (10 intervals between 140-500ms). SpTMS impaired participants' performance (accuracy decrease) with a distinct spatiotemporal pattern. Interference with the task was induced earlier in the parietal cortex than in the prefrontal cortex, and earlier over the right than the left hemisphere, suggesting a propagation of information from posterior to anterior sites possibly converging in the left prefrontal cortex (Mottaghy et al., 2003).

When the hypothesis does not require testing for a chronometry of function, TMS can be delivered in short trains of pulses during the task execution (online rTMS) so that a larger time window can be covered, also increasing the chances of obtaining behavioural effects (Fig 3B). This approach will provide information about where the cognitive process is taking place rather than when the area is engaged. Online rTMS protocols therefore refer to the application of short trains of a few hundreds of milliseconds during a cognitive task trial in order to modulate neuronal activity of the target area (Paulus, Peterchev, & Ridding, 2013). The frequency of stimulation (number of pulses in a second) can span from 1 to 50 Hz, although in most cases 4 Hz- to 25 Hz-trains have been tailored to cover usually 0.1–1 second of a trial (for a review see Rossi, Hallett, Rossini, & Pascual-Leone, 2009), with higher frequencies being more effective in interfering with behaviour (Luber & Lisanby, 2014; Rossi et al., 2009).

Offline rTMS refers to the application of trains of stimuli before task execution (Fig. 3C). Offline protocols rely on the evidence that rTMS can promote changes in cortical excitability that outlast stimulation. Stimulation frequency will determine stimulation outcome, with low frequency rTMS (defined as <1Hz) traditionally associated with a decrease in cortical excitability and high frequency rTMS (defined as >5Hz) associated with an increase in cortical excitability (Chen et al., 1997). This distinction is based on studies performed on the primary motor cortex, where low and high frequency rTMS tend to reduce or increase the amplitude of MEPs respectively (for a review see Fitzgerald, Fountain, & Daskalakis, 2006). The physiological mechanisms responsible for these long-lasting effects of rTMS are still largely unknown, although as for tES, several indirect evidence suggests that such changes reflect alterations in synaptic efficacy and are largely due to spike-timing dependent plasticity such as long-term potentiation (LTP) and long-term depression (LTD) (Thickbroom, 2007). However, it is worth noting that the offline rTMS outcome likely depends on a complex interaction between TMS frequency, intensity and duration. In the cognitive domain, low frequency offline rTMS is generally applied with the aim to reduce the activity of a region and therefore impair performance, whereas high frequency rTMS is used to increase the excitability and boost performance, in analogy with motor cortex studies. While coming at the cost of losing the temporal information about the involvement of the target area in a cognitive function, the offline approach has the advantage of avoiding non-specific effects of TMS on behavioural performance, that originate in the TMS-induced noise or peripheral muscle twitches which can distract the participant, especially when TMS is applied over more frontal areas (Sandrini et al., 2011).

A newer variant of offline rTMS is the theta burst stimulation (TBS) protocol, in which 3 50Hz pulse trains are applied every 200ms (i.e. at theta frequency). The temporal pattern used determines whether the protocol has an inhibitory or facilitatory effect. When TBS is continuously applied for 40 seconds (also called continuous TBS; cTBS; Fig 3D), it tends to lead to cortical inhibition that lasts up to 1 hour. In contrast, when broken up in burst of 2 seconds that are repeated every 8 seconds (also called intermittent TBS; iTBS, Fig 3E), the same protocol can lead to a long lasting increase in excitability (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The advantage of TBS as compared to low and high frequency rTMS is that by using a similar number of pulses but considerably shorter duration and lower intensity of stimulation (80% of MT), experimental time is reduced without jeopardizing effect strength (as the effects tend to last longer than with the classical low and high frequency rTMS protocols). For this reason TBS protocols are increasingly being used in offline cognitive studies (e.g. Galea, Albert, Ditye, & Miall, 2010; Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010).

[Insert figure 3 here]

It has to be noted that a specific rTMS protocol may be associated with more than one effect, depending on conditions. For instance, when repetitive TMS is delivered in rhythmic patterns (e.g. 10Hz) that are matched to known, task-related brain oscillations (e.g. alpha-oscillations), frequency specific effects may occur (in analogy to tACS, see below). The logic is that stimulation at physiologically meaningful rhythms will enhance the oscillatory activity that matches the stimulation frequency. This entrainment will have domain-specific effects on cognitive functions depending on the role of a specific brain rhythm being enhanced. As an example, rTMS applied at alpha rhythm over the parietal lobe has been shown to alter location-based attention and working memory (Romei et al., 2010; Sauseng et al., 2009) and to enhance cognitive performance in visuospatial tasks (Klimesch, Sauseng, & Gerloff, 2003; Ruzzoli & Soto-Faraco, 2014). Such entrainment is prominently observed during stimulation (when rTMS is frequency tuned to underlying brain oscillations), but with prolonged stimulation, plasticity effects will emerge that outlast stimulation as outlined above. Whether this is a two stage process where entrainment leads to plasticity changes has not been formally tested, but there is evidence that short-term entrainment and long-term plasticity are dissociated to a large extent in rTMS protocols (see Veniero, Vossen, Gross, & Thut, 2015).

Control condition

Since TMS is associated with a number of sensory experiences that can affect the behavioural performance, implementing control conditions is crucial in order to rule out possible unspecific effects (at least for online TMS). These sensations include a clicking sound produced by the stimulator when the coil is discharged which has been demonstrated to affect performance via inter-sensory facilitation (Marzi et al., 1998). Other unspecific effects are the direct activation of cranial or neck muscles, which depends on the stimulation site and can cause some discomfort. Moreover, even when no muscle is activated, the pulse is associated with scalp sensations.

A simple approach is the use of sham stimulation, which can be carried out by tilting the coil by 90° so that the upper edge of the coil is positioned over the site of real stimulation (e.g. Romei et al., 2010). This will produce the same auditory stimulation but will not be able to generate any scalp sensation. To overcome this limitation, an alternative sham protocol is to turn over the real coil and attach a 30 mm-thick plywood shield of the same shape and size to it (Rossi et al., 2007; Veniero, Bortoletto, & Miniussi, 2009). Sham coils are also available which are designed to replicate the standard of figure-of-eight coil in looks, and discharge without stimulating cortical tissues since the magnetic field output is approximately 10-fold lower than that delivered by the standard coil (Veniero et al., 2009). However, no sham stimulation is able to perfectly mimic the exact sensations associated with a real stimulation. For these reasons, alternative strategies to control for unspecific effects can be used where possible. One possibility is the use of control sites (active control), where difference in outcome across sites indicates a specific involvement of one of the TMS target regions (e.g. Bonni et al., 2015). However, it is possible that different sites are associated with different scalp sensations or can cause different muscle activation. In this respect, an elegant way of demonstrating the specific involvement of one region in a cognitive task is the use of a control task rather than a control site (e.g. Dormal, Andres, & Pesenti, 2008).

The potential of TMS for cognitive enhancement

In contrast to tES (which is a more neuromodulatory technique), TMS is traditionally used with the aim to interfere with cognitive processes by disrupting the functioning of the stimulated area, in particular with the online TMS approach in cognitive sciences. For this reason, reports of performance improvement with cognitive tasks are less frequent and have often been labeled as "paradoxical" (Miniussi, Harris, & Ruzzoli, 2013). However, whether TMS disrupts or facilitates a behavioural performance may depend on the stimulation parameters, such as frequency and the timing of TMS relative to the task. Nonetheless, enhancement has been reported with spTMS and rTMS both online and offline and, rather than being paradoxical, has been explained as the result of TMS effects over the area involved in a given task, or as a result of TMS-inhibition of competing or distracting processing. In the first case, TMS enhancement effects have been interpreted to be brought about by forms of potentiation of functionally relevant neuronal activity or enhancement of cortical excitability through spTMS during task execution or through online or offline rTMS at high frequencies (Luber et al, 2014, Reis et al, 2008). Another mechanism that has been advocated to possibly enhance task performance by direct interaction with the target area (online design) is stochastic resonance, where the induction of a medium amount of noise by TMS may be of benefit for task execution (Abrahamyan, Clifford, Arabzadeh, & Harris, 2011; Schwarzkopf, Silvanto, & Rees, 2011). For the second case (TMS-disinhibiting), behavioural effects are more likely to occur when low frequencies are applied offline. For an excellent review on cognitive enhancement with TMS see (Luber & Lisanby, 2014).

Executive functions/ Cognitive control

Online rTMS has been repeatedly shown to enhance working memory (WM) performance when participants are asked to perform a delayed match-to-sample tasks. Luber et al (2007) applied rTMS at 1, 5, or 20 Hz to either left dorsolateral prefrontal or midline parietal cortex during the retention (delay) phase or during presentation of the recognition probe and found an improved performance only when rTMS was applied over the parietal cortex in the retention phase. Interestingly, only 5 Hz rTMS was able to affect the performance, perhaps suggesting the involvement of theta oscillation in WM in line with some tACS results.

Similar results have been reported by Yamanaka et al. (2010), when 5 Hz rTMS was applied over the right (but not left) parietal cortex during the delay period of a spatial WM task.

Offline rTMS have been used to investigate the involvement of DLPC in decision making (Knoch et al., 2006; van 't Wout, Kahn, Sanfey, & Aleman, 2005). Knoch et al. (2006) applied 1Hz rTMS for 15 minutes over the right or left DLPC and then asked participant to perform in a gambling paradigm (Risk Task; Rogers et al., 1999) that probes decision-making under risk. Participant showed riskier decision-making after receiving rTMS of the right but not left DLPC, suggesting an asymmetry between left and right DLPC in decision-making.

Learning and memory

As with tES, i.e. given the possible involvement of LTP/LTP like phenomena in the generation of both tES and TMS effects, one interesting question is whether TMS has the potential to promote and accelerate new skill acquisition.

Buterfisch et al. (2004) showed that application of single pulse TMS to the primary motor cortex contralateral to the hand practicing a thumb abduction task simultaneously with the movement enhanced the accuracy of movement execution for 1 hour. Using rTMS online at 10Hz over the primary motor area, Kim et al (2004) reported similar results with rTMS increasing movement accuracy and reducing movement execution time.

In line with the idea of TMS interfering with hemispheric competition (i.e. a disinhibition effect), offline 1Hz rTMS applied over the primary motor cortex ipsilateral to the trained hand has been consistently shown to increases motor cortical excitability of the opposite motor area and to improve motor sequence learning (Kobayashi, 2010; Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004; Kobayashi, Theoret, & Pascual-Leone, 2009). Offline rTMS has also been applied to increase motor learning using 5Hz over the dorsal premotor cortex for 15 minutes increasing subjects' performance at least for one day (Boyd & Linsdell, 2009).

This same approach has been used to investigate whether procedural consolidation processes can be enhanced by interfering with the declarative memory system with the hypothesis that two processes can compete for cognitive resources, and inhibition with one may release the other. Galea et al. (2010) applied cTBS over the left or right DLPC, which is thought to support declarative memory formation after a training on a serial reaction time task, and reported an increase in motor skill following right DLPFC inhibition.

TMS safety

It is important that all parameters and participants are selected in accordance with safety guidelines (Rossi et al., 2009) to avoid the most severe risk which is acute seizure induction. Parameters that are considered safe depend on several factors (spTMS versus repetitive TMS, the chosen frequency, intensity, number of pulses etc), including the population being tested. For instance, TMS is not recommended for certain populations, such as people with metal in the head or with personal or family history of epilepsy. It is therefore recommended to screen participants before any TMS experiment, using a standard screening questionnaire (see Rossi et al., 2009).

Transcranial electric stimulation

Basic principles of tES

In contrast to TMS, which is able to stimulate neurons above-threshold and generate action potentials, tES is not strong enough to discharge resting neurons directly if applied at the usual intensities of 1-2 mA. Instead, it leads to more subtle changes in the neuronal resting membrane potential, thereby modifying spontaneous firing rates and cortical excitability (Paulus, 2011). However, the exact physiological mechanisms by which tES exerts its effects on the neural tissue differ according to the type of current used in the different tES techniques (i.e., DC vs. AC). Furthermore, it is of importance to differentiate stimulation effects occurring during stimulation (i.e., immediate or online-effects) from those that outlast stimulation offset (i.e., offline- or after-effects). For that reason, the physiological mechanisms underlying online- vs. after-effects are described separately for tDCS and AC-based methods in the following.

Transcranial direct current stimulation (tDCS)

tDCS is the most well-known and frequently used tES technique. It involves the application of a low-intensity constant direct current that enters the brain via the anode and leaves the tissue via the cathode (i.e., the application is polarity-dependent). Accordingly, anodal stimulation increases neuronal excitability and spontaneous firing rate by depolarizing resting membrane potentials, whereas cathodal stimulation leads to hyperpolarization resulting in a decrease of excitability. This shift in resting membrane potential occurs during stimulation (i.e., online) without any direct effects on synaptic plasticity (Stagg & Nitsche, 2011; Fig.4).

[Insert figure 4 here]

Synaptic plasticity, on the other hand, has been proposed to induce long-lasting tDCS after-effects by modulating the strength of neuronal connections via long-term potentiation (LTP) under the anode, and by its counterpart long-term depression (LTD) under the cathode (Stagg & Nitsche, 2011). LTP-like plasticity is believed to underlie learning and memory formation in the brain (Malenka & Bear, 2004). Therefore, this is a plausible candidate mechanism to explain the observed tDCS after-effect durations in the range of hours following stimulation (Stagg & Nitsche, 2011). However, the exact neurophysiological basis of the observed tDCS effects on brain activity and how that relates to behavioral change has yet to be fully determined (Bestmann, de Berker, & Bonaiuto, 2015).

In sum, tDCS is an established brain stimulation method allowing the induction of excitability enhancements or reductions of a targeted brain area in a polarity-dependent manner. tDCS affects spontaneous cortical activity by modulating membrane potentials and it can induce long-lasting after-effects through LTP-like neuroplastic mechanisms.

Transcranial random noise stimulation (tRNS)

tRNS is a relatively new stimulation technique that is based on alternating current. It has been originally introduced in the context of motor learning, where it induced a consistent excitability enhancement in physiological and behavioral measures lasting at least 1 hour (Terney et al., 2008). Whereas this output is similar to that of anodal tDCS, the underlying mechanism probably differs due to the lack of a DC component in tRNS.

In contrast to tDCS, tRNS is polarity-independent and employs a repetitive stimulation that comprises random frequencies of a wide range (0.1–640 Hz) with different intensities (Terney et al., 2008). However, separating the full spectrum into lower (0.1–100 Hz) and higher (101–640 Hz) frequencies in the Terney et al. study revealed that predominantly the higher frequencies were responsible for the physiological after-effects. Furthermore, it was shown that tRNS in the high-frequency range yields larger effects compared to anodal tDCS in the visual cortex (Fertonani, Pirulli, & Miniussi, 2011).

The physiological mechanisms underlying tRNS-induced after-effects are not yet clear. One suggestion is that a phenomenon called “stochastic resonance” might come into play, because tRNS adds “white noise” to brain activity. Stochastic resonance refers to the amplifying effect of adding noise to a signal that is too weak to exceed a threshold on its own (McDonnell & Abbott, 2009). How can noise that normally decreases relative signal strength help a signal to exceed a threshold? Since neural networks often oscillate sinusoidally at a certain frequency, there are up- and down-states of the sine wave. If a neural oscillation remains sub-threshold within a given noise level (i.e., the up-states of the sine wave do not reach the threshold), an increase in noise by tRNS could shift the oscillation above-threshold at those points in time when the noise signal adds up with the up-states of the sine wave. Therefore, the existing sub-threshold neural oscillation determines the frequency of the superthreshold signal (Fig. 5). Thus, stochastic resonance would explain how tRNS could result in an enhanced amplitude of an existing brain oscillation during the time of stimulation. The effect of stochastic resonance, however, would not outlast stimulation offset. In order to explain also the after-effects of tRNS, we assume a two-stage process. In a first stage, stochastic resonance leads to the enhanced amplitude of an intrinsic brain oscillation. In a second step, this enhanced amplitude results in neural plasticity as in the case of tACS if applied for a sufficient duration of time. This neural plasticity then results in enhanced amplitudes of the brain oscillation for some time after the end of stimulation and the accompanying behavioral effects.

[Insert figure 5 here]

In sum, tRNS is a polarity-independent method applying alternating currents at random frequencies to the brain. It induces only excitatory effects at both electrodes that might last for at least 60 min. It is suggested that tRNS enhances sub-threshold neural signals by adding noise to the system (stochastic resonance).

Transcranial alternating current stimulation (tACS)

Like tRNS, tACS is a new AC-based stimulation technique that has also been introduced in the context of motor learning by the same research group in the same year (Antal et al., 2008). In contrast to tRNS containing a full frequency spectrum, tACS is typically applied at one specific frequency only (e.g., 10 Hz). In theory however, it is possible to apply more or less narrow frequency bands (e.g., 5–7 Hz, 40–60 Hz), or to combine multiple frequencies resulting in increasingly tRNS-like conditions dependent on the number of frequencies involved (Paulus, 2011).

In general, tACS allows to modulate ongoing cortical oscillations by applying external sinusoidal currents that are bound to one frequency of interest and in turn to influence cognitive processes that are related to that frequency (Herrmann, Rach, Neuling, & Struber, 2013). Physiologically, it is thought that the externally applied tACS-oscillation forces its frequency and phase on the endogenous neural oscillators, resulting in a synchronization of external and internal oscillators, which is known from physical systems as “entrainment”(Pikovsky, Rosenblum, & Kurths, 2001; Fig. 6). The phenomenon of entrainment occurs when one oscillation, e.g. the sinusoidal current applied via tACS, modulates the amplitude and/or phase of another oscillation, e.g. an endogenous brain oscillation. Only recently, it could be demonstrated directly by a parallel measurement of stimulation in the alpha frequency range (~10 Hz) and EEG that entrainment is indeed responsible for the immediate (online) effects of tACS (Helfrich et al., 2014).

[Insert figure 6 here]

However, it is still unclear how the immediate tACS effects translate into different types of longer lasting after-effects, that have been found with varying tACS protocols to persist from approximately 2 to 60 minutes (Struber, Rach, Neuling, & Herrmann, 2015). If entrainment would be responsible for inducing after-effects, one would expect the synchronized activity to continue oscillating for a considerable amount of time (i.e., entrainment echoes), but up to now there is no direct evidence for this to happen. Alternatively, after-effects might originate from LTP-like plasticity as has been demonstrated for tDCS, which would be independent of the underlying oscillatory activity. Current modeling of human tACS after-effects suggests a different form of plasticity (e.g., spike-timing dependent plasticity; Vossen, Gross, & Thut, 2015; Zaehle, Rach, & Herrmann, 2010), although the exact mechanism needs to be revealed by future animal research (Struber et al., 2015).

In sum, tACS is a polarity-independent method affecting endogenous brain oscillations of a specific frequency. Immediate tACS effects arise from entrainment, whereas tACS after-effects originate from some form of neuroplasticity.

How to design a tES experiment

Given the relevance of higher cognitive processes for organizational research and other fields of applied psychology, tES might become a useful tool in the future. However, an effective application of tES in these areas requires the persistence of a tES effect after stimulation offset. Therefore, it is crucial to choose important stimulation parameters like duration, intensity, frequency as well as the electrode positions and control conditions in a theory-based manner related to the cognitive process of interest. In the following, we give a short overview of the most relevant issues that need to be addressed when planning a tES experiment.

Stimulation duration

Stimulation duration is one important parameter for the induction of tES after-effects. It has been demonstrated that brief durations in the range of seconds do not produce after-effects, whereas stimulation in the range of minutes (commonly 10-20 min) reliably elicits after-effects of varying durations following tDCS (Nitsche et al., 2008), tACS (Neuling, Rach, & Herrmann, 2013; Struber et al., 2015) or tRNS (Terney et al., 2008). A minimum duration of three minutes with an intensity of 0.6 mA have been reported for producing tDCS after-effects (Nitsche & Paulus, 2000). Most systematic research on the timing of stimulation to induce after-effects has been conducted with regard to tDCS.

Earlier studies seemed to indicate an increasing duration of tDCS after-effects with increasing stimulation duration by showing that 5-13 minutes of anodal tDCS led to a proportional increase of after-effects lasting 1-2 hours (Paulus, 2011). However, a more recent study suggests an upper limit for further increasing excitatory tDCS after-effects, since an excitatory effect after 13 minutes of continuous anodal tDCS switched to inhibition after 26 minutes of stimulation (Monte-Silva et al., 2013). Therefore, in order to prolong plastic after-effects it might be more effective to stimulate intermittently with shorter durations than continuously with longer durations (Monte-Silva et al., 2013).

Stimulation intensity

Ideally, participants do not sense stimulation and are, therefore, not able to differentiate between verum (tES) and placebo (sham) conditions. Unfortunately, a sensation-free stimulation intensity would be too low to be effective. Most tES-studies use a stimulation intensity of 1-2 mA, which is considered not only to be effective but also to be safe and painless if the size of the electrodes is large enough (~35 cm2) to prevent skin burns (Paulus, 2011). Nevertheless, mild skin sensations like itching and tingling might occur underneath the stimulation electrodes (Brunoni et al., 2011). Furthermore, the sensation of light-flashes, so-called phosphenes, have been reported when using tACS, especially at frontal regions and higher frequencies (>16 Hz) with an intensity of ~1-1.5 mA (Raco, Bauer, Olenik, Brkic, & Gharabaghi, 2014). Also with tDCS, retinal phosphenes might occur when a reference point is used close to the eyes (Paulus, 2011). It has been discussed whether the origin of phosphenes is retinal or cortical (Schwiedrzik, 2009; Schutter & Hortensius, 2010). In any case, phosphenes would be a potential problem for tES studies, since it would not be clear whether entrainment would be the result of flickering light or neural synchronization.

Phosphenes and other adverse effects are undesired not only because they hinder the interpretation of results but also because they cause inconvenience for the participants and complicate experimental blinding. Moreover, the sensibility to somatosensory and visual sensations varies inter-individually. Therefore, a fixed stimulation intensity might be sensed by more sensitive study participants (via skin sensation or phosphenes), whereas less sensitive participants would not sense the stimulation.

One possibility to deal with this problem is to adapt the stimulation intensity to the individual somatosensory and phosphene threshold in such a way that the final stimulation intensity is below the threshold as determined by psychophysical measurements (Zaehle et al., 2010). However, this procedure is time consuming and it might happen that the participants' sensibility changes during the threshold determination measurements. Furthermore, each participant ends up with an individual stimulation intensity, which may complicate the interpretation of group differences.

Alternatively, the stimulation amplitude could be faded in over a time interval of ∼30 s, which reduces the skin sensations and ensures that the same final stimulation intensity is applied to all participants. This procedure is referred to as "ramping-in" and has been frequently used in tDCS experiments. Another possibility for blinding of the experimental conditions makes use of the fact that stimulation is usually only felt transiently during the first seconds following stimulation onset. Accordingly, a short active stimulation period that is faded out after ~30 s at the beginning of a sham condition can mimic a stimulation condition in that it is too brief to effectively modulate neuronal activity but still leads to skin sensations as in the verum condition.

Stimulation frequency

This issue is of relevance only for otDCS, tACS, and tRNS but not tDCS. Whereas otDCS and tACS are applied at a specific single frequency (e.g., 10 Hz), tRNS involves broad-band stimulation of varying frequency range (e.g., 0.1-100 Hz or 101-640 Hz). However, one has to consider that physiologically meaningful frequencies (i.e., frequencies that exist in the brain) are restricted to the range from delta (∼0.5–4Hz) to high gamma (∼200 Hz). Therefore, the stimulation frequency should be selected according to an existing brain oscillation if a study aims at modulating brain oscillations by tACS/otDCS.

However, of more practical relevance is the question how tACS/otDCS can be used to influence cognitive processes. A presupposition for an informed application of these methods is an established connection between the cognitive process of interest and a brain oscillation of a certain frequency. The most relevant source for identifying such correlations are existing EEG studies. Alternatively, one has to conduct an own EEG experiment in advance to the planned tACS/otDCS study to define the relevant oscillation. This procedure bears the advantage that the experimental conditions for the EEG and tACS/otDCS study are identical.

Unfortunately, EEG correlates do not refer to isolated oscillations like for instance 6 Hz or 42 Hz that would directly translate into a tACS/otDCS study. Instead, the reported correlations usually relate to one of the classical frequency bands (i.e., delta, theta, alpha, beta, or gamma). Thus, a given correlation between a cognitive function and oscillatory EEG activity in the alpha range comprises all frequencies between 8 Hz and 12 Hz, becoming even worth with increasing frequencies like the gamma band (~30-80 Hz). One possible solution is to select a center frequency that "best" represents the band activity by inspection of the power spectrum or time-frequency plot. Another, though more costly, possibility is to sample the frequency band by applying tACS/otDCS at multiple frequencies (e.g., 40 Hz, 60 Hz, 80 Hz within the gamma band).

A further problem concerns the inter-individual variation of EEG peak frequencies within a certain frequency band. If, for example, an experiment aimed at modulating the alpha activity or a related cognitive function, one has to take into account that some participants may exhibit their dominant frequency within the alpha range at 8 Hz, whereas others at 9 Hz or 10 Hz. In order to optimize the effect of tACS/otDCS, it might be useful to determine the individual alpha frequency by inspecting the spontaneous EEG and then adapt the stimulation frequency to the individual frequency (Zaehle et al., 2010).

Electrode montage

Conventionally, two ~5 x 7 cm sized conducting rubber electrodes inserted into saline-soaked sponge envelopes are located on the scalp and fixed either with rubber head straps or by sticking them underneath an EEG electrode cap. The stimulation electrode position usually refers to the international 10-20 system for the placement of EEG electrodes (Jasper, 1958). Where to place the electrodes is largely determined by the brain area supporting the cognitive function of interest. For most of the higher-level cognitive processes mentioned above this is the (pre)frontal cortex. Furthermore, the function of interest might be lateralized, i.e., predominantly supported by only one of the two hemispheres. In that case, the active "stimulating" electrode is placed on either the right (i.e., electrode position F4) or the left (F3) prefrontal cortex. If no lateralization is assumed, the active electrode can be centrally arranged (Fz).

Placement of the secondary "reference" electrode is more critical for tDCS than for tACS or tRNS, because only direct current is sensitive to the direction of current flow, resulting in the differentiation between excitatory "anodal" and inhibitory "cathodal" stimulation (Woods et al., 2016). Nevertheless, it should be mentioned that also tACS-induced behavioral effects have been reported recently to be dependent on the position of the reference electrode (Mehta, Pogosyan, Brown, & Brittain, 2015).

In general, the reference electrode can be either placed on the scalp (like the stimulating electrode) or on extra-cephalic locations like the arm. For most research scenarios, the reference electrode is predominantly needed to close the electrical circuit, whereas the stimulating electrode does the job, i.e., modulating the neuronal activity in the targeted brain region.

It is important to note that it cannot be assumed that the stimulation is limited to the areas under the electrodes. Consequently, individual head and brain models of the participants are required to predict precisely the patterns of intra-cortical current flow (see Figure 7).

[Insert figure 7 here]

Control conditions

In general, the effects of an active stimulation condition (verum) have to be compared with a control condition of sham stimulation (placebo) in order to demonstrate that tES has an effect. The sham condition should be identical to the verum condition regarding stimulation duration, possible sensations, time of day, experimenter and so on. Furthermore, it is desirable to employ a double-blind procedure, i.e., neither experimenter nor participant knows whether the verum or placebo stimulation is applied.

In case of planning a tACS experiment, a simple comparison with a sham condition would only reveal a general stimulation effect that might be independent of the specific frequency of interest. Therefore, in order to demonstrate frequency specificity of the stimulation effect, at least one additional control condition employing a different frequency has to be included. Although adding more than one control frequency might enhance frequency specificity, one should take care that none of the chosen frequencies correlates with another cognitive function overlapping with the cognitive process at hand.

It has been suggested that the control conditions should consist of two frequencies above and below the frequency of the verum condition demonstrating that the cognitive effect is absent or diminished at those control frequencies (Thut, Schyns, & Gross, 2011). We would like to note, however, that currently no clear procedure exists for defining appropriate control frequencies, including the number of frequencies and the distance in Hertz from the verum frequency.

Another issue concerns the order of conditions. To prevent carry-over effects in a within-subject design from the verum to the sham condition due to after-effects, the sham condition should precede the verum condition. If, however, counterbalancing is preferred to rule out order effects, the sham condition should follow on the verum condition after a time lag exceeding the supposed after-effect duration. Alternatively, a between-subject design might be an option, especially in case of more than one control condition (e.g., several control frequencies in a tACS experiment).

The potential of tES for cognitive enhancement

Causal relationships have been demonstrated in numerous neurocognitive studies on sensory, motor, perceptual, and even higher cognitive processes like attention, memory function, decision making and intelligence (Coffman, Clark, & Parasuraman, 2014; Cohen Kadosh, 2015; Herrmann et al., 2013; Kuo & Nitsche, 2012). In this section, we will summarize some representative studies on the influence of different tES methods on higher-level cognition in order to illustrate the potential of tES for improving cognitive functions, which might be of special relevance for management and organizational research. For reasons of clarity, we sorted the different cognitive processes into broader categories.

Executive functions/ Cognitive control

Executive functions or cognitive control refer to a set of processes allowing for flexibly adapting behavior and information processing depending on current goals. Although cognitive control includes a wide range of cognitive domains, one common feature is the involvement of the prefrontal cortex, making it a preferred target for different cognitive enhancement strategies including brain stimulation (Enriquez-Geppert, Huster, & Herrmann, 2013).

One prominent example of an executive function is *working memory* (WM), a basic cognitive function involving the temporary storage and manipulation of information necessary to execute a complex task. WM is one of several functions relying on the lateral parts of the prefrontal cortex referred to as the dorsolateral prefrontal cortex (DLPFC). Accordingly, attempts to enhance WM performance by tES have mostly targeted the DLPFC. An often used task to measure WM functioning is the n-back task, in which participants are asked to indicate whether a currently presented stimulus is the same as the one presented n trials before.

In a 3-back WM task, Fregni et al. (2005) applied anodal and cathodal tDCS over the left DLPFC for 10 min and compared the results with a sham condition. Only anodal stimulation of the left DLPFC increased the number of correct responses with decreasing error rates compared to sham. Along the same lines, Zaehle et al. (2011) were able to demonstrate that tDCS of the left DLPFC modulates performance in a WM task. When participants were stimulated anodally over the left DLPFC, WM performance increased compared to a sham condition, whereas cathodal stimulation led to a decrease of WM performance in comparison to sham. Mulquiney et al. (2011) compared the effect of anodal tDCS and tRNS over the left DLPFC on WM performance. For a 2-back WM task, the authors found a decrease in reaction times (RTs) after anodal tDCS but not tRNS.

Polanía et al. (2012) studied the functional role of synchronized theta oscillations for cognitive performance in a WM matching task. In an EEG experiment, the authors found an increase of phase synchronization between left frontal and parietal electrode sites in the theta frequency range (4-7 Hz) during memory matching. In addition, RTs decreased with increasing synchronization at 0° phase lag between frontal and parietal oscillations. In a subsequent tACS experiment, this fronto-parietal network was stimulated with an oscillatory current at 6 Hz and a relative 0° or 180° phase difference. In line with the EEG findings, RTs decreased during synchronization of fronto-parietal regions with 0° phase lag and increased during desynchronization with 180° compared to sham stimulation. Stimulation at 35 Hz had no effect, demonstrating frequency specificity of the effect. These findings provide causal evidence for the relevance of theta phase-coupling in a fronto-parietal network during WM task.

Another example of great practical importance is *vigilance*, or sustained attention, protecting monitoring performance against fatigue and cognitive defocusing (Clayton, Yeung, & Cohen Kadosh, 2015). In a recent study, the functional role of the prefrontal cortex for vigilance was probed by applying tDCS vs. sham stimulation to the DLPFC, while the participants had to detect infrequent collision paths of aircraft for 40 min (Nelson, McKinley, Golob, Warm, & Parasuraman, 2014). During sham, a typical vigilance decrement was observed as indicated by decreasing target detection rates and increasing RTs with more time-on-task. During tDCS, however, target detection performance improved compared to sham, indicating that tDCS might be a useful tool in work settings that require maintained vigilance over extended periods of time.

Weighing of risks and benefits when making choices under uncertainty reflects another example of cognitive control, which is referred to as *decision-making*. In this context, tACS was applied in the theta frequency range (6.5 Hz) over left or right DLPFC to examine the laterality effects on risk-taking behavior (Sela, Kilim, & Lavidor, 2012), while the participants performed a task that requires decision-making under risk (balloon analog risk task, BART). Results showed that left hemispheric stimulation led to a riskier decision-making strategy compared to the groups of participants that received right DLPFC stimulation and sham, which did not differ from each other. These findings demonstrate a causal influence of both the DLPFC and theta oscillations on decision-making style. A causal role of the DLPFC for risky decision making has also been demonstrated using a different measure of risk preference during tDCS (Ye, Chen, Huang, Wang, & Luo, 2015), although the size of the effect seems to depend on the individual impulsivity level (Cheng & Lee, 2015).

Learning and memory

The acquisition of new cognitive skills requires intensive practice for a considerable amount of time. Since these behavioral improvements are based on accompanying neuroplastic changes in the brain, it is a long-standing question whether it is possible to facilitate learning and memory consolidation directly by “brain training”. Therefore, applying tES might be especially fruitful if combined with cognitive training. This has been demonstrated recently in the context of arithmetic learning (Snowball et al., 2013). The authors applied tRNS over the DLPFC for five consecutive days while the participants learned to solve arithmetic tasks by applying a specific algorithm, which is based on deep-level cognitive processing, or by drill learning. Interestingly, tRNS during learning led to an improvement of both learning forms, but long-term memory effects of at least six months duration were found for algorithm learning but not for drill learning. Moreover, the deep-level cognitive processing involved in algorithm learning also resulted in a transfer effect to new, unlearned tasks.

Intensified learning and improved performance during and immediately after brain stimulation was also reported for a novel unassisted discovery-learning task in which participants learned to recognize concealed threat-related objects in virtual naturalistic settings (Clark et al., 2012). tDCS was applied over the right inferior frontal and parietal cortex that had been selected from several task-relevant brain areas as revealed by fMRI. For both targeted areas, anodal tDCS with an intensity of 2 mA enhanced learning rate and accuracy compared to a low-intensity control condition (0.1 mA). After one hour, performance levels were assessed again revealing an increase of the difference between current intensities to a factor of two for frontal tDCS, indicating the involvement of neural plasticity.

In one of the first tES studies on cognitive enhancement, Marshall et al. (2006) investigated the functional role of anodal otDCS in the low-frequency range (<1Hz) for the formation of declarative memories during sleep. Participants were stimulated while they were sleeping with otDCS at 0.75 Hz over both sides of the forehead subsequent to an evening learning phase. The authors were able to demonstrate that boosting slow EEG-oscillations during non-rapid-eye-movement sleep improved memory performance (recall of words) after sleep compared to evening performance before sleep. These stimulation-induced effects on EEG oscillations and long-term memory were not obtained with sham stimulation (placebo) or a control frequency at 5 Hz (i.e., they were frequency specific).

Using the same otDCS protocol during wakefulness led to an EEG power increase in the slow oscillation frequency band but did not influence memory consolidation after the learning phase (Kirov, Weiss, Siebner, Born, & Marshall, 2009). However, when Kirov et al. (2009) applied the stimulation not during *consolidation* but during *encoding* of the learning material (i.e., during the learning period), there was an increase of the immediate recall performance. See Marshall and Binder (2013) for a review of similar studies.

Whereas the studies described above were exclusively concerned with learning and long-term memory, there are first attempts to use tES also for an improvement of short-term memory (STM). This attempt is based on the suggested role of oscillatory brain activity in the theta and gamma frequency range (30-80 Hz) for STM functioning. As stated in the theta-gamma coding theory of STM, the rehearsal of all items from a list that have to be stored is represented by one theta cycle, whereas each single item relates to one gamma cycle (Lisman & Idiart, 1995). Thus, the famous limitation of STM span to 7 +/- 2 items as formulated by George Miller (Miller, 1956) has been conceptualized as a phenomenon based on the ratio of gamma to theta frequencies in the brain (Fig. 8A).

[Insert figure 8 here]

According to this model, both a slowing of theta frequency and/or an increase in gamma frequency should improve the memory span. Regarding the theta cycle, this hypothesis was recently tested by applying tACS at a frequency slightly below the individual theta frequency (Vosskuhl et al., 2015). Indeed, the authors were able to demonstrate an increase in STM span (Fig. 8B).

Intelligence and creativity

Intelligence is a basic trait-like mental ability of high importance for an effective use of higher cognitive functions as discussed above. Creativity reflects the ability to produce original and unique work that is of use within a social context (Fink & Benedek, 2014). Both intelligence and creativity are highly demanded not only in culture, science and education but also in economic and industrial realms (Fink & Benedek, 2014).

Using tACS at different frequencies over the left frontal cortex, Santarnecchi et al. (2013) aimed at improving fluid intelligence, which they defined as “the ability to go beyond experience by efficiently encoding and manipulating new information” (p. 1449). Differences in fluid intelligence were assessed by the time needed to solve logical reasoning tasks of varying complexity from the Raven’s matrices (a non-verbal test of general intelligence). Frequency specificity was addressed by comparing the effects of four different frequencies in the theta (5 Hz), alpha (10 Hz), beta (20 Hz), and gamma (40 Hz) range. The only improving effect was found for gamma tACS, which selectively reduced the time needed to solve the more complex tasks involving conditional abstract reasoning. These findings support a direct role of frontal gamma oscillations for high-level cognition.

Interestingly, a recent study using anodal tDCS to stimulate frontal regions immediately before participants completed the Wechsler Adult Intelligence Scale (WAIS-IV) found a *decrease* in test performance compared to sham stimulation (Sellers et al., 2015). The WAIS-IV is a standardized instrument for assessing general intellectual ability as reflected by the full scale IQ score (FSIQ), which is composed of different subtests representing more specific cognitive functions. The authors obtained detrimental tDCS effects not only for the FSIQ but also for a specific perceptual reasoning task, showing similarities to the Raven’s matrices used by Santarnecchi et al. (2013) to study tACS effects on fluid intelligence. Therefore, Sellers et al. (2015) suggest opposing effects of tACS and tDCS on fluid intelligence.

The same research group also assessed the role of the frontal cortex for creativity (Lustenberger, Boyle, Foulser, Mellin, & Frohlich, 2015). Building on previously reported connections between creative ideation and alpha oscillations (Fink & Benedek, 2014), the authors applied tACS in the alpha range (10 Hz) vs. sham stimulation over the left and right frontal cortex, while participants worked on a standardized divergent thinking test (Torrance Test of Creative Thinking). In a control condition, participants received tACS at 40 Hz. As hypothesized by Lustenberger et al. (2015), creative ideation improved during tACS at 10 Hz but remained unaffected by 40 Hz, demonstrating the first direct evidence for a functional role of frontal alpha oscillations in creativity.

TES Safety

Up to now, there are no human studies available defining exact limits of safety with regard to the maximum possible stimulation duration. For healthy individuals, 20 minutes of tDCS with 2 mA is considered save, as was shown with frontal tDCS (Iyer et al., 2005). However, even longer durations of up to 50 minutes might be safe, since no cognitive or emotional disturbances have been observed using such a long-lasting protocol (Nitsche et al., 2008, see also for further aspects of safety requirements).

Limitations of both electric and magnetic techniques

So far, we have outlined available protocols and experimental parameters to choose from when designing a study involving brain stimulation, with an emphasis on their primary (expected) outcomes. However, usually not all participants of a tES study will show the desired effect. All of these techniques come with a number of caveats that need to be considered when designing a study and interpreting results. Excellent papers and reviews have discussed these points, such as Silvanto & Muggleton, 2008, Wagner, Rushmore, Eden, & Valero-Cabre, 2009, Sack et al., 2009, Ruff et al., 2009, Pell, Roth, & Zangen, 2011, Woods et al., 2016. One of the main problems is certainly the current poor understanding of the mechanism of actions of these techniques which often leads to uncertainty about and hence arbitrary choices of the stimulation parameters.

Some of the associated limitations are in many instances weak and short lasting effects for TMS and even more so for tES, hence being of interest more in a laboratory setting than for cognitive enhancement in the real world and for sustained effects (Parkin, Ekhtiari, & Walsh, 2015, Horvath, Forte, & Carter, 2015). Also, inter-individual and intra-individual variability can be considerable. A number of factors have been suggested that may play a role, including genetics, age, gender, physiological differences, anatomical variations, among others (for a review about variability determinants in TMS outcome see Ridding & Ziemann, 2010; for a review about tES see Krause & Cohen Kadosh, 2014). In addition, homeostatic plasticity may have a considerable role and leads to inverse effects in the course of a study (Ziemann & Siebner, 2008). However, at present, no deterministic model as to outcome is available and it is not clear why a certain participant is a responder or non-responder. Also, current computational and anatomical models of the effect distribution and spreading are insufficient to fully understand what exactly is being stimulated (e.g. region, neurotransmitter system; Bestmann, de Berker, & Bonaiuto, 2015; Hartwigsen et al., 2015).

Moreover, although it is reasonable to assume that the area being stimulated contributes to the behavioural changes, one should keep in mind that TMS affects the activity within a network of cerebral areas that are functionally connected to the target region (Bortoletto, Veniero, Thut, & Miniussi, 2015; Miniussi & Thut, 2009; Ruff, Driver, & Bestmann, 2009; Sack & Linden, 2003). Besides areas on the cortical mantle, subcortical brain regions will also experience elevated levels of current densities both during TMS and tES (as evidenced for instance by simultaneous neuroimaging, see Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Bestmann et al., 2008; Denslow, Lomarev, George, & Bohning, 2005; Strafella, Paus, Barrett, & Dagher, 2001) but again it is very difficult to predict which subcortical regions are targeted solely by the placement of the stimulation coil/electrode on the scalp. Individual head and brain models of the participants are required to predict precisely the patterns of intra-cortical current flow.

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Captions

Figure 1. A participant receiving tES from two electrodes positioned at the vertex (anode, red) and over visual cortex (cathode, blue) while performing a cognitive task on a computer. The portable, battery-operated tES device is located next to the monitor.

Figure 2. A) A participant receiving TMS over the left primary motor cortex with a figure-of-eight coil held in place by means of a mechanic arm. B) Two different coil designs: figure-of-eight on the left and a circular coil on the right.

Figure 3. Schematic representation of different TMS protocols. A: Single pulse TMS (spTMS) is applied during a cognitive task at single trial level. Repetitive TMS can be applied either task at trial level during (online) a cognitive task (B) or before the task execution (offline, C). Panels D and C illustrate the two stimulation paradigms used for continuous (cTBS) or intermittent (iTBS) theta burst stimulation.

Figure 4. Assumed neural mechanism of tDCS. Left panel: Without tDCS, the resting potential of the cell is at -70 mV and an incoming excitatory post-synaptic potential (EPSP) arriving 100 ms after onset of the experiment does not reach the threshold for firing at -50 mV (dashed line). Middle panel: If the neuron is close to an anode, the positive voltage from the anode will raise the resting potential towards a more positive voltage and the same EPSP will exceed the threshold and result in a neural spike. Right panel: If the neuron is close to a cathode, the negative voltage from the cathode will lower the resting potential towards a more negative voltage and the same EPSP will not exceed the threshold.

Figure 5. Stochastic resonance. Left: Consider the case that both the amplitude of a sinusoidal signal (red) and that of wide-band noise (blue) are too weak to exceed a threshold (black line). Right: If signal and noise are added, the resulting signal (gray) will exceed the threshold. Interestingly, the frequency of the sine wave determines the frequency at which the resulting signal will exceed the threshold. In case of tRNS, the red sine wave represents a sub-threshold neural oscillation and the blue signal the external tRNS signal.

Figure 6. Theory of entrainment. If the brain is stimulated near the frequency of an ongoing brain oscillation (intrinsic frequency), i.e. the individual alpha activity around 10 Hz, the EEG will synchronize to the frequency of the driving force (e.g. tACS). This is considered synchronization or entrainment of an oscillator by an external driving force and depicted in gray (1:1 region). If, however, the stimulation frequency is far from the intrinsic frequency, the EEG will be dominated by its intrinsic frequency (white regions of diagram, no entrainment). If the strength of the external driving force (tACS) increases, the synchronization regions will become wider in frequency. Due to this triangular shape the synchronization region is referred to as an Arnold tongue (Pikovsky et al., 2001). Synchronization can also happen at harmonics (N * intrinsic frequency) and subharmonics (intrinsic frequency/N) where N is an integer (1:2 and 2:1 show here).

Figure 7. Intracranial current flow due to tES. Strongest increases in current density (red and orange colors) are in the vicinity of the stimulation electrodes (red and blue patches on the scalp). Subcortical regions also receive electrical stimulation. However, the exact location depends more on individual cortex anatomy than on the placement of the electrodes, since convex curvatures of cortical tissue into cerebral fluid experience strongest current densities. Reproduced with permission of the authors from Herrmann et al. (2013).

Figure 8. Interaction of theta and gamma oscillations assumed to explain human memory span. A: The number of cycles of a gamma oscillations (here ~23 ms due to a frequency of 42 Hz) that fit into one theta cycle (here ~142 ms due to a frequency of 7 Hz) determines the memory span (here six items). B: If the frequency of the theta oscillation is lower (6 Hz resulting in ~17 ms) while the gamma frequency stays stable, the memory span increases to seven items. Reproduced with permission of the authors (Vosskuhl, Huster, & Herrmann, 2015).