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Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)—From insights into human memory to therapy of its dysfunction

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Abstract

Noninvasive stimulation of the brain by means of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) has driven important discoveries in the field of human memory functions. Stand-alone or in combination with other brain mapping techniques noninvasive brain stimulation can assess issues such as location and timing of brain activity, connectivity and plasticity of neural circuits and functional relevance of a circumscribed brain area to a given cognitive task. In this emerging field, major advances in technology have been made in a relatively short period. New stimulation protocols and, especially, the progress in the application of tDCS have made it possible to obtain longer and much clearer inhibitory or facilitatory effects even after the stimulation has ceased. In this introductory review, we outline the basic principles, discuss technical limitations and describe how noninvasive brain stimulation can be used to study human memory functions in vivo. Though improvement of cognitive functions through noninvasive brain stimulation is promising, it still remains an exciting challenge to extend the use of TMS and tDCS from research tools in neuroscience to the treatment of neurological and psychiatric patients.

Keywords: Transcranial magnetic stimulation; TMS; Repetitive TMS; rTMS; Transcranial direct current stimulation; DCS; Cortical excitability; Human memory functions; Brain mapping; Brain polarization

1. Introduction

The noninvasive stimulation of the human brain has achieved enormous progress in the study of human cognition over the last two decades. Electrical stimulation of the cortex has been already used centuries ago to make fundamental discoveries on brain organization and function (important contributions result from the works of e.g., Fritsch (1838–1927) and Hitzig (1838–1907), Ferrier (1843–1928), Sherrington (1856–1952) and Penfield (1991–1976)). In 1980, Merton and Morton described the first stimulation of the human motor cortex through the intact skull of an unanesthetized human [1]. However, transcranial electrical stimulation (TES) is not widely used because of the undesirable pain it causes. A much more convenient method was invented by Barker and colleagues only five years later, namely transcranial magnetic stimulation (TMS) [2]. Since this approach relies on the induction of small electrical currents in the brain by a magnetic field which passes through the skull, the application of TMS is painless and therefore widely used for noninvasive stimulation of the human brain.

Recently, another stimulation technique available that existed since the beginning of the last century, regained

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attention in neuroscience: the transcranial direct current stimulation (tDCS) [for reviews see 3,4]. In contrast to TES, electrical currents are applied constantly over a longer period of time, usually in the order of minutes, at much lower intensities to achieve changes in cortical excitability that persist even after stimulation has ceased.

There have been a number of comprehensive reviews on the general use of TMS in cognitive neuroscience [5–9]. In this article, we give an introductory conceptual overview of noninvasive brain stimulation as a method to study human memory functions in vivo. We illustrate different methodological approaches using examples taken from the large body of studies that have been performed in the memory domain in the past few years [for a recent review, see [10]]. We also discuss important technical shortcomings and limitations and, furthermore, how they can be overcome to some extent, for instance, by the combined use of other brain mapping techniques.

1.1. Basic principles of TMS/rTMS

To perform TMS experiments, a stimulator (i.e., pulse generator) is needed to which different stimulation coils can be connected to apply brief magnetic pulses of up to several Tesla. Such systems consisting of a stimulator and a coil can be obtained from various manufacturers (e.g., MAG & More, Munich, Germany; Magstim, Whitland, Wales, UK; Medtronic/Dantec, Minneapolis, Minnesota, US). It is necessary to note that both, the type of stimulator and the type of TMS coil may have a profound impact on the results obtained. This issue should be taken into account when comparing the results of different studies, and, in particular, when rTMS is used for therapeutic purposes [11]. The stimulation works by passing a large (~5 kA or more), brief (<1 ms) current through the wired and insulated coil placed on the subject's scalp. The brief current flowing through the coil generates a magnetic pulse that penetrates the skull and in turn induces small eddy currents in electrically conductive regions (i.e., in the underlying brain tissue). Relatively focal stimulation can be achieved by combining two circular coils to form a figure-of-eight (or butterfly) coil. The magnetic fields sum up at the point of intersection of both coils. Using spherical model approximation, it has been estimated that the spatial resolution of TMS lies in the cm range (10–20 mm) [12]. As per the physical law of electromagnetic induction, the secondary induced current flows in the direction opposite to the primary current in the coil. Since it has been shown that different current directions may significantly affect the results [e.g., 13–16], probably by exciting different neuronal populations [13], the coil orientation has to be controlled carefully. The real magnitude of the induced currents remains unknown. However, current densities have been measured in a patient with implanted depth electrodes [17]. The rapid decline in magnetic field strength with distance depending on coil size and stimulation intensity is a critical issue in cortical stimulation [18] and thereby limits its application to areas within the vicinity of not deeper than 2–3 cm [19]. Imaging studies using functional magnetic resonance imaging (fMRI) [e.g., 20] and positron emission imaging (PET) [e.g., 21,22 demonstrated that TMS may affect remotely-located networks which are transsynaptically connected to the stimulated area.

Neurophysiological studies of motor cortex excitability made significant contributions to our knowledge about which particular neuronal structures are activated by TMS. The observation that TMS produces a corticospinal volley with indirect waves (I-waves) rather than with an early direct wave (D-wave) suggests that TMS excites corticospinal neurons indirectly through synaptic inputs [23]. Furthermore, certain neuronal populations (e.g., inhibitory interneurons) can be activated differentially if TMS is applied using sophisticated stimulation protocols (e.g., paired-pulse stimulation [for a review, see 24,25]). However, the exact mechanisms of TMS outside the motor cortex (i.e., non-motor areas) remain still unknown (Fig. 1).

TMS studies can be carried out with various stimulation parameters and protocols. The main stimulation characteristics are (1) strength of stimulation, usually expressed as percentage of the maximum stimulator output, and (2) frequency of stimulation. Single pulses guarantee a very high temporal precision (in the ms range). If, however, a train of multiple pulses of the same intensity is applied at

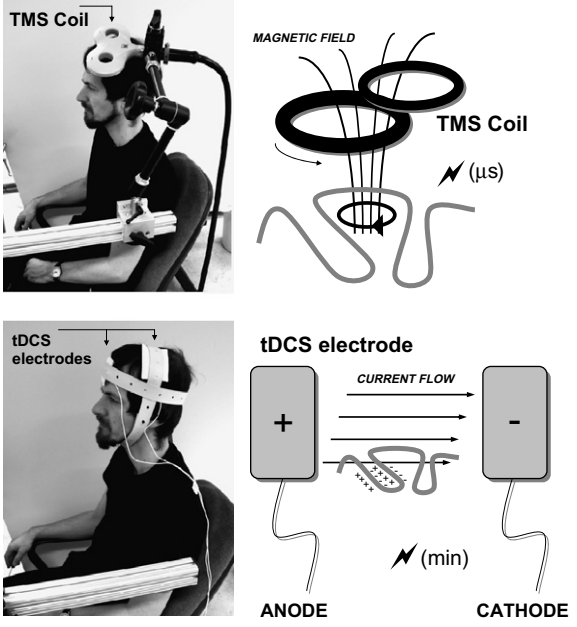

Fig. 1. Upper part: TMS, a figure-of-eight shaped TMS coil placed on the subject's head using a mechanical coil holder. A brief electrical current (uS) generates a magnetic field around the coil windings, which, in turn, induces electrical currents in the brain that flows in parallel, but opposite to those in the TMS coil. Lower part: tDCS, two 35 cm^2 sponge electrodes (i.e., anode or cathode depending on DC polarity) are fixed to the subject's head. A constant electrical current generated by the tDCS stimulator is, usually, applied over a few minutes (e.g., 3–20 min). The electrical current flows from the anode (+) to the cathode (−) through the superficial cortical areas leading to polarization.

a particular frequency, the stimulation is called repetitive TMS (rTMS). In the motor cortex, rTMS can induce modulation of cortical excitability that outlasts the actual stimulation by several minutes [26–28]. In general, lower frequencies (in the range of 1 Hz) are thought to suppress excitability [27,28], while high frequency rTMS (10–20 Hz) may result in a temporary increase in cortical excitability [26]. Likewise, similar effects can be observed in studies of non-motor areas. The higher the stimulation frequency and intensity, the greater is the interference with cortical function during stimulation in most cases. Depending on the stimulation parameters, especially the stimulation frequency, inhibitory (e.g., increase of error rates [29]) or facilitatory (e.g., decrease in reaction times [30]) effects have been observed at the behavioral level. The perturbation of brain activity resulting from low-frequency rTMS, in particular, has been applied to study brain-behavior relations (see below). The physiological mechanisms of these after-effects are still unclear. It has been hypothesized that long-term potentiation (LTP) and depression (LTD) of cortical synapses [31] could play a key role. Modulation of neurotransmitters [e.g., 32] and genetic mechanisms [e.g., 33] may also contribute to these effects as suggested by animal studies.

1.2. Basic principles of tDCS

In comparison to TMS, tDCS requires inexpensive hardware and the procedure is simple. The most important component is a current generator, which is capable of delivering a constant electrical current flow of up to 2 mA. In principal, the building of such a battery-driven device should not be a complicated task for an experienced electronic technician. However, there are specialized manufactures who incorporated some additional safety features into their commercially available stimulators (e.g., NeuroConn/Eldith, Ilmenau, Germany; Rolf Schneider Electronics, Gleichen, Germany). The electrical current is delivered through two sponge electrodes soaked in saline solution. Typically, these electrodes have a relatively large surface of 20–35 cm^2 that limits the focality of stimulation. However, the large size keeps current densities low, which constitutes one of the critical safety parameters. Nevertheless, subjects may feel a mild tingling or itching sensation on the scalp beneath the electrodes. tDCS relies on the assumption that a weak constant direct current (DC) polarizes tissue [3]. Stimulation is usually applied for a few minutes (up to 30 min). Depending on the direction of current flow, i.e. polarity, tDCS can be delivered either ''cathodal'' or ''anodal''.

Studies on cortical excitability showed that tDCS of the motor cortex results in significant excitability shifts during and after stimulation [34,35]. Moreover, the nature of these modulations seem to depend critically on tDCS polarity. Anodal tDCS enhances excitability, whereas cathodal tDCS reduces it [34,35]. Recent pharmacological studies suggest that the immediate short-lasting effects of tDCS are probably generated solely by polarity-specific shifts of the cell's resting membrane potential. On the contrary, the formation of the long-lasting after-effects depends on membrane potential changes as well as modulations of NMDA receptor efficacy [36,37]. In simple terms, tDCS does not cause resting neurons to fire; it rather modulated the spontaneous firing rate of neurons by acting at the level of the membrane potential. This quality distinguishes tDCS from other stimulation techniques, which excite neurons directly, such as TMS/rTMS, conventional TES or electroconvulsive therapy in psychiatry. The observation that tDCS, if delivered at intensities of approx. 1–2 mA and over a period of >8 min or so, can induce persisting changes in brain excitability for hours opened not only the possibility to further investigate human cognition, but also to evaluate its potential application as a complementary treatment in neurological rehabilitation [38].

1.3. Safety

Though TMS and tDCS are noninvasive by nature, both stimulation techniques are associated with potential risks that require certain precautions. If, however, the experienced investigator follows the appropriate guidelines and recommendations [e.g., TMS: 39–41 and DCS: 4,42,43] both techniques can be applied safely with minimal adverse effects.

1.4. Technical limitations

TMS in cognitive studies has many potential pitfalls [for in-depth review, see 44] and success appears to depend not only on the degree of stimulation (i.e., intensity and frequency), but also crucially on the experimental design. In studies on cognitive functions there is often insufficient knowledge about the where and when of TMS application. Ideally, the precise time course at which a certain brain area makes critical contribution to a given behavior is known in advance. Such information could be derived from previous studies that used other brain mapping techniques, such as event-related potentials (time) or functional magnetic resonance imaging (location). Alternatively, the application of rTMS, which covers a larger time window, might be beneficial, if there is uncertainty about the temporal profile of the target area. Even if the exact temporal and spatial information is available, the precise and reliable positioning of the TMS coil is, however, not a simple task. It has to be noted that magnetic stimulation outside the motor and visual cortex does not result in an overt response such as muscle twitches or visual sensations (i.e., phosphenes), respectively. Optically tracked frameless stereotaxic neuronavigation systems, which incorporate individual MRI data, have been developed to tackle this problem. While the first systems were designed for stereotaxic neurosurgery, there are meanwhile systems available designed specifically for TMS research (Brainsight/Rogue Research, Montreal Canada; Localite, Sankt Augustin,

Germany; Nexstim, Helsinki, Finland). These systems achieve the virtual linkage between MR images and real anatomy, and allow three-dimensional (3D) orientation by interactive visual navigation. In principle, neuronavigation can be based on the structural (anatomical) MRI or the functional MRI obtained in the same subject. Another approach represents the use of functional neuroimaging data from the literature, so-called "probabilistic approach" [7,45]. The latter assumes consistency across individuals in the location of task-related "activations" in standardized stereotaxic space. On the other hand, conventional non-stereotaxic navigated localization of brain areas is still a common method to define coil position. For instance, researchers often use the International 10-20 EEG system for the coil positioning [e.g., 46,47] or standardized function-guided procedures [e.g., 48]. Such procedures include, for instance, localization of the primary motor or visual cortex by recording, respectively, TMS-induced motor responses [e.g., 29] or phosphenes [e.g., 49]. The above mentioned strategies differ not only in time and effort, but certainly in accuracy also. Recently, we compared in a combined fMRI and TMS experiment the accuracy of TMS coil positioning of five different localization approaches (two conventional and three stereotaxic neuronavigational strategies) [50]. The results showed that accuracy benefits from the use of stereotaxy in general (spatial deviations in millimeter range). In particular, very consistent results were obtained with the "probabilistic" approach. In future, the development of more focal TMS coils [e.g., 51] and mechanical positioning aids may increase the accuracy and reproducibility of stereotaxic coil positioning. For instance, Lancaster et al. reported that they were able to achieve an overall accuracy in positioning of about 2 mm by means of an image-guided robotically positioned TMS system [52]. Recently, Knecht et al. investigated another frequently unrecognized, but critical issue [53]. For identical TMS intensities they found that regional differences in scalp-to-cortex distance (there is usually large lateral to medial gradient) can translate into differences in electric field strength in the underlying superficial cortex of up to a factor of two. Further software developments may also contribute to higher accuracy [54]. In comparison to TMS, the major limitation of tDCS is probably that it is not focal enough to map cortical functions precisely. Furthermore, it cannot produce temporally focused effects like TMS. On the other hand however, the application is simple. Successful blinding of subjects and investigators is possible to conduct double-blind and sham-controlled trials [55].

2. Applications in memory research

During the last 10–15 years TMS has been used with increasing success in the study of learning and memory processes. Nevertheless, researchers in the field of memory first had to acknowledge a major drawback of TMS: the limited depth of penetration [19]. Despite many technical progresses, focusing the magnetic field directly into brain areas located many centimeters below the scalp (i.e., hippocampus, amygdala or mammillary bodies) remains impractical at present. Meanwhile, however, neuroscientists discovered that memory processes can be also attributed to several other cortical and subcortical structures. For instance, while the hippocampus plays a key role in memory formation and retrieval, frontoparietal networks are involved in working memory (WM) as well as the encoding and retrieval of novel items. In the following section we give some examples in which memory can be studied in humans using noninvasive brain stimulation.

2.1. Interference—the "virtual lesion technique"

Before the advent of TMS and functional neuroimaging, most data on human memory were derived from lesion studies and neuropsychological investigations. The purpose of lesion studies is to establish a correlation between a circumscribed brain region and changes in behavior. Likewise, rTMS has the capacity to perturb human brain function by adding temporary noise to cortical processing. In accordance with the "creation of virtual patients" researchers have named this approach the "virtual lesion technique" [6]. In general, a distinction can be made between off-line and on-line rTMS studies (Fig. 2a and b). The off-line method uses relatively long trains of rTMS to achieve lasting effects even after stimulation has ceased. In studies that use an on-line rTMS design, short trains are delivered while subjects perform a certain task. While low-frequency rTMS (1–2 Hz) is often used to decrease excitability in the off-line mode, short trains are delivered at high frequencies (>10 Hz) during the task if rTMS is applied on-line.

2.1.1. On-line rTMS

A relatively large number of studies have applied rTMS during the performance of a memory-related task [e.g., 56–66]. Using a typical on-line rTMS approach Nixon et al. examined the role of the left inferior frontal gyrus (IFG) in phonological processing and verbal working memory [60]. Trains of five pulses (10 Hz, 500 ms duration) were applied over the frontal operculum while subjects performed a delayed phonological matching task. Delivered at a time when subjects were required to remember the sound of a visually presented word, rTMS impaired the accuracy with which they subsequently performed the task. However, when delivered later in the trial, as the subjects compared the remembered word with a given pseudoword, rTMS did not impair accuracy. The authors concluded that the opercular region of the IFG is therefore necessary for the normal operation of phonologically based WM mechanisms. Likewise, Romero et al. investigated the neural correlates of phonological short-term memory [62]. rTMS was delivered at 5 Hz frequency in train of 1500 ms duration during the performance of phonological judgments and two control tasks (digit and pattern span, respectively).

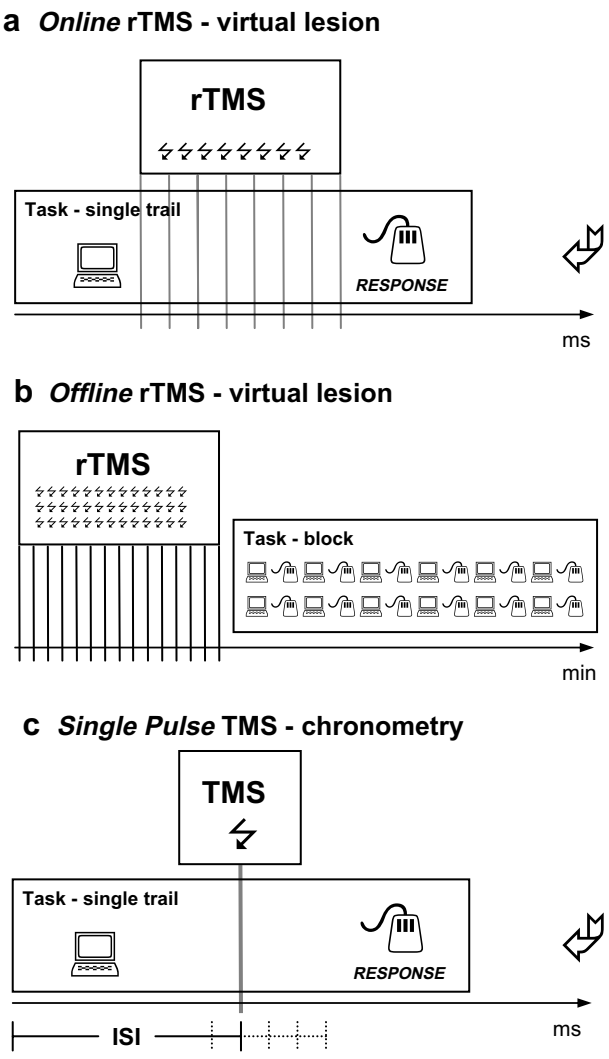

Fig. 2. Shematic illustration of different TMS approaches. (a) "Online rTMS"—a brief train of magnetic pulses (e.g., 5–8 pulses at 10 Hz) is applied during each single trail to modulate the brain activity of the targeted region and to measure changes in performance behaviourally. (b) "Offline TMS"—a large number of magnetic pulses (e.g., 600 pulses at 1 Hz) is applied to modulate brain activity temporarily. In this case, the task is performed blockwise. The induced after-effects, i.e. the "virtual lesion", last approx. for a few minutes. The results (e.g., reaction times) are usually compared to a baseline block acquired before the application of rTMS for statistical analysis. (c) "Single-pulse TMS-chronometry"—a single TMS pulse is given during each trail at various interstimulus intervals (ISIs). This elegant approach can be used to trace precisely the timing at which activity in a particular cortical region contributes to a given task.

Reaction times increased and accuracy decreased in the case of the phonological judgments and digit span after stimulation of both left sites, suggesting that Brodmann Area (BA) 40, in addition to BA 44, is involved in phonological judgments.

2.1.2. Off-line rTMS

The off-line approach relies on the induced after-effects of rTMS. Since behavioral measures are compared before and after rTMS, it is unlikely that non-specific effects of the stimulation (i.e., the noise and skin sensation of stimulation) interfere with the task performance. A number of studies demonstrated that memory functions can be studied using off-line rTMS [29,67–69]. For instance, the domain-specific segregation of WM between ventral and dorsal prefrontal cortex was investigated [29]. Subjects performed either a spatial or a face-recognition delayed-response task. Task performance was compared prior and post a rTMS train of 1 Hz rTMS/10 min. In separate sessions, rTMS was applied to the dorsomedial (DMPFC), dorsolateral (DLPFC) or ventral prefrontal cortex (VPFC). Each trial contained 15 spatial dWM trials and 15 dWM trials for faces in random order. A double dissociation was found: rTMS disrupted WM for faces when applied to VPFC or DLPFC. Spatial WM was only impaired after rTMS to the DLPFC and to the more mediodorsal region (DMPFC), around the superior frontal sulcus.

2.2. Interference with single pulses-chronometry

If single pulses are applied at different poststimulus onset times, TMS can assess the timing of the critical contributions of a given cortical area (Fig. 2c). In this way, several studies have provided information about which cortical area contributes to performance in a specific task, and at what precise moment the contribution is critical [70–76]. In a series of experiments, Oliveri et al. investigated the contributions of the superior frontal gyrus (SFG), the DLPFC, middle temporal regions and posterior parietal cortex (PPC) to visual-object and visual-spatial WM [76]. Unilateral and bilateral single-pulse TMS was delivered at different delays during visual n-back tasks. Bilateral temporal TMS decreased performance in the visual-object, whereas bilateral parietal TMS selectively increased reaction times in the visual-spatial WM task. These effects were evident at a delay of 300 ms. TMS of the SFG selectively slowed reaction times in the visuospatial WM task, whereas TMS of the DLPFC interfered with both WM tasks. These effects were evident when TMS was applied after a delay of 600 ms, but not after 300 ms. Overall, the findings contributed to the concept of segregation of WM buffers for object and spatial information. Recently, Kahn et al. investigated both the involvement of the prefrontal cortex during the verbal encoding of familiar and unfamiliar words, and the timing of this involvement [74]. Single-pulse TMS was pseudo-randomly given at one of 11 different delays (between 250 and 600 ms). Results revealed differential contributions of left and right VPFC to encoding of familiar words which peaked at 380 ms, as observed by a decline in subsequent high confidence recognition when left VPFC was disrupted and an increase in subsequent medium confidence recognition when right VPFC processing was disrupted. In contrast, right VPFC disruption facilitated subsequent memory for familiar words, expressed as an increase in medium confidence recognition,

the facilitation being maximal at 380 ms. Finally, phonological (syllable) decision was facilitated by disruption of right VPFC, the effect being strongest at 340 ms for both familiar and unfamiliar words.

2.3. TMS in combination with other brain mapping techniques—multimodality

A major drawback intrinsically tied to most neuroimaging techniques consists of the fact that these methods only establish correlations between performing a task and activity in certain brain areas. This applies to changes in blood oxygenation level dependent (BOLD) signals as well as changes in regional cerebral blood flow (rCBF) and electric potentials as measured using fMRI, positron emissions tomography (PET) or electroencephalography (EEG), respectively. Furthermore, interference techniques, such as TMS, possess the ability to disentangle areas activated due to task performance from epiphenomenally activated areas [9]. Very interesting studies of the past years represent those combining the interference approach TMS with different correlational neuroimaging methods such as PET [e.g., [45,77]], fMRI (e.g., 20, 78) or EEG [79,80]. In this way, neuroimaging techniques can benefit from the combination with TMS-induced virtual lesions to gain information not only about functional relevance and specialization, but also about functional connectivity in the brain [7].

To investigate human memory, multimodal approaches (e.g., combining fMRI and TMS) are usually performed sequentially (i.e. at two stages). This can be done in two different ways: (1) fMRI can be used to guide the application of TMS (e.g., [57,59,61]). In this case, researchers typically aim to test for causality. (2) It is possible to investigate the after-effects or behavioral effects of rTMS with fMRI [e.g., 66,69]. In recent years, major advances have also been made in the simultaneous combination of TMS and fMRI (“concurrent TMS–fMRI”) [20,78]. Nevertheless, a concurrent TMS–fMRI study has not been conducted in the field of memory research so far. In comparison to fMRI, the combination of TMS with PET benefits from less interference of conflicting magnetic fields. In a series of two PET experiments the brain-behavior relationship (BBR) as defined by the correlation of individual rCBF changes and individual performance was studied [81,82]. Subjects received short trains of rTMS (120 stimuli at 4 Hz = 30 s) over frontal and parietal cortex during the performance of a 2-back task in the scanner. As a main finding it was found that online rTMS over the left and right DLPFC differentially modulates the BBR within the left DLPFC. With right DLPFC rTMS the correlation between left DLPFC rCBF and performance was no longer detectable. Moreover, a “new” BBR in Broca’s area which is presumed to be activated earlier in time was found most probably as a compensatory mechanism. These modulations might be indicative for the capacity of the brain to immediately react to a disruption of a cortical network by recruiting adjacent neuronal assemblies in the sense of short-term plasticity. Finally, the results demonstrate the feasibility of the combination of cognitive tasks, functional imaging and online rTMS [for a review, see [83]].

2.4. Special approaches

Important insights into human memory function have been derived from studies on eye movement control and memory-guided saccades, in particular [84]. It should be mentioned that TMS made valuable contributions to this field in a number of studies, which are not addressed in this article [for a review, see [85]]. TMS can also provide insights into brain function beyond that which can be obtained from interference studies. In the motor system, the combined application of TMS and neuropsychiatric drugs with well-defined actions on a given neurotransmitter system has been proved useful to investigate changes of cortical excitability and short-term plasticity, the latter probably relying on LTP-like strengthening of synaptic efficacy [for a review, see [86]]. It seems reasonable that such approaches of “neuropharmacological TMS” could also contribute to a better understanding of human memory functions in the near future.

2.5. Animals studies

Compared with the growing number of human trials, there are relatively few studies that have used TMS in animal models to identify direct neuronal effects of rTMS on memory and learning [87–91]. In general, spatial accuracy of TMS in small animals with standard coils is poor, the temporal resolution of interfering with the activity of the brain remains, however, precise. In the auditory cortex of rodents, it has been demonstrated that TMS can induce long-term depression (LTD) and potentiation (LTP) [91]. Moreover, Ahmed and Wieraszko investigated the influence of high-frequency rTMS on learning process in mice and on neuronal excitability of the hippocampal tissue obtained from stimulated animals [87]. While the stimulation with rTMS at higher frequency (15 Hz) improved in vivo animals’ performance in novel object recognition test, lower frequency (1 and 8 Hz) impaired the memory temporarily. In parallel, there was a significant enhancement of the synaptic efficiency in vitro expressed as the LTP recorded from hippocampal slices prepared from the animals exposed to 15 Hz rTMS. Lasting effects of tDCS on cortical excitability have also been reported in animals [92].

2.6. Enhancing of brain functions

Though it is well accepted that TMS can disrupt normal brain function, the enhancement of cognitive (i.e. non-motor) functions by TMS or rTMS [e.g. 30,93–96] is still controversial [44]. In particular, it has been claimed that enhancement of function at least in part might be a

non-specific effect of brain stimulation or due to intersensory facilitation, non-specific arousal reactions or enhancement of attention, respectively [97]. These arguments, however, do not apply in turn to tDCS which effects can be tested in placebo-controlled trials much better than rTMS [55]. Anodal tDCS has been proved to ameliorate brain functions in several "placebo-controlled" trials [e.g., 98–102]. Marshall et al. showed that the application of tDCS is even repeatedly possible over frontal cortical areas during slow-wave rich sleep, which showed to improve declarative memory consolidation [100].

2.7. Studies in patients

In recent years, a growing number of studies set out to evaluate noninvasive brain stimulation techniques as a potential complementary treatment of cognitive deficits [e.g., 103–105]; for a review, see [38], [106]. Using an innovative approach, Sole-Padulles et al. investigated the effects of rTMS on memory performance and brain activity in elderly subjects presenting with memory complaints [69]. The authors assessed the effects of off-line high-frequency rTMS (10 rTMS trains of 10 s at 5 Hz during a 5-min period) with fMRI in addition to behavioral measurements. Subjects who received active rTMS improved significantly in associative memory. This effect was accompanied by additional recruitment of right prefrontal and bilaterial posterior cortical regions as revealed by fMRI. The results suggest that rTMS may be capable of transiently and positively influencing brain function and cognition among the elderly with memory complaints. Recently, Boggio et al. investigated the effect of anodal tDCS on WM task performance in Parkinson patients [103]. The results revealed a significant improvement in working memory as indexed by task accuracy, after active anodal tDCS of the DLPFC.

3. Conclusion

Noninvasive brain stimulation has developed as a sophisticated tool for cognitive neuroscience research and driven further discoveries in the field of human memory functions. The combination of brain stimulation with other brain mapping techniques holds great potential to provide even more valuable advances in our understanding of human cognition. Furthermore, evolving new stimulation protocols have shown to produce even longer and much clearer inhibitory or facilitatory after-effects [e.g., 107]. In particular, the potential of enhancing behavior by anodal tDCS is intriguing and could have significant impact on neurorehabilitative treatments. Nevertheless, studies to date have not provided enough data to proceed to a systematic application of noninvasive brain stimulation in the clinical routine. Promising therapeutic uses are, however, on the horizon [e.g., 38,106,108]. Major advances in technology have been made in a relatively short period. It seems therefore not inconceivable that significant further achievements will be realized in the near future.

4. Conflict of interest

We have no conflicts of interest.

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References

[1] P.A. Merton, Nature 285 (1980) 227.
[2] A.T. Barker, R. Jalinous, I.L. Freeston, Lancet 8437 (1985) 1106–1107.
[3] W. Paulus, Suppl. Clin. Neurophysiol. 56 (2003) 249–254.
[4] A. Priori, Clin. Neurophysiol. 114 (2003) 589–595.
[5] M. Jahanshahi, J.C. Rothwell, Exp. Brain Res. 131 (2000) 1–9.
[6] A. Pascual-Leone, D. Bartres-Faz, J.P. Keenan, Philos. Trans. R. Soc. Lond. B. Biol. Sci. 354 (1999) 1229–1238.
[7] T. Paus, Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (2005) 1109–1114.
[8] A.T. Sack, D.E. Linden, Brain Res. Brain Res. Rev. 43 (2003) 41–56.
[9] V. Walsh, A. Cowey, Nat. Rev. Neurosci. 1 (2000) 73–79.
[10] A. Floel, L.G. Cohen, Brain Res. Brain Res. Rev. (2006), [Epub ahead of print].
[11] N. Lang, J. Harms, T. Weyh, R.N. Lemon, W. Paulus, J.C. Rothwell, H.R. Siebner, Clin. Neurophysiol. 117 (2006) 2292–2301.
[12] D.E. Bohning, L. He, M.S. George, C.M. Epstein, J. Neural. Transm. 108 (2001) 35–52.
[13] J.P. Brasil-Neto, L.G. Cohen, M. Panizza, J. Nilsson, B.J. Roth, M. Hallett, J. Clin. Neurophysiol. 9 (1992) 132–136.
[14] P.T. Fox, S. Narayana, N. Tandon, H. Sandoval, S.P. Fox, P. Kochunov, J.L. Lancaster, Hum. Brain Mapp. 22 (2004) 1–14.
[15] A.C. Hill, N.J. Davey, C. Kennard, Neuroreport 11 (2000) 3257–3259.
[16] T. Kammer, S. Beck, M. Erb, W. Grodd, Clin. Neurophysiol. 112 (2001) 2015–2021.
[17] T. Wagner, M. Gangitano, R. Romero, H. Theoret, M. Kobayashi, D. Anschel, J. Ives, N. Cuffin, D. Schomer, A. Pascual-Leone, Neurosci. Lett. 354 (2004) 91–94.
[18] J. Ruohonen, R.J. Ilmoniemi, Electroencephalogr. Clin. Neurophysiol. 51 (Suppl.) (1999) 30–40.
[19] D. Rudiak, E. Marg, Electroencephalogr. Clin. Neurophysiol. 93 (1994) 358–371.
[20] S. Bestmann, J. Baudewig, H.R. Siebner, J.C. Rothwell, J. Frahm, Neuroimage 28 (2005) 22–29.
[21] P.A. Chouinard, Y.D. Van der Werf, G. Leonard, T. Paus, J. Neurophysiol. 90 (2003) 1071–1083.
[22] T. Paus, R. Jech, C.J. Thompson, R. Comeau, T. Peters, A.C. Evans, J. Neurophysiol. 79 (1998) 1102–1107.
[23] V. Di Lazzaro, A. Oliviero, F. Pilato, P. Mazzone, A. Insola, F. Ranieri, P.A. Tonali, Neurol. Res. 25 (2003) 143–150.
[24] M. Kobayashi, A. Pascual-Leone, Lancet Neurol. 2 (2003) 145–156.
[25] R. Chen, Muscle Nerve 9 (Suppl) (2000) S26–S32.
[26] A. Berardelli, M. Inghilleri, J.C. Rothwell, S. Romeo, A. Curra, F. Gilio, N. Modugno, M. Manfredi, Exp. Brain Res. 122 (1998) 79–84.
[27] R. Chen, J. Classen, C. Gerloff, P. Celnik, E.M. Wassermann, M. Hallett, L.G. Cohen, Neurology 48 (1997) 1398–1403.
[28] J.R. Romero, D. Anschel, R. Sparing, M. Gangitano, A. Pascual-Leone, Clin. Neurophysiol. 113 (2002) 101–107.
[29] F.M. Mottaghy, M. Gangitano, R. Sparing, B.J. Krause, A. Pascual-Leone, Cereb. Cortex 12 (2002) 369–375.
[30] F.M. Mottaghy, M. Hungs, M. Brugmann, R. Sparing, B. Boroojerdi, H. Foltys, W. Huber, R. Topper, Neurology 53 (1999) 1806–1812.

[31] S.F. Cooke, T.V. Bliss, Brain 129 (2006) 1659–1673.
[32] M.E. Keck, I. Sillaber, K. Ebner, T. Welt, N. Toschi, S.T. Kaehler, N. Singewald, A. Philippu, G.K. Elbel, C.T. Wotjak, F. Holsboer, R. Landgraf, M. Engelmann, Eur. J. Neurosci. 12 (2000) 3713–3720.
[33] R.R. Ji, T.E. Schlaepfer, C.D. Aizenman, C.M. Epstein, D. Qiu, J.C. Huang, F. Rupp, Proc. Natl. Acad. Sci. USA 95 (1998) 15635–15640.
[34] M.A. Nitsche, A. Seeber, K. Frommann, C.C. Klein, C. Rochford, M.S. Nitsche, K. Fricke, D. Liebetanz, N. Lang, A. Antal, W. Paulus, F. Tergau, J. Physiol. 568 (2005) 291–303.
[35] M.A. Nitsche, W. Paulus, J. Physiol. 527 (2000) 633–639.
[36] D. Liebetanz, M.A. Nitsche, F. Tergau, W. Paulus, Brain 125 (2002) 2238–2247.
[37] M.A. Nitsche, W. Jaussi, D. Liebetanz, N. Lang, F. Tergau, W. Paulus, Neuropsychopharmacology 29 (2004) 1573–1578.
[38] F.C. Hummel, L.G. Cohen, Lancet Neurol. 5 (2006) 708–712.
[39] B. Belmaker, P. Fitzgerald, M.S. George, S.H. Lisanby, A. Pascual-Leone, T.E. Schlaepfer, E. Wassermann, CNS Spectr. 8 (2003) 489.
[40] K. Machii, D. Cohen, C. Ramos-Estebanez, A. Pascual-Leone, Clin. Neurophysiol. 117 (2006) 455–471.
[41] E.M. Wassermann, Electroencephalogr. Clin. Neurophysiol. 108 (1998) 1–16.
[42] M.B. Iyer, U. Mattu, J. Grafman, M. Lomarev, S. Sato, E.M. Wassermann, Neurology 64 (2005) 872–875.
[43] M.A. Nitsche, D. Liebetanz, N. Lang, A. Antal, F. Tergau, W. Paulus, Clin. Neurophysiol. 114 (2003) 2220–2223.
[44] E.M. Robertson, H. Theoret, A. Pascual-Leone, J. Cogn. Neurosci. 15 (2003) 948–960.
[45] T. Paus, R. Jech, C.J. Thompson, R. Comeau, T. Peters, A.C. Evans, J. Neurosci. 17 (1997) 3178–3184.
[46] U. Herwig, P. Satrapi, C. Schonfeldt-Lecuona, Brain Topogr. 16 (2003) 95–99.
[47] M. Okamoto, H. Dan, K. Sakamoto, K. Takeo, K. Shimizu, S. Kohno, I. Oda, S. Isobe, T. Suzuki, K. Kohyama, I. Dan, Neuroimage 21 (2004) 99–111.
[48] U. Herwig, F. Padberg, J. Unger, M. Spitzer, C. Schonfeldt-Lecuona, Biol. Psychiatry 50 (2001) 58–61.
[49] A. Cowey, V. Walsh, Neuroreport 11 (2000) 3269–3273.
[50] R. Sparing, D. Buelte, I.G. Meister, T. Paus, G.R. Fink, Hum. Brain Mapp. (2007). Available online 22 February, doi:10.1002/hbm.20360.
[51] D.H. Kim, G.E. Georghiou, C. Won, IEEE Trans. Biomed. Eng. 53 (2006) 720–725.
[52] J.L. Lancaster, S. Narayana, D. Wenzel, J. Luckemeyer, J. Roby, P. Fox, Hum. Brain Mapp. 22 (2004) 329–340.
[53] S. Knecht, J. Sommer, M. Deppe, O. Steinstrater, Clin. Neurophysiol. 116 (2005) 1988–1993.
[54] Q. Noirhomme, M. Ferrant, Y. Vandermeeren, E. Olivier, B. Macq, O. Cuisenaire, IEEE Trans. Biomed. Eng. 51 (2004) 1994–2005.
[55] P.C. Gandiga, F.C. Hummel, L.G. Cohen, Clin. Neurophysiol. 117 (2006) 845–850.
[56] A. Floel, D. Poeppel, E.A. Buffalo, A. Braun, C.W. Wu, H.J. Seo, K. Stefan, S. Knecht, L.G. Cohen, Cereb. Cortex 14 (2004) 404–409.
[57] U. Herwig, B. Abler, C. Schonfeldt-Lecuona, A. Wunderlich, J. Grothe, M. Spitzer, H. Walter, Neuroimage 20 (2003) 1032–1041.
[58] G. Koch, M. Oliveri, S. Torriero, G.A. Carlesimo, P. Turriziani, C. Caltagirone, Neuroimage 24 (2005) 34–39.
[59] S. Kohler, T. Paus, R.L. Buckner, B. Milner, J. Cogn. Neurosci. 16 (2004) 178–188.
[60] P. Nixon, J. Lazarova, I. Hodinott-Hill, P. Gough, R. Passingham, J. Cogn. Neurosci. 16 (2004) 289–300.
[61] B.R. Postle, F. Ferrarelli, M. Hamidi, E. Feredoes, M. Massimini, M. Peterson, A. Alexander, G. Tononi, J. Cogn. Neurosci. 18 (2006) 1712–1722.
[62] L. Romero, V. Walsh, C. Papagno, J. Cogn. Neurosci. 18 (2006) 1147–1155.
[63] S. Rossi, P. Pasqualetti, G. Zito, F. Vecchio, S.F. Cappa, C. Miniussi, C. Babiloni, P.M. Rossini, Eur. J. Neurosci. 23 (2006) 793–800.
[64] S. Rossi, S.F. Cappa, C. Babiloni, P. Pasqualetti, C. Miniussi, F. Carducci, F. Babiloni, P.M. Rossini, Nat. Neurosci. 4 (2001) 948–952.
[65] M. Sandrini, S.F. Cappa, S. Rossi, P.M. Rossini, C. Miniussi, J. Cogn. Neurosci. 15 (2003) 855–861.
[66] G.S. Wig, S.T. Grafton, K.E. Demos, W.M. Kelley, Nat. Neurosci. 8 (2005) 1228–1233.
[67] R.P. Kessels, A.A. d'Alfonso, A. Postma, E.H. de Haan, Neurosci. Lett. 287 (2000) 68–70.
[68] D.J. Schutter, J. van Honk, J. Psychiatry Neurosci. 31 (2006) 101–104.
[69] C. Sole-Padulles, D. Bartres-Faz, C. Junque, I.C. Clemente, J.L. Molinuevo, N. Bargallo, J. Sanchez-Aldeguer, B. Bosch, C. Falcon, J. Valls-Sole, Cereb. Cortex 16 (2006) 1487–1493.
[70] G. Beckers, V. Homberg, Exp. Brain Res. 87 (1991) 421–432.
[71] J.E. Desmond, S.H. Chen, P.B. Shieh, Ann. Neurol. 58 (2005) 553–560.
[72] E. Duzel, A. Hufnagel, C. Helmstaedter, C. Elger, Neuropsychologia 34 (1996) 775–783.
[73] J. Grafman, A. Pascual-Leone, D. Alway, P. Nichelli, E. Gomez-Tortosa, M. Hallett, Neuroreport 5 (1994) 1157–1160.
[74] I. Kahn, A. Pascual-Leone, H. Theoret, F. Fregni, D. Clark, A.D. Wagner, J. Neurophysiol. 94 (2005) 688–698.
[75] F.M. Mottaghy, M. Gangitano, B.J. Krause, A. Pascual-Leone, Neuroimage 18 (2003) 565–575.
[76] M. Oliveri, P. Turriziani, G.A. Carlesimo, G. Koch, F. Tomaiuolo, M. Panella, C. Caltagirone, Cereb. Cortex 11 (2001) 606–618.
[77] A.P. Strafella, T. Paus, M. Fraraccio, A. Dagher, Brain 126 (2003) 2609–2615.
[78] D.E. Bohning, A.P. Pecheny, C.M. Epstein, A.M. Speer, D.J. Vincent, W. Dannels, M.S. George, Neuroreport 8 (1997) 2535–2538.
[79] R.J. Ilmoniemi, J. Ruohonen, J. Virtanen, H.J. Aronen, J. Karhu, Electroencephalogr. Clin. Neurophysiol. 51 (Suppl) (1999) 22–29.
[80] G. Thut, J.R. Ives, F. Kampmann, M.A. Pastor, A. Pascual-Leone, J. Neurosci. Methods 141 (2005) 207–217.
[81] F.M. Mottaghy, A. Pascual-Leone, L.J. Kemna, R. Topper, H. Herzog, H.W. Muller-Gartner, B.J. Krause, Brain Res. Cogn. Brain Res. 15 (2003) 241–249.
[82] F.M. Mottaghy, B.J. Krause, L.J. Kemna, R. Topper, L. Tellmann, M. Beu, A. Pascual-Leone, H.W. Muller-Gartner, Neurosci. Lett. 280 (2000) 167–170.
[83] F.M. Mottaghy, Neuroscience 139 (2006) 85–90.
[84] R.J. Leigh, C. Kennard, Brain 127 (2004) 460–477.
[85] C. Pierrot-Deseilligny, D. Milea, R.M. Muri, Curr. Opin. Neurol. 17 (2004) 17–25.
[86] U. Ziemann, Clin. Neurophysiol. 115 (2004) 1717–1729.
[87] Z. Ahmed, A. Wieraszko, Bioelectromagnetics 27 (2006) 288–294.
[88] E.J. Kim, W.R. Kim, S.E. Chi, K.H. Lee, E.H. Park, J.H. Chae, S.K. Park, H.T. Kim, J.S. Choi, Neurosci. Lett. 405 (2006) 79–83.
[89] H. Wang, X. Wang, W. Wetzel, H. Scheich, Eur. J. Neurosci. 23 (2006) 2176–2184.
[90] J.W. Kling, M. Yarita, T. Yamamoto, Y. Matsumiya, Physiol. Behav. 48 (1990) 713–717.
[91] H. Wang, X. Wang, H. Scheich, Neuroreport 7 (1996) 521–525.
[92] D. Liebetanz, F. Klinker, D. Hering, R. Koch, M.A. Nitsche, H. Potschka, W. Loscher, W. Paulus, F. Tergau, Epilepsia 47 (2006) 1216–1224.
[93] J. Andoh, E. Artiges, C. Pallier, D. Riviere, J.F. Mangin, A. Cachia, M. Plaze, M.L. Paillere-Martinot, J.L. Martinot, Neuroimage 29 (2006) 619–627.
[94] B. Boroojerdi, M. Phipps, L. Kopylev, C.M. Wharton, L.G. Cohen, J. Grafman, Neurology 56 (2001) 526–528.
[95] F.M. Mottaghy, R. Sparing, R. Topper, Behav. Neurol. 17 (2006) 177–186.
[96] R. Sparing, F.M. Mottaghy, M. Hungs, M. Brugmann, H. Foltys, W. Huber, R. Topper, J. Clin. Neurophysiol. 18 (2001) 326–330.
[97] B. Drager, C. Breitenstein, U. Helmke, S. Kamping, S. Knecht, Eur. J. Neurosci. 20 (2004) 1681–1687.

[98] F. Fregni, P.S. Boggio, M.A. Nitsche, F. Bermpohl, A. Antal, E. Feredoes, M.A. Marcolin, S.P. Rigonatti, M.T. Silva, W. Paulus, A. Pascual-Leone, Exp. Brain Res. 166 (2005) 23–30.
[99] L. Marshall, M. Molle, H.R. Siebner, J. Born, BMC Neurosci. 6 (2005) 23.
[100] L. Marshall, M. Molle, M. Hallschmid, J. Born, J. Neurosci. 24 (2004) 9985–9992.
[101] T.Z. Kincses, A. Antal, M.A. Nitsche, O. Bartfai, W. Paulus, Neuropsychologia 42 (2004) 113–117.
[102] M.A. Nitsche, A. Schauenburg, N. Lang, D. Liebetanz, C. Exner, W. Paulus, F. Tergau, J. Cogn. Neurosci. 15 (2003) 619–626.
[103] P.S. Boggio, R. Ferrucci, S.P. Rigonatti, P. Covre, M.A. Nitsche, A. Pascual-Leone, F. Fregni, J. Neurol. Sci. 249 (2006) 31–38.
[104] I. Rektorova, S. Megova, M. Bares, I. Rektor, J. Neurol. Sci. 229 (2005) 157–161.
[105] S. Rossi, C. Miniussi, P. Pasqualetti, C. Babiloni, P.M. Rossini, S.F. Cappa, J. Neurosci. 24 (2004) 7939–7944.
[106] S. Rossi, P.M. Rossini, Trends Cogn. Sci. 8 (2004) 273–279.
[107] Y.Z. Huang, M.J. Edwards, E. Rounis, K.P. Bhatia, J.C. Rothwell, Neuron 45 (2005) 201–206.
[108] S.H. Lisanby, L.H. Kinnunen, M.J. Crupain, J. Clin. Neurophysiol. 19 (2002) 344–360.