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BRAIN RESEARCH REVIEWS

Review

Contribution of noninvasive cortical stimulation to the study of memory functions

A. Floel[a,b,*], L.G. Cohen[a]

[a]Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, USA
[b]Department of Neurology, University of Münster, Münster, Germany

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ABSTRACT

In the memory domain, a large body of experimental evidence about subsystems of memory has been collected from classic lesion studies and functional brain imaging. Animal studies have provided information on molecular mechanisms of memory formation. Compared to this work, transcranial magnetic stimulation and transcranial direct current stimulation have made their own unique contribution. Here, we describe how noninvasive brain stimulation has been used to study the functional contribution of specific cortical areas during a given memory task, how these techniques can be used to assess LTP- and LTD-like plasticity in the living human brain, and how they can be employed to modulate memory formation in humans, suggesting an adjuvant role in neurorehabilitative treatments following brain injury.

Contents

* *Corresponding author*. Department of Neurology, University of Muenster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany. Fax: +49 251 83 48181.
E-mail address: floeel@uni-muenster.de (A. Floel).

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1. Introduction

1.1. General remarks

Early work in patients with localized brain lesions demonstrated that memory function does not represent a single unity, but is comprised of different systems supported by differentiated cortico-subcortical networks (Milner, 2005). Considerable advances have been made in the understanding of the neural substrates (for review see Squire, 2004) and the molecular mechanisms (for review see Kandel, 2001) underlying encoding and storage of memory functions. Examples of these advances include the identification of simple forms of implicit memory storage in the invertebrates Aplysia and *Drosophila* and parallel studies in mammals (for review see Kandel, 2001).

At a systems level, functional imaging techniques (positron emission tomography [PET], functional magnetic resonance imaging [fMRI], electroencephalography [EEG] and magnetoencephalography [MEG]) contributed experimental flexibility and temporal and spatial resolution to the study of the functional neuroanatomy of memory processes in intact humans (for review see Cabeza and Nyberg, 2000). Studies using these tools provided unique information on the activity of various brain regions and networks associated with performance of memory tasks. From this information, the functional relationship between brain activity and the investigated cognitive functions has been inferred (Raichle, 1998).

In the last few years, noninvasive brain stimulation, most notably transcranial magnetic stimulation (TMS) and, more recently, transcranial direct current stimulation (tDCS) became widely available. For the first time, these tools made it possible to test novel hypotheses on memory function emerging from basic science studies and neuroimaging protocols in humans with and without brain lesions. These techniques have been used for three fundamental purposes in the study of memory function (I) to test to which extent inferences or hypotheses linking activity in specific cortical regions and memory function are correct. Most studies along this line evaluated the behavioral consequences of a focal "transient virtual lesion" of the target cortical area on the specific memory function tested; (II) to test in humans the ability of motor training to encode elementary motor memories, for example in the primary motor cortex, and to induce long-term potentiation (LTP) – and long-term depression (LTD) – like plasticity in the living human brain; and (III) to test the general hypothesis that noninvasive cortical stimulation could modulate memory formation and learning, an issue of obvious relevance in neurorehabilitation and cognitive neuroscience. This review first provides an overview of the techniques of TMS and tDCS (see Fig. 1), and then discusses the status of studies performed in these particular areas.

1.2. Noninvasive cortical stimulation

TMS is a noninvasive, well-tolerated technique that delivers focal currents into targeted cortical areas with high temporal and fair spatial resolution (for "physical properties of TMS and tDCS" see below). In the past 15 years the use of TMS expanded from its application as a diagnostic routine procedure in neurology to assess central motor conduction time, to the study of cognitive functions. In addition to local effects, TMS activates remote cortical sites trans-synaptically (Paus, 1999). TMS is applied as single pulse (spTMS, approximately 50- to 100-μs duration) or trains of pulses (rTMS). Stimulation rates of ≤1 Hz are referred to as low-frequency rTMS, those >1 Hz as high-frequency rTMS. In the motor system, the former typically leads to depression of cortical excitability, the latter to facilitation (Chen et al., 1997; Maeda et al., 2000, but see also

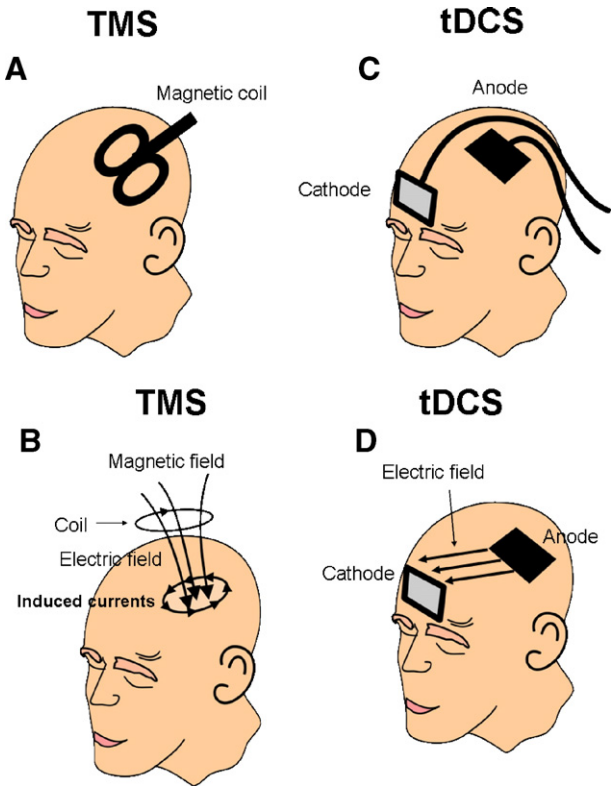

Fig. 1 – Principles of TMS and tDCS. TMS (left): a figure-eight-shaped coil connected to a pulse generation unit is placed on the subject's scalp overlying a particular region of the cortex (in this case, the motor cortex) (A). If a brief pulse of current is then sent through the coil (circular coil here), a magnetic field is generated which, in turn, results in an electric field and currents in the brain that flow parallel to those in the coil, but in the opposite direction (B). TDCS (right): weak electric currents are generated by a battery device connected to surface electrodes placed on the subject's scalp (C). For motor cortex stimulation, the stimulating electrode (anode) is placed over the motor cortex and the reference electrode (cathode) over the contralateral eyebrow. The induced electric current then flows from the anode to the cathode through the cortex leading to brain polarization (D).

Huang et al., 2005). This frequency-dependent effect has been demonstrated during (Pascual-Leone et al., 1994) and following the end of TMS stimulation (Chen et al., 1997; Maeda et al., 2000; Pascual-Leone et al., 1998). TMS is further characterized by its intensity, which is reported either in Tesla, in percent of maximal stimulator output of the specific device, or in percent of the minimum intensity required to elicit a motor-evoked potential (MEP) in a chosen muscle (motor threshold), most often one of the small hand muscles (Rothwell, 1993).

TDCS is a noninvasive technique, available since the early 1900s, for delivery of low currents that results in modulation of cortical excitability for variable periods outlasting the stimulation period (Bindman et al., 1962). In the motor domain, tDCS applied to the primary motor cortex (M1) modulates cortical excitability in a polarity-specific manner. Anodal tDCS results in increased motor cortical excitability lasting 25–120 min while cathodal tDCS leads to decreases in cortical excitability (Hummel et al., 2005; Nitsche and Paulus, 2000, 2001). The after-effects of tDCS on corticomotoneuronal excitability are significantly influenced by *N*-methyl-D-aspartate (NMDA)-receptor-dependent processes (Nitsche et al., 2003a, 2004a).

1.2.1. *Excurse: physical properties of TMS and tDCS*

Transcranial magnetic stimulation (TMS) is based on Faraday's principle of electromagnetic induction. A brief pulse of current flowing through a coil of wire generates a magnetic field which, in turn, results in an electric field and currents that flow parallel to the plane of the coil. The strength of the induced electric field mainly depends on the rate of change of the electrical current in the coil. Due to the electrical conductivity of living tissue, the electric field leads to an electrical current in the cortex parallel, but opposite in direction to, the current in the coil (Lenz's law) and subsequently to depolarization of the underlying neurons (Hallett, 2000; Rothwell, 1993). The TMS apparatus itself consists of two major devices: a main power pulse generation unit that charges a bank of capacitors capable of producing high discharge currents, and an electromagnetic stimulating coil to apply magnetic pulses of up to several Tesla. The two types of coils most widely used are the circular coil, with a maximum current in the entire outer winding that produces a ring-shaped magnetic field around the coil, and the figure-of-eight coil consisting of two circular ring-shaped coils mounted next to each other, inducing the maximum field strength at the intersection of the two rings (Cohen et al., 1990). Since neurons usually have a threshold for stimulation, it can reasonably be assumed that over a given range of intensities, stimulation is limited to sites under the junction region (Jahanshahi and Rothwell, 2000).

The magnetic field strength decreases logarithmically with the distance from the coil, which limits the area of direct depolarization to about 2–3 cm in depth with current standard TMS devices (Rudiak and Marg, 1994).TMS application in the form of paired-pulses with a conditioning TMS stimulus preceding a test stimulus (TS) by a specific interstimulus interval (ISI), either in the same or separate hemispheres (see Chen et al., 1998 for review) allows the study of intracortical inhibition, facilitation and interhemispheric interactions. Safety: undergoing TMS is not painful; subjects feel as though someone is tapping them on the head as the coil causes their scalp muscles to contract. Single-pulse TMS has now been used for about two decades in clinical neurology and neuroscience, and can be considered safe when applied to healthy volunteers (Wassermann, 1998). For rTMS, the most severe complication when used beyond published safety guidelines (Wassermann, 1998) is its potential to induce epileptic seizures.

Transcranial direct current stimulation (tDCS) modulates cortical excitability by application of weak electrical currents in the form of direct current brain polarization. Depending on direct current (DC) polarity, neuronal firing rates increase or decrease, presumably due to DC-induced changes in resting membrane potentials. TCDS, delivered through gel-sponge electrodes with surface areas between 25 (Hummel et al., 2005) and 35 cm^2 (Nitsche and Paulus, 2000), is at present less focal and has a poorer time resolution than TMS stimulation using figure-eight-shaped coils (Nitsche and Paulus, 2000, 2001). On the other hand, it elicits less sensations than TMS and is more portable, due to the stimulator device being smaller and lighter, for application in association with training protocols (Hummel et al., 2005). Safety: noninvasive transcranial weak direct currents as applied to humans are painless. The induced focal (prolonged) changes of excitability are reversible (Nitsche and Paulus, 2000, 2001). There are no known risks of percutaneous, transcranial DC stimulation of the brain at the intensities and durations commonly used, other than transient mild 'itching" at the electrode sites. No change in serum neuron-specific enolase has been reported in 5 subjects immediately and 1 h after exposure to 13 min of 1 mA anodal DC to motor cortex (Nitsche et al., 2003b). Similarly, no changes in diffusion-weighted and contrast-enhanced MRI have been seen after exposure to tDCS (Nitsche et al., 2004b). So far, safety studies with TMS have been more extensive than with tDCS (Priori, 2003).

1.3. *Memory in the brain*

Memory is composed of multiple separate systems (see Fig. 2). The most widely used taxonomy distinguishes between declarative memory as the recollection of facts and events, and nondeclarative memory for the acquisition of skills (procedural memory) (Squire, 2004). Declarative memory relies primarily on the integrity of the hippocampus and its related medial temporal lobe structures, while procedural memory relies to a larger extent on the integrity of cortical structures and the basal ganglia (Cohen and Squire, 1980). In contrast to long-term memory storage and retrieval, the ability to retain information available over a short time span has been termed working memory (Baddeley, 1992). According to the model proposed by Baddeley (1992), a central executive in the frontal lobes operates on the contents of storage buffers for verbal (left) and visual–spatial (right) information in a frontal–parietal network (Smith and Jonides, 1999). A short-term memory system for procedural motor memories has been proposed to exist in the primary motor cortex (Classen et al., 1998; Shadmehr and Mussa-Ivaldi, 1994). While the mechanisms underlying formation and storage of memory functions in humans are incompletely understood, they are likely to involve NMDA and AMPA receptors, and the influx of ions like calcium into the cell (Butefisch et al., 2000; Donchin et al.,

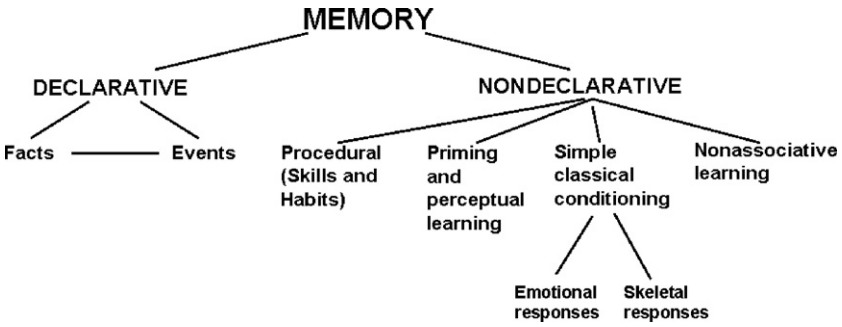

Fig. 2 – Taxonomy of memory systems. This figure displays the different forms of declarative and nondeclarative memory (adapted from (Squire, 2004)).

2002). Long-term storage involves the synthesis of new proteins and the growth of new synaptic connections (for review see Kandel, 2001).

2. Part I. Study of memory function by induction of transient virtual lesions

Lesion studies provide information on the behavioral consequences of specific brain lesions. One caveat of these studies is that patients are usually evaluated in the chronic stage following the injury and the tested behavior may be the consequence of the lesion itself, of subsequent cortical reorganization, or both (Paus, 1999; Raichle, 1998). Functional neuroimaging methods have overcome some of these problems and can demonstrate an association between behavior and patterns of activity in cortical and subcortical structures. However, imaging alone cannot prove causal relationships between activity at a cortical site and behavior (Hallett et al., 2000). To address this issue, TMS is often used to determine the behavioral consequences of disruption of a focal cortical region ("virtual lesion;" Pascual-Leone et al., 2000). In the memory domain, behavioral effects of TMS or tDCS could represent the consequence of disrupted memory formation as such, or disruption of the expression of the acquired memory if not evaluated separately. TMS-induced modifications in behavior can be brought about by different mechanisms, including modulation of activity in the stimulated area but also by changes in activity of distant areas elicited trans-synaptically. This caveat should be kept in mind as well when interpreting results from TMS studies. Multimodal approaches involving TMS, EEG or MEG and neuroimaging tools have been developed to overcome this problem (see Jahanshahi and Rothwell, 2000 for review). These combined approaches allow the researcher not only to disentangle local from distant effects of TMS, but opens the possibility to explore functional and anatomical connectivity in the intact human brain (Jahanshahi and Rothwell, 2000; Paus, 1999). Thus, the property of TMS to affect distant areas trans-synaptically may not only be disadvantageous, in that it compromises focality of stimulation. Rather, it may pose the possibility to also modulate deep structures within the brain that are connected to a given cortical area. In the memory domain, this may be of particular importance in the study of prefrontal–hippocampal interactions in the encoding and retrieving of memory, since the hippocampus and surrounding structures lie deeper than 2 cm below the surface of the skull in humans, the current limiting distance for application of TMS (Bohning et al., 1997) (see also section 1.2.1). In early studies of TMS exact coil placement outside the motor cortex was a major challenge, addressed by using the international 10–20 EEG system or arbitrary distances from M1. Nowadays, accurate frameless stereotactic tools allow precise positioning based on individual subject's brain anatomy (Paus, 1999).

2.1. *Long-term memory*

Lesion and functional imaging reports suggested a link between lateralization of prefrontal cortex activity, and the processed material type (verbal versus nonverbal), which might also be influenced by the stage of memory processing (encoding versus retrieval) (Brewer et al., 1998; Golby et al., 2001; Wagner et al., 1998). However, a cause–effect link between prefrontal activation and memory encoding or retrieval was still debated, since lesion studies have not shown consistently memory impairments with frontal lesions (Fletcher and Henson, 2001). Recent studies using rTMS now conclusively showed that episodic encoding of verbal (Floel et al., 2004; Kohler et al., 2004; Rami et al., 2003) or verbalizable (Rossi et al., 2001) material critically depends on the left, whereas encoding of nonverbalizable material (Epstein et al., 2002) depends on the right prefrontal cortex. Sandrini et al. (2003) and Rossi et al. (2004) examined episodic memory retrieval, and reported a right prefrontal involvement for retrieval of verbalizable items that showed a left (Rossi et al., 2004) or bilateral (Sandrini et al., 2003) lateralization during encoding, thereby adding support to the neuroimaging-based hemispheric encoding–retrieval asymmetry (HERA) theory (Tulving et al., 1994). Fig. 3 presents an overview of previous TMS studies on memory encoding and retrieval. Most of these studies assessed one specific aspect of this process, e.g., memory encoding in the verbal domain (Rami et al., 2003; Kohler et al., 2004; Kahn et al., 2005; Skrdlantova et al., 2005), while others assessed both encoding and retrieval within the verbal domain, or encoding of both verbal and nonverbal items (Floel et al., 2004; Rossi et al., 2001, 2006). Fig. 4 provides an example of a study that examined the differential involvement of left and right prefrontal cortex in the encoding of verbal and nonverbal items, thus allowing a more comprehensive assessment of

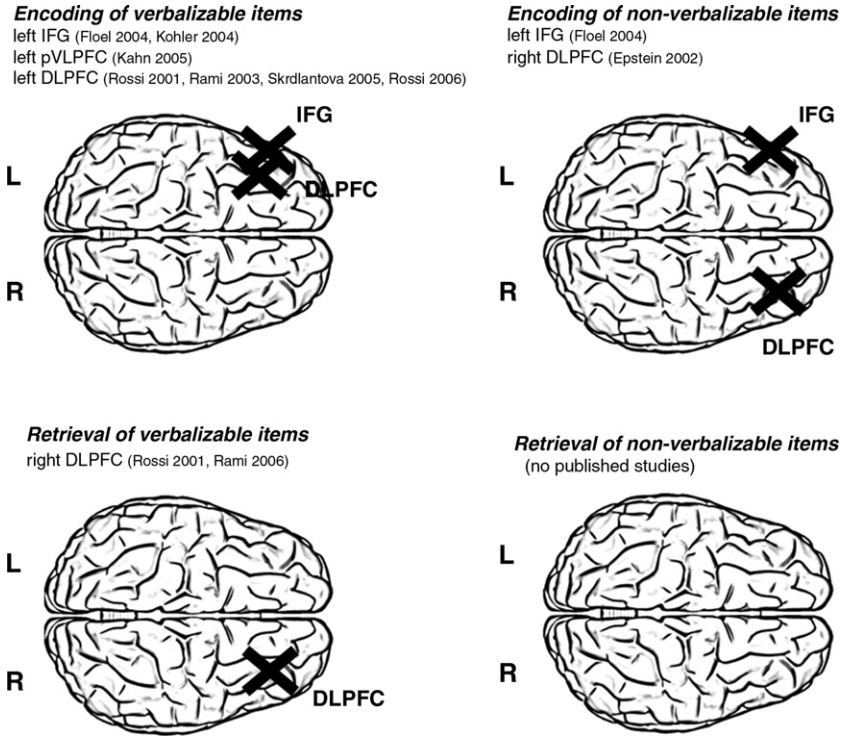

Fig. 3 – Overview of previous rTMS studies examining the contribution of prefrontal cortex to memory encoding and retrieval. The top row shows studies on encoding the bottom row on retrieval, of verbal (left) and nonverbalizable (right) items. While a number of studies have looked into encoding of verbal items, encoding of nonverbalizable and retrieval of verbal items have been studied less extensively; retrieval of nonverbalizable material has not been studied so far. IFG = inferior frontal gyrus; pVLPC = posterior ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; L = left; R = right; X = stimulus site.

the prefrontal regions crucially involved in the encoding process (Floel et al., 2004).

None of these studies used the combined approach of rTMS of a specific cortical area with concomitant or immediately subsequent imaging to visualize the effects of rTMS on interconnected regions like the hippocampus, a paradigm of interest for future studies. Animal experiments that studied the influence of high-frequency repetitive rTMS on learning processes in mice and on neuronal excitability of the hippocampal tissue found that rTMS at higher frequency (15 Hz) improved animals' performance in novel object recognition test and in parallel significantly enhanced synaptic efficiency expressed as long-term potentiation (LTP) recorded from hippocampal slices of these animals (Ahmed and Wieraszko, 2006).

The ability to learn and remember new information declines with aging. Functional imaging studies in elder individuals showed a relative loss of lateralization during encoding and retrieval of episodic information, conceptualized in the so-called HAROLD (Hemispheric Asymmetry Reduction in OLDer adults) model (Cabeza, 2002). This finding could reflect compensatory mechanisms, de-differentiation processes, or simply an epiphenomenon (Sack and Linden, 2003). Rossi and colleagues, using a visuospatial recognition task, addressed this problem and reported that in the young, recognition of indoor and outdoor scenes was more affected by rTMS of the right than left dorsolateral prefrontal cortex (DLPFC), whereas in the elderly, the effects of stimulation of either DLPFC were comparable (Rossi et al., 2004). These results provide strong support to the notion that the neural substrates of successful memory functions change over time, and that these changes are likely to play a compensatory role when elder individuals perform episodic memory tasks.

2.2. *Working memory*

Neuroimaging studies of working memory (WM) identified neural networks activated in association with performance of memory tasks. Taking advantage of the temporal resolution of this technique, TMS has been used to study the chronometry of activation in different nodes of these networks. For verbal WM, it was found that spTMS applied to the parietal cortex interfered earlier than stimulation of the prefrontal cortex with performance of a standard N-backward verbal WM task (Mottaghy et al., 2003a). This effect was more prominent with right than left hemisphere stimulation, suggesting a propagation of information from posterior to anterior cortical sites converging in the left prefrontal cortex. At the same time, these results suggest a parallel processing of semantic and object features of the stimuli in left- and right-sided brain areas. In a separate study, rTMS was used to interfere with left or right medial frontal gyrus activity during the N-backward task, while participants were simultaneously scanned with PET. The study revealed that healthy individuals are able to shift their main activation to adjacent areas

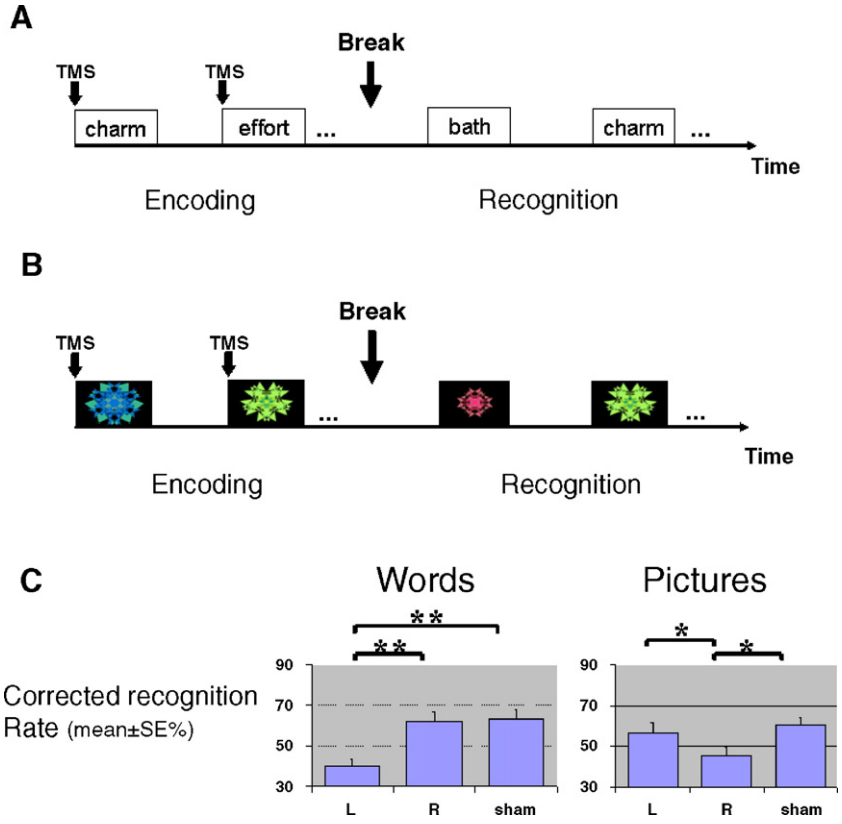

Fig. 4 – Experimental paradigm for words (A) and pictures (B), and recognition memory for words and pictures (C). In one session (A), subjects were instructed to memorize words, in the other session (B) pictures. rTMS was applied to right prefrontal, left prefrontal (PFC), and in a sham condition synchronously with the presentation of each word or picture during the encoding period. During recognition, subjects were shown the words (session I) and pictures (session II) already seen during encoding, in addition to the same number of new words and pictures. The instruction was to identify each word or picture as "well remembered", "familiar", or "new". (C) Left prefrontal (PFC) rTMS disrupted the corrected recognition rate for words significantly more than right PFC rTMS and than Sham. On the other hand, right PFC rTMS disrupted corrected recognition rate for pictures significantly more than left PFC rTMS and Sham. Data reported as mean ± SE; significance values corrected for multiple comparisons. L = left PFC stimulation, R = right PFC stimulation, sham = sham stimulation, * = significance level < 0.05, ** = significance level < 0.01 (modified from Floel et al., 2004).

in the frontal lobes, while maintaining task performance, supporting the view of functionally relevant short-term plasticity in WM systems (Mottaghy et al., 2003b). In accordance with these findings, Rami et al. (2003) did not observe an effect of left prefrontal rTMS on immediate and verbal WM. For visuospatial WM, Oliveri et al. using spTMS (Oliveri et al., 2001) found evidence for segregation of WM buffers for object and spatial information in the temporal and the parietal lobe. DLPFC was crucial for processing both types of information. A recent study by Koch et al. (2005) used rTMS to study the temporal dynamics and the reciprocal interactions of the different areas of the parieto-frontal network in normal humans during spatial WM. They found an interference effect with parietal and DLPFC stimulation, but not with premotor stimulation, during the delay phase of their spatial WM task. In the decision phase of the task, interference was only observed for DLPFC stimulation. Thus, this study provided new evidence for parallel processing in the parieto-frontal network of spatial WM during the delay phase, with the DLPFC being crucial for both delay and decision phases.

2.3. *Procedural memory*

The role of DLPFC in procedural memory is controversial. Recent studies using TMS contributed to unveil the role of this region in performance of complex motor sequences requiring retention of the order of key presses. In one of these studies, rTMS was used to demonstrate that the critical role played by DLPFC in sequence learning is related predominantly to spatial cues (Robertson et al., 2001). Based on their findings, the authors proposed that the DLPFC operates over a short-term to retain and manipulate spatial information to allow cortical and subcortical structures to learn a predictable sequence of actions. Torriero et al. (2004) used rTMS to study the role of the cerebellar hemispheres in procedural motor learning. They found that interference with the right cerebellar hemisphere induced a significant decrease in procedural learning regardless of the hand used to perform the task, whereas left cerebellar rTMS only impaired procedural learning acquired by the ipsilateral hand. The authors interpreted their findings as supportive of the role of the cerebellar cortex in procedural learning. It

remains to be determined if rTMS disrupted the learning process or the expression of a correctly learned task (Seidler et al., 2002).

3. Part II. Assessment of LTP-/LTD-like plasticity

Long-term potentiation (LTP) and depression (LTD) are activity-dependent processes in which a brief episode of strong synaptic activation leads to a persistent strengthening (LTD) or persistent weakening (LTD) of synaptic transmission (Bliss and Collingridge, 1993). LTP and LTD, widely accepted models of neural plasticity presumed to underlie learning and memory, can be induced in various brain structures involved in memory formation including the motor cortex (Iriki et al., 1989). In awake humans, long-lasting changes in cortical output, most often referred to as "LTP- and LTD-like", have been induced using TMS stimulation protocols similar to those that have been used to induce synaptic plasticity in animals (Stefan et al., 2000; Wolters et al., 2003; Ziemann et al., 2004; Cooke and Bliss, 2006). It still remains to be demonstrated, though, that the site of this change is the synapse (Cooke and Bliss, 2006). TMS has also been used to assess noninvasively LTP- and LTD-like plasticity in the motor cortex: motor training resulted in encoding of motor memory traces in the primary motor cortex that encoded the kinematic details of the practiced movements as tested by TMS (Butefisch et al., 2000; Classen et al., 1998). This form of use-dependent plasticity may underlie the initial stages in acquisition of motor skills (Shadmehr and Mussa-Ivaldi, 1994) and may be one of the crucial functions that operate during recovery of motor function after stroke (Butefisch et al., 1995; Nudo et al., 1996). Thus, this paradigm offers neuroscientists a model to test the mechanisms operating in the formation of motor memories, and possible strategies to modulate memory formation. A group of studies showed that formation of a motor memory is associated with changes in the balance of excitation and inhibition within the primary motor cortex (Classen et al., 1998; Shadmehr and Mussa-Ivaldi, 1994) and is influenced by GABAergic, cholinergic, alpha-adrenergic and dopaminergic (Butefisch et al., 2002, 2000; Donchin et al., 2002; Floel et al., 2005a; Sawaki et al., 2002; Sawaki et al., 2003a) systems, by age (Sawaki et al., 2003b) and brain lesions (Floel et al., 2005b). Taken together, these TMS studies support the involvement of an activity-dependent LTP-like mechanism in formation of a motor memory, consistent with the finding that LTP in motor cortex requires activation of NMDA receptors (Butefisch et al., 2000; Donchin et al., 2002). Direct evidence for the involvement of these mechanisms in human memory formation remains to be shown (Wolters et al., 2003).

4. Part III. Strategies under investigation to enhance memory formation

Recent investigations identified possible approaches to enhance memory formation using noninvasive stimulation (see Rossi and Rossini, 2004 for review). The general hypothesis has been that stimulation of a cortical region involved in performance of a training task could enhance the beneficial effects of training. For example, story recall may be enhanced by rTMS (Pascual-Leone et al., 1993), an effect that was replicated for verbal short-term memory tasks (Wassermann, 1998). Similarly, rTMS appears to modulate aspects of cognitive processing like the P300 component (Evers et al., 2001). One caveat of these studies is that the magnitude of the effects identified in healthy subjects was small, quite variable across individuals and short-lived (Boroojerdi et al., 2001; Mottaghy et al., 1999; Topper et al., 1998), and therefore has not warranted larger trials in patients with overt memory problems up to now. Using tDCS, it was shown that anodal tDCS can facilitate procedural, visuo-motor, and probabilistic classification learning, as well as word generation (Antal et al., 2004a,b; Iyer et al., 2005; Kincses et al., 2004; Nitsche et al., 2003c) contributing to our understanding of the functional contribution of the stimulated brain area to the task under study. A recent elegant tDCS study by Marshall et al. (2004) demonstrated that bilateral anodal tDCS over the frontal cortex during slow wave sleep at night improved retention of declarative memories (word pairs), as assessed the next morning (Marshall et al., 2004). Taken together, these results are consistent with the proposal that noninvasive cortical stimulation, in combination with training protocols, could enhance training effects on cognitive functions. Another study from 2004 supported this point, showing that Hebbian synchronous application of spTMS to the motor cortex contralateral to a training hand results in enhancement of a motor memory (Butefisch et al., 2004).

Other strategies that could possibly influence memory formation or expression include: Theta burst stimulation (TBS): in a recently proposed TMS protocol, Huang et al. (2005) showed that 20 s of short TMS trains of 3 stimuli at 50 Hz, repeated at intervals of 200 ms (i.e., 5 Hz) elicited powerful modulation of motor cortical excitability for about 60 min, possibly through modulation of I1 wave amplitudes (Iriki et al., 1989) and impacted performance of a reaction time task. Siebner et al. used anodal tDCS to enhance the effects of subsequent 1 Hz TMS stimulation and cathodal tDCS to decrease its effects on motor cortical excitability (Siebner et al., 2004). Iyer et al. introduced another technique to increase the duration of LTD-like depression of human motor cortex elicited with 1 Hz rTMS (Iyer et al., 2003), by preconditioning the motor cortex with subthreshold, 6 Hz rTMS. This technique produced a depression of motor cortex excitability stronger than 1 Hz TMS alone, and lasted up to 60 min. These strategies, while not formally tested on memory formation, may evolve into promising tools in this field.

In summary, TMS and tDCS are capable of enhancing or decreasing plasticity in the cerebral cortex. On the basis of these findings, interventional strategies to induce lasting behavioral changes in memory functions (both motor and cognitive) are presently being tested in experimental studies in different laboratories (Hummel et al., 2005; Iyer et al., 2005).

5. Outlook

Noninvasive brain stimulation provides a unique research tool for the investigation of a broad variety of issues in

cognitive neuroscience. Experimental TMS and tDCS protocols contribute, in combination with lesion and neuroimaging studies, to the understanding of mechanisms of memory formation in humans, addressing issues like location, timing, lateralization, functional relevance, and plasticity of the neural networks involved. TMS has been used to assess the ability of the motor cortex to form elementary motor memories in response to training protocols. Preliminary studies using TMS and tDCS to stimulate cognitive processes are promising but have not crossed the boundary between proof of principle experiments and clinical applications in cognitive neurology or neurorehabilitation, an exciting area of research at this time.

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