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Chapter 55

Learning and memory

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INTRODUCTION

A fairly large number of studies to date have investigated the nature of learning and memory processes in brain-injured and healthy subjects with noninvasive brain stimulation (NBS) methods. NBS techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), can alter brain activity in targeted cortical areas and distributed brain networks. The effects depend on the stimulation parameters. TMS and tDCS can be used to interfere with ongoing brain activity ("virtual lesion") and thus help to characterize brain–behavior relations, give information about the chronometry of cognitive processes, and reveal causal relationships. Particularly in real-time combination with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI), TMS and tDCS are valuable tools for neuropsychological research. They offer the combination of interference methods (TMS, tDCS) with techniques to record ongoing brain activity with high temporal (EEG) and spatial (MRI) resolution. This can: (1) shed unique insights into physiological and behavioral interactions, and (2) test, refine, and improve cognitive models; and (3) might ultimately lead to better neurorehabilitative methods.

The main goals of research with NBS in learning and memory have been to: (1) identify underlying neuropsychological processes and neurobiological components; (2) find out how this knowledge can be used to diagnose and restore dysfunctions of learning and memory in various patient populations; and (3) assess the use of NBS for enhancement purposes in healthy subjects.

In the present chapter, we first review and define memory and learning processes from a neuropsychological perspective. Then we provide a systematic and comprehensive summary of available research that investigates the neurobiological substrates of memory and aims to improve memory functions in patient populations, as well as in healthy subjects. Finally, we discuss methodological considerations and limitations, as well as the promise of the approach.

FRAMING APPLICATION OF NONINVASIVE BRAIN STIMULATION IN THE CONTEXT OF NEUROPSYCHOLOGICAL DEFINITIONS

Learning and memory are cognitive functions that encompass a variety of subcomponents. These components can be structured in different ways. For example, we can focus on their temporal dimension, or differentiate various forms of memory by virtue of their content or mechanisms of acquisition (Fig. 55.1). It seems clear that the cognitive structure of learning and memory is complex, and that, given the many interactions and overlaps between key subcomponents, neither neuropsychological nor neurobiological models can give us a fully satisfying taxonomy.

A key advance in the study of the neurobiological substrates of memory was Squire's (1987, 2004) distinction between declarative and nondeclarative memory functions related to their differential reliance on distinct neural structures (Cohen and Squire, 1980). Declarative memory incorporates semantic and episodic memory, and refers to everyday memory functions, which are typically impaired in amnesic patients. Declarative memory is thought to rely primarily on medial temporal lobe structures, including the hippocampus. Nondeclarative

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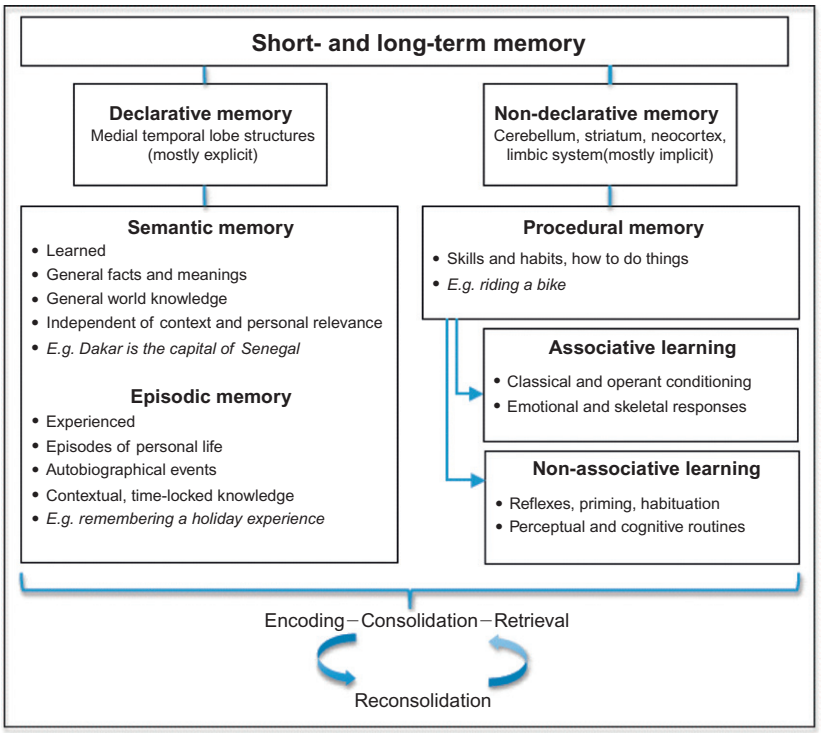

Fig. 55.1. Classification of different types of memory process.

memory includes various subcomponents, of which procedural memory or formation of motor memories is the most prominent. Nondeclarative memory is thought to depend mostly on striatum, cerebellum, and cortical association areas (Cohen and Squire, 1980). However, procedural memory also includes associative learning forms, such as classical and operant conditioning, and nonassociative learning forms such as priming, habituation, and learning of perceptual and cognitive routines. Notably, motor learning has been regarded as a less cognitive form of memory functions, and most research makes a clear distinction between motor and nonmotor memory functions. Thus, it seems clear that declarative and nondeclarative memory processes are interactive and partly overlapping domains.

Historically, the distinction between explicit and implicit memory has been associated with declarative and nondeclarative memory. It is often argued that declarative memory (semantic and episodic memory) corresponds to explicit memories that are conscious and verbally transmittable. On the other hand, nondeclarative memory is thought to represent an implicit and nonverbal type of memory that is acquired subconsciously. Although most declarative memory contents seem to be acquired explicitly, and most nondeclarative memory contents appear to be acquired implicitly, this dichotomy is an oversimplification and ultimately not accurate. For example, declarative memories can be acquired subconsciously (e.g., memories of an emotionally intense event or subliminal priming effects), and nondeclarative memories can be acquired with conscious engagement (e.g., learning of motor movements playing sports or a musical instrument).

Another important dichotomy, first proposed by William James (1890), differentiates memory subcomponents along a temporal dimension of duration (short- versus long-term memory, STM versus LTM). Since then researchers have proposed that STM and LTM are dependent on different neural substrates. More recently, however, it has been argued that the same representations that are active during encoding are also active during STM or during retrieval from LTM. According to these models, medial temporal lobe structures are responsible for the establishment of new representations independent of their duration, and the same binding processes are active in both STM and LTM (Wheeler et al., 2000; Jonides et al., 2008). A related temporal dichotomy separates retrograde and anterograde memory processes (Hartje and Poeck, 2002; Markowitsch and Staniloiu, 2013). Access to memories of the past enables us to improve current decisions, while mental time traveling and the imagination of future experiences helps us to follow long-term goals (Boyer, 2008).

These are some of the complex and not mutually exclusive dichotomies of memory processes that NBS could help link to specific neural substrates.

For example, one can conceive of experiments aimed at assessing whether disruption of specific brain regions affects one type of memory process and not another (e.g., Basso et al., 2010), or experiments evaluating the time at which disruption of a given brain region interferes with a specific memory step (e.g., Oliveri et al., 2001). One can use NBS to explore the nature of the relation between different processes within or across different dichotomies. Finally, one can compare the effects of NBS in healthy individuals and those with deficits in specific memory processes, and evaluate the impact on the deficit or even on other, apparently unaffected, memory and learning types.

It is also apparent that memory is tightly connected to time perception, attention, and emotional valence of memory contents, and there is evidence that brain circuits implicated with these functions are overlapping with areas involved in processing of memory functions. For example, with an increasing load of varying experiences stored in memory, time intervals are perceived to be longer (Bailey and Areni, 2006), and the subjective perception of a long time interval recruits areas such as the medial temporal cortex, which is known to be involved in binding episodic memory features (Noulhiane et al., 2007). State-dependent models have proposed that there is no "centralized clock," but that there are time-dependent neural changes, such as short-term synaptic plasticity, accounting for the decoding of temporal information (Karmarkar and Buonomano, 2007). It has been suggested that there is no linear metric of time, but that short time intervals are rather encoded in the context of (memory) events and therefore a state of local neural networks. In the same way as long-term plasticity may provide a memory of a learning experience (Martin et al., 2000), state-dependent networks may use short-term plasticity to provide a memory trace of the recent stimulus history of a network (Buonomano, 2000). These are further examples of questions that NBS can help address. Pharmacological experimental interventions suggest that affecting working memory (WM) also interferes with temporal processing (Rammsayer et al., 2001). However, NBS offers a promise of spatial and temporal precision that pharmacological agents lack.

Currently, researchers are trying to integrate findings in the memory domain into comprehensive models aiming to account for the wealth of data on functional characteristics of memory networks. There are debates over the implication of attention functions to memory and specifically, for example, of the role of parietal regions to retrieval of episodic memory. For instance, the Attention to Memory (AtoM) model postulates that the dorsal parietal cortex mediates top-down attention processes guided by retrieval goals (orienting), while ventral parietal cortex mediates automatic bottom-up attention processes captured by retrieved memory output (detection) (Ciaramelli et al., 2008; Cabeza et al., 2011). Cabeza and colleagues (2011) have proposed that parietal regions control attention in a similar way to perception processes. While orienting-related activity for memory and perception are thought to overlap in dorsoparietal cortex (DPC), detection-related activity is believed to overlap in ventroparietal cortex (VPC). Furthermore, both DPC and VPC show strong connectivity with medial–temporal lobe (MTL) during a memory task, which can, however, shift to strong connectivity with visual cortex during a perception task. Accordingly, the DPC appears to be collaborating with the prefrontal cortex (PFC) to induce top-down attention to salient retrieval paths, while the VPC seems to be involved in the activation of episodic features in alliance with the MTL. Thus, current models of memory processes integrate dynamic concepts of distributed network interactions and plasticity. These and other conclusions are derived from brain imaging studies, which, although extremely valuable, cannot offer insights into causality (Silvanto and Pascual-Leone, 2012). Here again, NBS offers the promise of a transformative approach.

Procedural memory

Motor learning and the formation of motor memories can be defined as an improvement of motor skills through practice, which are associated with long-lasting neuronal changes. They rely primarily on the primary motor cortex, premotor and supplementary motor cortices, cerebellum, thalamus, and striatal areas (Karni et al., 1998; Muellbacher et al., 2002; Seidler et al., 2002; Ungerleider et al., 2002). As learned from patients with apraxia, the parietal cortex is furthermore implicated in accessing long-term stored motor skills and contributes to visuospatial processing during motor learning (Halsband and Lange, 2006). Frontoparietal networks may become important after learning has been established, and play key roles in consolidation and storage of skill (Wheaton and Hallett, 2007).

Motor learning and memory take a special place within the memory domain and have been studied extensively. However, procedural memories build on subprocesses similar to those of nonmotor memories: they are divided into encoding, consolidation and long-term stability, retrieval (Karni et al., 1998; Robertson et al., 2005), and even a short-term memory system has been suggested to exist in the primary motor cortex (Classen et al., 1998). Robertson (2009) has further proposed that motor and nonmotor memory processes may be fully or partially supported by the same neuronal resources during wakefulness, but not during sleep.

Indeed, the MTL – which is known to support declarative memory formation – also contributes to implicit procedural learning (Schendan et al., 2003; Robertson, 2007; Albouy et al., 2008). During sleep, motor and nonmotor memory systems may be functionally disengaged, which may promote independent offline consolidation within systems (Robertson, 2009). As we shall see, key aspects of such insights have been derived from recent studies using NBS.

Short-term memory

STM is an essential component of cognition and is defined as the maintenance of information over a short period of time (seconds). Multistore models differentiate between STM and LTM. STM can remain unimpaired in amnesic patients who show distinct LTM impairments (Scoville and Milner, 1957; Cave and Squire, 1992). However, STM can be impaired while LTM functions remain intact (Shallice and Warrington, 1970). According to William James (1890), STM (primary memory) involves a conscious maintenance of sensory stimuli over a short period of time after which they are not present anymore. On the other hand, LTM (secondary memory) involves the reactivation of past experiences that were not consciously available between the time of encoding and retrieval. This led to the assumption, going back to Hebb (1940s), that STM and LTM are based on separate neural systems. While STM engages repeated excitation of a cellular compound, LTM leads to structural changes on the synaptic level, which are preceded by consolidation processes that are thought to be highly dependent on hippocampal functions. NBS, particularly TMS combined with EEG, MRI, or other brain imaging methods, has provided valuable insights on such neurobiological questions.

Baddeley also proposed a multistore architecture of STM and LTM (Baddeley and Hitch, 1974; Baddeley, 1986). In his model, STM consists of a "verbal buffer" (phonological loop) and a "visuospatial sketchpad" (maintenance of visual information). He later added an "episodic buffer" that is supposed to draw on the other buffers and LTM (Baddeley, 2000). Finally, a "central executive" is argued to be responsible for orchestrating all components. As we shall see, such cognitive models lend themselves exquisitely well to hypothesis testing with NBS.

Unitary store models assume that the MTL is engaged in both STM and LTM, and that its function is the establishment of new representations independent of their duration. Accordingly, information that does not require binding processes can be preserved in amnesic patients, which might also explain often preserved retrieval of consolidated preinjury memories. In a comprehensive review, Jonides and colleagues (2008) concluded that STM and LTM are not separable, but that STM consists of temporarily activated LTM representations. Several studies have confirmed these assumptions (Ranganath and D'Esposito, 2001; Hannula et al., 2006; Olson et al., 2006a, b). According to their assumptions, initial neural representations are also the repository of long-term representations, as they are active during encoding, as well as during STM, or the retrieval from LTM into STM (Wheeler et al., 2000). Chronometric brain stimulation experimental designs can be applied to explore such questions (e.g., Mottaghy et al., 2003a).

Long-term memory

LTM refers to the mechanism by which acquired memories gain stability or are strengthened over time, and become resistant to interference (Brashers-Krug et al., 1996; McGaugh, 2000; Dudai, 2004). Consolidation is assessed as a change in performance between testing and retesting (Robertson et al., 2004; Walker, 2005) and provides a direct measure of "offline" changes.

Mainly two components of LTM are described in the literature and frequently included under the term "declarative memory" – episodic and semantic memory. They rely mostly on MTL structures. Episodic memory refers to contents that can be located within a spatiotemporal context, such as holiday memories or autobiographical events. On the other hand, semantic memories are independent of context and are not personally relevant. They consist of general and factual world knowledge, such as "Dakar is the capital city of Senegal." However, "nondeclarative" memory functions, such as procedural memory (see above), also involve LTM consolidation processes, such as knowing how to ride a bike.

Successful long-term storage includes several steps starting with the encoding of information, followed by short-term storage and consolidation from STM to LTM, as well as repeated reconsolidation. Consolidation is thought to occur in a structured way allowing for prompt and precise retrieval. Elegant work from Muellbacher and colleagues (2002) pioneered the use of NBS approaches to explore the neurobiology of such processes in humans. During consolidation, memories can undergo changes that can be quantitative (enhancement, strengthening) as well as qualitative in nature (e.g., awareness of underlying sequences) (Wagner et al., 2004; Walker, 2005; Robertson and Cohen, 2006). Chronometric brain stimulation paradigms are contributing to clarify some of these issues. Consolidation mechanisms may depend on neuronal reactivation (signal increase), on the removal of noise-inducing synaptic changes (noise decrease), or their combination, all of which can be examined with NBS. For example, offline

performance changes seem to be causally associated with neuronal reactivation (Rasch et al., 2007). However, it remains to be shown that disruption of reactivation would impair consolidation processes, a problem that seems experimentally approachable with TMS.

It has been shown that sleep plays an important role in the consolidation of memories (Walker et al., 2002; Korman et al., 2007), and it has been argued (synaptic homeostasis hypothesis) that a net increase in the efficacy and number of synapses during wakefulness may add noise to the network. The reduction of noise would therefore improve the signal-to-noise ratio. Slow-wave sleep is thought to be responsible for downscaling synaptic strength and therefore noise reduction (Tononi and Cirelli, 2003, 2006), and has been associated with learning and the induction of brain plasticity (Huber et al., 2004, 2006; De Gennaro et al., 2008). NBS, in this case, particularly tDCS, is being elegantly employed to test some of these notions, while TMS–EEG studies are providing experimental support for the underlying hypotheses (e.g., Marshall et al., 2004, 2011).

Encoding and retrieval

During encoding, various event features distributed across neocortical areas are held actively online through processes guided by the PFC (Miller and Cohen, 2001; D'Esposito, 2007). TMS and tDCS lend themselves well to experimentally test such notions and evaluate precise spatial and temporal aspects of the hypothesized neural substrates.

The MTL is thought to be responsible for binding these representations in a highly structured way to enable optimal retrieval at a later timepoint (Cohen and Eichenbaum, 1991; Squire and Zola, 1998), and activity in PFC and MTL during encoding is correlated with successful retrieval (Paller and Wagner, 2002). Moreover, intermediate processes such as additional encoding or consolidation processes, are relevant for further stabilization of memories (Squire, 1984; Nadel et al., 2000; Paller, 2002). Critical encoding components include bottom-up sensory processes as well as top-down processes that select/engage, maintain, and update relevant features (Shimamura, 2011). Here again, NBS is a valuable experimental tool, thanks to the opportunity of interference with ongoing neural activity in a spatially and temporally controlled manner.

Retrieval of episodic memories depends on the recollection of encoded contextual features of a past event, such as time, place, people, sights, thoughts, and emotions (Mitchell and Johnson, 2009). Source memory is therefore an important element of episodic memory (Tulving, 2002; Shimamura and Wickens, 2009). MTL plays its part in memory retrieval by reinstating these features (Eldridge et al., 2005; Moscovitch et al, 2006). Successful retrieval has also been associated with the PFC (Buckner et al., 1998; Dobbins et al., 2002; Simons and Spiers, 2003), which is involved in top-down executive control. The HERA (Hemispheric Encoding/Retrieval Asymmetry) model proposed by Tulving and colleagues (1994) postulates that both prefrontal lobes subserve memory processes, but play different roles. While the left PFC is believed to be more involved in encoding and semantic retrieval, the right PFC is thought to be more important in episodic memory retrieval. Early functional imaging studies proposed an asymmetry in memory processes irrespective of modality, with encoding and retrieval being associated with left and right/bilateral PFC respectively (Cabeza and Nyberg, 2000; Haxby et al., 2000; Fletcher and Henson, 2001). The HAROLD (Hemispheric Asymmetry Reduction in OLDer adults) model suggests that prefrontal activity during cognitive performance becomes less lateralized with advancing age (Cabeza, 2002). In particular, the role of the PFC can be evaluated with TMS or tDCS, as the PFC is easily accessible to modulation with NBS (e.g., Gagnon et al., 2010, 2011).

Besides MTL, PFC, and cortical sites that store contextual features, brain imaging studies suggest that parietal areas also play an important role in episodic memory retrieval (Wagner et al., 2005; Cabeza et al., 2008). For instance, according to a recently proposed theory ("COrtical Binding of Relational Activity", CoBRA), the VPC acts as a binding zone for episodic features and linking these to long-term memory networks (Shimamura, 2011). Both the CoBRA model and the AtoM model (see above) share some similarities, as both suggest that MTL and VPC are linked. Although the role assigned to the VPC differs between the AtoM model (bottom-up processes) and the CoBRA model (integration of event-related activity), they might complement each other. Paired-pulse TMS and the combination of TMS with brain imaging are well suited to examine such notions of corticocortical interactions.

Prospective memory

Prospective memory involves an intention to carry out a psychological or physical act and is related to future-oriented behaviors. In order to realize a goal in the future, it is necessary to retain intentions and activate them at the right time and/or in the appropriate context (Ellis et al., 1999). Depending on the time that passes in between the creation of the intention and the action, and depending on whether the action is triggered externally (context feature) or internally (internal pacemaker), prospective memory involves working and long-term memory processes, as well as attentional processes

(Wittmann, 2009). Within this context it has been proposed that, during encoding, prospective memory contents obtain a special status, where they are tagged as not being achieved yet. During the presentation of prospective memory cues, temporal areas are active, possibly representing stimulus-driven attentional processes (Reynolds et al., 2009). The delay period between encoding the intention and the actual act is filled with cognitive activity that prevents active and conscious rehearsal, which differentiates prospective memory from WM or vigilance (Reynolds et al., 2009; Burgess et al., 2011). Prospective memory and WM take a special place within the memory domain as they rely strongly on executive processes. However, prospective memory and WM engage different brain areas. Whereas WM demands dorsolateral prefrontal cortex (DLPFC) activity, prospective memory has been associated mainly with activation in the rostral PFC (Okuda et al., 1998, 2007; Reynolds et al., 2009), which is implicated in "future thinking" (Atance and O'Neill, 2001). Such, largely theoretical, considerations derived from careful task analysis and psychological and cognitive model formation can be tested experimentally using NBS.

Working memory

WM refers to the temporary, active maintenance and manipulation of information necessary for complex tasks, while ignoring irrelevant information. It involves the temporary manipulation of external (experienced) or internal (retrieved) stimuli. Like other memory components, it also involves an encoding and retrieval stage. The PFC is an integral component for successful WM performance (Missonnier et al., 2003, 2004; Jaeggi et al., 2007), and NBS offers experimental approaches that were previously limited to animal models.

WM takes a special place within the memory functions, as it is highly dependent on top-down processing and selective attention. Top-down modulation allows us to focus attention on relevant stimuli and ignore irrelevant distractors. This is achieved through an improvement of the signal-to-noise ratio by increasing sensory activity for relevant items and decreasing activity for irrelevant items (Gazzaley and Nobre, 2012). Successful manipulation of information is necessary for encoding as well as the integration of memory functions with other so-called higher cognitive functions associated with conscious processing, such as decision-making, mental imagery, interference control, or language functions. State-dependency experimental designs with NBS (Silvanto and Pascual-Leone, 2008) might allow selective modulation of different items of information and thus shifting of the signal-to-noise ratio. This offers intriguing promises for translational applications of such NBS to populations with WM deficits, such as the elderly or patients with attention-deficit disorders, Parkinson's disease, or schizophrenia.

UNDERSTANDING THE NEURAL MECHANISMS OF LEARNING AND MEMORY

Learning and memory processes are investigated with a wealth of methods. In the literature we find studies that use brain imaging during memory tasks, analyze the number of remembered items correlated with EEG activity, look at the influence of state changes as captured by various brain imaging and neurophysiological measures, or "borrow patients' illnesses" to investigate the impact of serendipitous lesions. The application of all these methods has led to valuable information about the neural mechanisms of memory. However, cause–effect relationships are difficult to establish. NBS is uniquely suited to provide this (Silvanto and Pascual-Leone, 2012).

Although TMS and tDCS both promote changes in excitability, they do not rely on the same processes (Wagner et al., 2007; Nitsche et al., 2008) and behavioral effects can be different. Neuronavigated TMS can serve to probe the spatiotemporal contribution of certain structures and processes important for learning and memory. It can reveal where and when certain memory processes happen and can shed light on the interplay of multiple processes. On the other hand, the temporal and spatial resolution is lower for tDCS, which is a reason why the utility of tDCS to study spatiotemporal properties of learning and memory is limited. In the following section we concentrate on studies applying TMS as a means to induce so-called "virtual lesions" in the healthy brain (Pascual-Leone et al., 2000). In recent years, research in this field has grown immensely.

Assessing memory functions by induction of virtual lesions in healthy subjects

The first systematic investigation of the contribution of certain brain areas to cognitive functions took place during World War I. Soldiers with circumscribed brain lesions after gunshots provided information about how certain brain regions are associated with cognitive functions (Lepore, 1994). Later, Luria's work with brain-damaged war veterans contributed strongly to rekindling of the interest in neuropsychology during World War II (Luria, 1972).

Although lesion studies with patients have been widely used since then to investigate learning and memory, they have some disadvantages. Important variables, such as, for example, lesion size, comorbidities, and age, cannot be controlled easily. On the other hand, modern brain imaging methods, such as positron emission tomography (PET) and fMRI, are able to detect regional

activation changes with an excellent spatial resolution, and allow for controlled, test–retest experimental designs, but their low temporal resolution does not allow investigation of the organization of distributed memory networks, and they cannot provide information on facilitatory or inhibitory effects or cause–effect relationships. EEG offers a direct measure of brain activity with exquisite temporal resolution, but spatial resolution is in turn limited.

Many of these disadvantages can be overcome when using TMS to induce a "virtual lesion" in an otherwise healthy brain (Pascual-Leone et al., 1999; Walsh and Pascual-Leone, 2003). Instead of studying cognitive functions in patients with brain lesions, we can use TMS as a means to induce virtual lesions in healthy subjects and, therefore, reproduce neurobehavioral patterns of patients with brain lesions. TMS is a method that interferes with brain activity and thereby allows probing the chronological contribution of underlying cortical areas. However, it is important to note that our understanding on the neural mechanisms underlying such "virtual lesions" is rather limited, and that a functional disruption is not simply dependent on a mere modification of cortical excitability in the targeted brain area, but appears to involve a complex interplay of inhibitory and excitatory mechanisms, disruption of oscillators, and modification of functional connectivity and synaptic efficacy across distributed neural networks.

TMS has been used in a vast number of studies investigating mechanisms of motor learning and memory (Bütefisch et al., 2004; Censor and Cohen, 2011), whereas studies looking at nonmotor memory functions are less numerous. However, recent technical advances allowing the combination of TMS with EEG and fMRI are promising and will allow further exploration of nonmotor memory processes (Miniussi and Thut, 2010; Thut and Pascual-Leone, 2010). The combination of methods has, furthermore, the advantage of helping to unravel local and distant effects of brain stimulation and give us insights into functional connectivity.

Most research groups that study WM or STM with NBS methods have focused on the DLPFC or the parietal cortex, believed to be core cortical structures for memory processes. Typically, these studies have used delayed response tasks or *n*-back tasks to measure STM or WM performance, respectively. A classical example of a delayed match-to-sample task is the Sternberg task (Sternberg, 1966), where the subject is shown a list of numbers or letters and is asked to memorize them. After the delay period, a probe number or letter is shown and the subject has to indicate whether the probe was in the list. Researchers have used several versions of this test using different stimuli and parameters. In "*n*-back tasks" a string of visual or auditory stimuli is presented, and subjects have to compare each new stimulus with a stimulus presented *n* trials back. *n*-back tasks with $n = 1$ involve a continuous maintenance and matching of stimuli, whereas *n*-back tasks with $n > 1$ furthermore require concurrent engagement of manipulation processes. The reallocation of attention and processing capacity away from mere matching to actual WM processes (by increasing *n*) is reflected in decreasing P300 amplitudes (Watter et al., 2001). As these tasks draw on different processes, we will address them in separate sections. Studies using delayed match-to-sample tasks will therefore be summarized under the STM section, whereas studies using the *n*-back task, or other tasks requiring the online manipulation and integration of stimuli, will be summarized under the WM section. Another major section gives an overview for studies that have investigated encoding, consolidation, and retrieval.

The number of studies that apply TMS and tDCS to address questions regarding the underlying neurobiological structure and modulation of memory functions has grown rapidly in past years. The studies presented in Table 55.1 have applied single-pulse TMS, paired-pulse TMS, repetitive TMS (rTMS), and theta-burst stimulation (TBS). The tasks that were used draw on various processes (attentional, sensory, motor, verbal/nonverbal, spatial/nonspatial, maintenance/manipulation) and stimulation parameters, such as pattern, timing, duration, intensity, and location, vary across studies. It is important to realize that memory tasks vary greatly regarding their specific cognitive demands. In addition, it is important to recognize TMS methodological factors. For example, online stimulation differs from offline stimulation in that underlying brain areas are concomitantly activated through TMS as well as through task performance. This combined activation may affect stimulation outcome. Finally, note that some studies report effects on accuracy, whereas others focus on response times (see Table 55.1). It is important to note, though, that the amount of time it takes to recognize an already encountered stimulus or to recall a memorized representation is far less important than the accuracy of this process. Finally, we have to keep in mind that the act of receiving TMS may have an influence on attentional processes that should be carefully controlled for.

Despite the many differences between studies, the growing literature summarized in Table 55.1 is providing important novel insights in the neurobiology of human learning and memory, and illustrates the power of NBS in this area of cognitive neuroscience.

Short-term memory

Prefrontal areas undoubtedly play an important role in STM processes. However, one of the questions that

Table 55.1

Synopsis of peer-reviewed, published studies applying noninvasive brain stimulation in the memory domain

Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
TMS in short-term memory					
Beckers and Hömberg (1991)	24	OC	Various intensities at 40–120 ms, during delay, active/sham	Trigram identification task and visual DMS	Stim during delay impaired identification of trigrams as compared to sham. Stim during delay of DMS decreased memory scanning rates. No impact on accuracy.
Kessels et al. (2000)	8	R/L PPC (P3/P4)	200 ms of 25 Hz rTMS at 115% rMT, during delay, active/sham	Spatial DMS	Stim to right PC during delay increased RT compared to left stim, but not sham (~561 ms vs. ~522 and ~540 ms).
Mottaghy et al. (2002b)	8	L DMPFC, DLPFC, VPFC	10 min of 1 Hz rTMS at 90% rMT, comparison with baseline	Spatial or face DMS (objects and faces)	Stim to DMPFC increased error rate for spatial task compared to baseline (2.88 vs. 1.58). Stim to DLPFC increased error rates for spatial (4.25 vs. 2.21) and face task (3.38 vs. 2.17). Stim to VPFC increased error rates for face task (3.63 vs. 1.96). No impact on RT.
Herwig et al. (2003)	9	L PFC, PMC, PC (fMRI-guided), homolog regions (control)	3 s of 15 Hz rTMS at 110% rMT, during delay (second half)	Verbal DMS (1 or 6 letters)	Stim over left PMC (~14.3 vs. 9.5%) but not PC or PFC increased error rate. No impact on RT.
Koch et al. (2005)	9	R PPC (P6), premotor cortex (SFG), and DLPFC (F4)	300 ms of 25 Hz rTMS at 110% rMT, during delay or decision, active/sham	Matching of spatial sequences	Stim over PPC (~29%) and DLPFC (~22%) but not SFG during the delay phase impaired RT. Stim over DLPFC during the decision phase selectively impaired RT (~38%). No impact on accuracy.
Desmond et al. (2005)	17	R superior Cb	sp TMS at 120% rMT, during delay, active/ non-active trials/ sham	Verbal DMS and motor control task	Stim at the beginning of the delay phase increased RT on correct trials compared to non-active trials, sham, and motor control task. No effect on accuracy.
Kirschen et al. (2006)	30	Left IPL	3 sp at 120% rMT, during delay (at 1,3,5 s), active/sham control region	Verbal DMS (phonologically similar/ dissimilar pseudo-words and distractors)	Stim during delay improved RT for similar pseudo-words as compared to sham. Accuracy improved marginally. No difference observed between TMS and placebo scores for dissimilar pairs.

Luber et al. (2007)	44	Exp. 1: Midline PC (precuneus) or left DLPFC Exp. 2: Midline PC (precuneus)	100% rMT, active/sham rTMS Exp. 1: 1 or 5 Hz (7 s) or 20 Hz (2 s), during delay Exp. 2: 5 Hz (7 s), during delay or decision	Verbal DMS (1 or 6 letters)	Exp. 1: Only 5 Hz rTMS over PC but not DLPFC during delay phase improved 6-letter RT compared to sham (626 vs. 702 ms, ~11%) and 1-letter RT (491 vs. 542 ms, ~ 9%). Exp. 2: 5 Hz rTMS over PC during delay but not decision phase improved RT by 88 ms. 1-letter accuracy improved during decision phase compared to sham (~97 vs. ~90, ~7%).
Hamidi et al. (2008)	Exp. 1: 30 Exp. 2: 24	Exp. 1: R/L DLPFC, SPL, PCG (control) Exp. 2: R/L FEF, IPS, PCG (control)	3 s of 10 Hz rTMS at 110% rMT, during delay, active/control	Spatial DMS	Exp. 1: Stim over SPL improved RT ~2% as compared to PCG-control (~950 ms vs. ~970 ms). Stim over LH impaired accuracy more as stim over RH (largest effect over DLPFC). Stim was more disruptive if applied contralaterally to the visual field (faster/slower RT for LH/RH stim). Exp. 2: Stim decreased accuracy overall and specifically for contralaterally presented stimuli.
Luber et al. (2008)	15 (sleep deprived for 48 h s)	BA 19 and midline PC, BA 18 (control), (as localized in fMRI)	7 s of 5 Hz rTMS at 100%rMT, during delay, active/sham	Visual DMS	Stim to the upper middle occipital region only reduced sleep-deprivation induced RT deficit compared to sham (1026 ms vs. 1169 ms). No impact on accuracy or non-sleep deprived subjects (state-dependency).
Hamidi et al. (2009)	24	R/L DLPFC, SPL, and PCG (control)	3 s of 10 Hz rTMS at 110% rMT, during decision, active/control	Spatial DMS (recognition) and recall	Recognition: Stim to right DLPFC resulted in accuracy improvement, stim to left DLPFC led to reduced accuracy. Recall: Stim to right DLPFC resulted in reduced accuracy. No impact of stim over SPL.
Cattaneo (2009)	Exp. 1: 14 Exp. 2: 11	OC (V1, V2) and vertex	sp TMS at 65% MSO, at beginning or end of delay, compared to baseline	Visual Imagery and visuospatial STM Exp. 1: at end of delay Exp. 2: at beginning of delay	Exp. 1: Stim facilitated both tasks compared to vertex stim and baseline. Exp. 2: Stim impaired STM compared to vertex and baseline but not visual imagery. No impact on accuracy.

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Table 55.1

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Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Preston et al. (2009)	32	R/L DLPFC (F3/F4)	5 5-s trains of 10 Hz rTMS, ITI 10 s, at 100% rMT, offline, active/sham	Verbal DMS	Stim decreased correct response RT in active (−21%) compared to sham (+0.3%). No impact on accuracy.
Yamanaka et al. (2010)	52	R/L PC	5 Hz rTMS at 100% rMT, during delay (6 s), active/sham	Spatial DMS and attentional control task	Stim over right PC during delay improved RT ∼7% compared to sham (∼800 ms vs. ∼865 ms). Increase of frontal oxygenated hemoglobin during DMS and decrease during control task.
Silvanto and Cattaneo (2010)	12	Exp. 1: R/L V5/MT (2 coils) Exp. 2: R/L lateral OC (2 coils)	sp TMS at 120% PT, at 3 s into delay, baseline phosphene	Delayed visual motion discrimination	Exp. 1: Reported phosphene motion was influenced by the motion component of the memory item: enhanced when direction was the same as in baseline phosphene, weakened if opposite direction. Exp. 2: No relation between task and phosphenes after stim of lateral occipital region.
Hannula et al. (2010)	Exp. 1: 6 Exp. 3: 6	MFG area with/without S1 connection	sp TMS at 120% rMT, at 300 or 1200 ms into delay, baseline control	Tactile STM (discrimination) without (Exp. 1) or with (Exp. 3) distraction	Exp. 1: Stim delivered during early but not late delay over MFG regions with connection to S1 decreased RT ∼15% compared to baseline (∼730 ms vs. ∼860 ms). Exp. 3: Distraction prolonged mean RT by 5%.
Feredoes et al. (2011)	16	R DLPFC, combined with fMRI	3 sp TMS at 110% rMT or 40% rMT (control), during delay	Visual DMS (face or house) with/without distractor interference	Stim (time-locked to distractors) over DLPFC increased activation in posterior areas (that represented stimuli but not distractors) only when distractors were present.
Zanto et al. (2011)	20	R IFJ (as localized in fMRI), combined with EEG	10 min of 1 Hz rTMS at 120% rMT offline, active/sham	Visual DMS (motion direction or color of dots)	Stim led to a decline of P1 and accuracy during the first half but not second half of the color condition, no effects during motion condition (P1 modulation predicted accuracy changes). The magnitude of phase locking value in the alpha band (but not beta or gamma) decreased after rTMS.

Higo et al. (2011) Exp. 2	9	L fO (as localized in fMRI in Exp. 1)	15 min 1 Hz rTMS, offline, adjusted to RMT, active	Visual delayed matching to stimulus class (houses, body parts, faces)	TMS over fO disrupted top-down selective attentional modulation in the occipitotemporal cortex but did not alter bottom-up activation. The fO may play a role in regulating activity levels of representations in posterior brain areas.
Savolainen et al. (2011)	12	MFG area with/without S1 connection	sp TMS at 120% rMT, at 300 ms into delay, baseline control	Tactile STM (discrimination) with tactile or visual distractor	Stim over MFG region with S1 connection followed by tactile (but not visual) distractor decreased RT ~4% compared to baseline (~770 ms vs. ~800 ms).
Soto et al. (2012) Exp. 2	8	L SFG and LOC (as localized in fMRI Exp. 1)	15 min of 1 Hz rTMS at 55% MSO, offline, active/sham	Visual and verbal DMS	Stim to left SFG increased RT for recognition of colored shapes compared to sham. Stim to the LOC increased RT for recognition of written words compared to sham. No impact on accuracy.
Morgan et al. (2013)	20	R PC, L IFG	40 s train of cTBS at 80% aMT, offline, active/sham	Object color, angle averaging, and combined task	Stim to right PC or left IFG selectively impaired WM for the combined task, but not single feature tasks as compared to sham.
van de Ven et al. (2012)	12	Lateral OC	sp TMS at 110% PT at 100, 200, or 400 ms into delay, active/sham	Modified change detection task with low or high memory loads	Stim delivered at 200 ms into the delay phase decreased accuracy for high but not low memory loads in the contralateral visual field compared to sham.
TMS in working memory and prospective memory					
Mottaghy et al. (2000)	14	R/L DLPFC, Fz (control), combined with PET	30 s of 4 Hz rTMS at 110% rMT, during task, active/control	Verbal 2-back, 0-back (control)	Stim over either R/L DLPFC reduced accuracy and rCBF in the targeted area as well as afferent networks specific to each hemisphere. Stim to Fz had no effect on WM task. Performance on the control task was not affected by stim.
Mull and Seyal et al. (2001)	7	R/L DLPFC	spTMS at 115% rMT, at 400 ms into delay, active/no TMS	Verbal 3-back	Stim over L DLPFC increased error rate compared to no TMS control (5.4%). No impact of stim over R DLPFC.

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Table 55.1

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Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Oliveri et al. (2001)	35 (5 Exp.: 8, 6, 6, 25, 6)	Exp. series 1: R/L or bilateral temporal (T5/T6) and parietal (P4/P5) Exp. series 2: Bilateral SFG and DLPFC	Uni- or bilateral spTMS at 130% rMT, at 300 or 600 ms, active/baseline	Spatial 2-back Visual-object 2-back (abstract patterns)	Exp. series 1: Bilateral parietal stim at 300 ms increased RT in visuospatial task compared to temporal (11%) and baseline (20%). Bilateral temporal stim at 300 ms impaired RT in visual-object task. No impact on accuracy. Exp. series 2: Bilateral stim over SFG at 600 ms increased RTs in visuospatial task compared to baseline (11%), whereas bilateral stim over DLPFC at 600 ms interfered in both tasks with accuracy (visuospatial: 10%, visual-object: 13%) and RT (visuospatial: 6%, visual-object: 6%).
Sandrini et al. (2003)	12	R/L DLPFC (F3/F4)	0.5 s of 20 Hz rTMS at 90% rMT, during encoding or retrieval, active/sham/baseline	Verbal LTM: Recognition of unrelated/related word pairs after 1 h	Impaired recognition accuracy of unrelated word pairs after stim over R and L DLPFC during encoding and right PFC in retrieval. No impact on RT besides faster RT for related as compared to unrelated words.
Mottaghy et al. (2003a)	6	R/L MFG, inferior PC	sp TMS at 120% rMT, at 140-500 (at 10 time points, ISI 40 ms) into delay, after every 4th letter, active/control	Exp. 1: Verbal 2-back Exp. 2: Choice reaction (control task)	Impaired accuracy occurred after stim of R PC (180 ms) of L PC (220 ms) and R MFG (220 ms), and L MFG (260 ms). RT was impaired only after L MFG stim (180 ms). No impact on control task.
Mottaghy et al. (2003b)	14	R/L DLPFC (F3/F4)	30 s of 4 Hz rTMS at 110% rMT, during task, active/control/baseline	Verbal 2-back, 0-back (control task)	Stim over L DLPFC led to a shift of BBR towards the SFG and to a positive BBR in anterior parts of the SFG. Stim over R DLPFC led to a shift of the BBR to left posterior and inferior IFG. Baseline measurements indicated a negative BBR in the left MFG and no significant BBR in the right MFG.

Rami et al. (2003)	16	HF stim to R/L DLFPC and right Cb, LF stim to L DLPFC	10-s trains of 1 or 5 Hz rTMS at 90% rMT, 30 s intervals, during encoding and retrieval, active/baseline	STM (digits forward), WM (digits backward, letter-number sequencing WAIS III), episodic memory (RBMT), verbal fluency	HF stim over L DLFPC impaired verbal episodic memory as compared to HF stim over R DLPFC, LF stim over L DLPFC, and baseline.
Postle et al. (2006)	R: 5 L: 7	R/L DLPFC, SPL, PCG (control) (as localized with fMRI)	6 s of 5 Hz rTMS at 100% rMT, during delay, active/control	Verbal STM or WM	Stim over DLPFC impaired accuracy of WM but not STM compared to control. Stim over SPL impaired accuracy of WM and STM. No impact on RT.
Osaka et al. (2007)	8	L DLPFC, Cz (control)	pp TMS (ISI 100 ms) at .47 T, during delay, active/sham/control	Reading span task (maintain target words)	Stim decreased mean accuracy compared to sham or stim over Cz (10.9% and 7.5%).
Sandrini et al. (2008)	Exp. 1: 9 Exp. 2: 14 Exp. 3: 9	R/L DLPFC	0.5 s of 10 Hz rTMS at 90% rMT, at end of delay, active/sham	Exp. 1: combined verbal/spatial 1-back Exp. 2: combined verbal/spatial 2-back Exp. 3: 2-back with one domain only	R DLPFC stim impaired RT in the verbal condition (~834 ms vs. ~790 and ~803 ms), whereas L DLPFC stim impaired RT in the spatial condition compared to opposite side and sham (792 ms vs. 728 and 737 ms). No impact on accuracy, variation of only one domain, or 1-back task.
Imm et al. (2008)	12	R/L DLPFC (F3/F4), inferior PC (P3/P4)	sp TMS at 100% rMT, at 250, 450, 650, or 850 ms into delay, active	Audioverbal 2-back Pitch 2-back	Stim over RH increased RT in the pitch 2-back at 650 and 850 ms (724 and 850 ms vs. 656 ms). Stim over P3 increased RT in the audioverbal 2-back at 450 ms.
Basso et al. (2010)	Exp. 1: 27 Exp. 2: 24 Exp. 3: 18	R/L DLPFC, interhemispheric sulcus (control)	spTMS at 100% rMT, delivered 300 ms into delay, active/control	Exp. 1: WM (medium = 3, high = 5) and lexical decision (word/pseudoword), prospective condition (react to specific words); Exp. 2: prospective condition 1 or 3 words; Exp. 3: with TMS	Stim increased error rates of the PM task more than the WM task and compared to sham. Exp. 1 and 2: Higher PM demand affected WM only at higher loads. Exp. 3: Stim over R/L DLPFC impaired accuracy of PM task regardless of WM load, while effect on WM was marginal.

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Table 55.1

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Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Costa et al. (2011)	Exp. 1: 8 Exp. 2: 8	Exp. 1: R/L BA 10 (frontal pole), Cz (control) Exp. 2: L BA 46 (DLPFC), Cz (control)	20 s of cTBS (3-pulse bursts at 50 Hz every 200 ms) at 80% aMT	Verbal forward/backward memorization task with simultaneous response to target word (PM task)	Exp. 1: Stim over left BA 10 decreased accuracy in PM compared to Cz stim (58.6% vs. 73.4%). Exp. 2: Stim over left DLPFC had no significant effect on accuracy or RT.
TMS in general learning and memory					
Grafman et al. (1994)	5	R/L hemisphere (F7/F8, T5/T6, P3/P4, O1/O2)	5 p of 20 Hz rTMS at 120% rMT, during encoding (at 0, 250, 500, 1000 ms), active/sham	Verbal memory (word recall)	Stim over T5, F7, and F8 at 0 and 250 ms showed highest impairment of recall as compared to sham. Furthermore stim over T5 and F7 at 500 ms impaired recall. Stim over T5 and F7 also impaired the primacy effect.
Rossi et al. (2001)	13	R/L DLPFC (F3/F4)	500 ms of 20 Hz rTMS at 90% rMT, during encoding or retrieval, active/sham/baseline	Visual memory (indoor/outdoor images)	Stim over R DLPFC during retrieval impaired accuracy, while stim over L DLPFC during encoding and over R DLPFC during retrieval impaired discrimination. No impact of R DLPFC stim during encoding and L DLPFC stim during retrieval.
Epstein et al. (2002)	10	R/L DLPFC, Cz (control)	pp TMS (ISI 60 ms), 120% rMT, during encoding at 180 ms, active/controls/no stim	Visual memory (associate Kanji words and abstract patterns)	Stim during encoding over R DLPFC decreased accuracy compared to stim over L DLPFC. RT was not measured.
Floel et al. (2004)	15	R/L IFG	0.5 s of 20 Hz rTMS at 90% rMT, during encoding, active/sham/no stim	Verbal (letters) and nonverbal (abstract shapes) memory	Stim over L IFG impaired word recognition, while stim over R IFG impaired image recognition, each as compared to opposite stim (words 20% and images 14%) or sham (words 24% and images 14%). No impact on RT.
Köhler et al. (2004)	12	L Inferior PFC (guided by fMRI) R inferior PFC and L PC (controls)	5 p of 7 Hz rTMS at 100% rMT, during encoding, active/control/no stim	During fMRI: semantic/non-semantic decisions, crosshair fixation During stim: semantic decisions After stim: verbal memory (recognition)	Stim over L PFC increased recognition accuracy compared to non-stim and control (R PFC, L PC). No impact on RT. But, RT for semantic decisions made under L PFC stim was impaired.

Skrdlantov et al. (2005)	10	L DLPFC	0.9 Hz rTMS at 110% rMT, during task (192 p per subtest), active/sham	Verbal memory (word recall) Visual memory (facial recognition)	Stim over L DLPFC during task impaired free recall of words but not recognition of faces as compared to sham.
Kahn et al. (2005)	14	R/L posterior VLPFC, (guided by fMRI)	spTMS at mean 66% MSO, during encoding (btw 250-600 ms), active/baseline	Verbal memory (decision if 2/3-syllable word or peusdo-word, then surpise recognition task with confidence judgments)	Stim over L VLPFC impaired word memory (confidence), while stim over R VLPFC facilitated word and pseudo- word memory (confidence, difference strongest at 380 ms). Phonological decision accuracy was facilitated for words and pseudo-words after stim over R VLPFC (strongest at 340 ms).
Rossi et al. (2006)	42	R/L DLPFC or IPS (P3/P4)	500 ms rTMS at 20 Hz at 90 or 120% rMT, during encoding, active/sham	Visual memory (indoor/outdoor images), visuospatial attention (Posner, control task)	L DLPFC stim interfered with encoding while R DLPFC stim interfered with retrieval. No impact of stim over IPS on encoding or retrieval even at higher intensity. However, stim over R IPS impaired RT in the attention task.
Schutter and van Honk (2006)	11	L OFC (Fp1), L DLPFC (F3)	20 min of 1 Hz rTMS at 80% rMT, offline, active/sham	Visual memory (neutral, fearful, and happy faces)	Stim over L OFC improved memory for happy faces compared to sham. Stim over L DLPFC improved memory marginally for happy faces compared to sham.
Gallate et al. (2009)	20	L ATL (between T7/FT7)	10 min of 1 Hz rTMS at 90% rMT, offline, active/sham	Verbal memory (false memories)	Stim decreased the number of false memories by 36% compared to sham (~3 vs. ~2 errors).
Sauseng et al. (2009)	Exp. 3: 7 Exp. 4: 13	Exp. 3: R/L PC (P3/P4), Cz (control) Exp. 4: R/L PC (P3/P4), centroparietal control	9 pulses of 10 Hz or 14 pulses of 15 Hz rTMS, at 110% rMT, during delay, active/sham	Visual STM (memorize color of a square presented in one but not other visual hemifield)	10 Hz rTMS to PC ipsilateral to the stimulus improved visual STM (Exp. 3/4: 40% less false alarms, 37% fewer missed trials), while contralateral stim over PC led to a decrease. No effect of 15 Hz rTMS over PC or 10 Hz rTMS over centroparietal sites.
Blanchet et al. (2010)	16	R/L DLPFC (F3/F4)	ppTMS, ISI 3 ms, 90% rMT, during encoding or retrieval, active/sham	Verbal (letters) and nonverbal (shapes) memory, under full or divided attention	Stim over L DLPFC impaired recall as compared to stim over R DLPFC under *full* attention encoding (but not as compared to sham). Stim over R DLPFC impaired recall as compared to sham under *divided* attention encoding (but not as compared to stim over L DLPFC).

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Table 55.1

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Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Gagnon et al. (2010)	18	R/L DLPFC	ppTMS, ISI 3 ms, at 90% rMT, during encoding or retrieval, active/sham	Verbal (letters) and nonverbal (abstract shapes) memory	Stim over L DLPFC during encoding decreased DR as compared to sham and stim over R DLPFC. Stim over the R DLPFC during retrieval decreased DR and hit rate compared to stim over L DLPFC. No significant differences between verbal/nonverbal material.
Gagnon et al. (2011)	11	R/L DLPFC (F3/F4)	ppTMS, ISI 15 ms, at 90% rMT, during encoding or retrieval, active/sham	Verbal (letters) and nonverbal (abstract shapes) memory	Stim over L DLPFC during encoding improved RT as compared to stim over R DLPFC or sham. Stim over R DLPFC during retrieval improved RT as compared to stim over L DLPFC. More false alarms for shapes than for words occurred after stim over R DLPFC or sham.
De Weerd et al. (2012)	13	R OC (V1) to interfere with lower-L (but not upper-R) quadrant	Priming with 20 trains of 30 pulses at 6 Hz (ITI 25 s) at 45% MSO, 6.7 min of 1 Hz rTMS at 50 MSO, 45 min after session 1 and 2, active/no stim	Visual orientation discrimination (day 1: lower L quadrant, upper R quadrant, day 2: opposite or vice versa)	Stim delivered 45 min after the first and second training session to interfere with lower-L quadrant strongly impaired learning as measured on the next day. This interference occurred only when training of the L visual field was followed by training of the R visual field before TMS and not vice versa. No differences between quadrants at baseline.
tDCS in short-term memory					
Marshall et al. (2005)	12	Bilateral RA/LA or RC/LC DLPFC (F3/F4), S	0.26 mA, intermittent on/off 15 s over 15 min, during task, ref mastoids, active/sham	Visual STM (modified Sternberg)	Bilateral A and C stim both impaired RT as compared to placebo. No impact on accuracy.
Ferrucci et al. (2008)	17	A/C/S, R/L Cb and PFC (btw Fp1/F3 and Fp2/F4)	2 mA, 15 min, offline, ref deltoid, active/sham	Numerical STM (modified Sternberg)	C-tDCS over PFC improved RT ~6% compared to sham (~625 ms vs. ~665 ms). No effect after A-tDCS. A-tDCS and C-tDCS blocked RT decrease induced by task repetition.

Berryhill et al. (2010)	11	A./C/S, R inferior PC (P4)	1.5 mA, 10 min, during learning, ref left cheek, active/sham	Visual STM (recognition and free recall of objects)	C-tDCS selectively impaired WM on recognition tasks versus anodal and sham. No impact on free recall.
Gladwin et al. (2012)	14	A/S, L DLPFC	1 mA, 10 min, during task, ref SOA, active/sham	Verbal STM (modified Sternberg)	A-tDCS improved RT when distractor was present compared to non-distractor and sham conditions. No impact on accuracy.
Heimrath et al. (2012)	12	A/C/S, R PC (btw P8/P10), combined with EEG	1 mA, 30 min, offline, ref btw P7/P9, active/sham	Spatial DMS	While A-tDCS over RH impaired capacity for contralateral stimuli, C-tDCS improved it. Both A-tDCS and C-tDCS affected capacity for ipsilateral stimuli compared to sham. tDCS altered ERPs (N2, P2, N3) and oscillatory power in the alpha band at posterior electrodes.
tDCS in working memory					
Fregni et al. (2005)	15	A/C/S, L DLPFC (F3), A M1 (control)	1 mA, 10 min, during task, ref SOA, active/sham/M1	Verbal 3-back (sequential-letter task)	A-tDCS over L DLPFC improved accuracy by ~10% (21.7 vs. 19.8) and decreased number of errors by ~28% as compared to sham (4.7 vs. 6.9). No impact after C-tDCS over LDLPFC or A-tDCS over M1. No impact on RT.
Ohn et al. (2008)	15	A/S, L DLPFC (F3)	1 mA, 30 min, during, ref SOA, active/sham	Verbal 3-back (assessed 10, 20, and 30 min into stim, and 30 min after)	A-tDCS improved accuracy by 10% (at 20 min), 16% (at 30 min), 14% (at 30 min after) as compared to sham. No impact on error rates or RT.
Mulquiney et al. (2011)	10	A, L DLPFC (F3)	1 mA, 10 min, during task, ref SOA active/sham/tRNS	Pre and post stimulation: visual STM (one card task, 1-back), WM (2-back) During stimulation: STM (Sternberg)	A-tDCS decreased RT in WM (2-back) for correct responses by ~2% compared to sham. No impact on accuracy. No impact on STM tasks.
Teo et al. (2011)	12	A/S, L DLPFC (F3)	1 or 2 mA, 20 min, during task, ref SOA, active/sham	Verbal 3-back during stim, STM (Sternberg) after stim	During the final 5 min of A-tDCS (2 mA) over L DLPFC RT improved significantly as compared to sham (~581 ms vs. ~605.25 and ~629.49 ms). No impact on accuracy. No impact on STM after stim.

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Table 55.1

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Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Zaehle et al. (2011)	16	A/C/S, L DLPFC (F3), combined with EEG	1 mA, 15 min, offline, ref mastoid, active/sham/control	Verbal 2-back (letters)	A-tDCS improved RT as compared to C-tDCS and resulted in amplified oscillatory power in the theta and alpha bands under posterior electrode sites. C-tDCS had opposite effects on EEG measures. No impact on accuracy.
Andrews et al. (2011)	10	A/S, L DLPFC (F3)	1 mA, 10 min, during task or offline, ref SOA, active/sham	During stim: verbal 2-back followed by 3-back (letters) Pre/post stim: STM (digit span forward) and WM (digit span backward)	Online A-tDCS improved digit span forward by 5.5% as compared to offline A-tDCS and sham. No information regarding online task outcome.
Mylius et al. (2012)	24	A/C/S, R/L DLPFC (F3/F4)	2 mA, 20 min, 15 min before and during task, ref SOA active/sham	Verbal 2-back Pain percpetion (warm/cold)	A-tDCS over R DLPFC increased tolerance to heat pain as compared to sham. During C-tDCS over the L DLPFC there were fewer outliers as compared to sham. No significant differences in accuracy (dissociation of analgesic effect from cognitive function).
Sandrini et al. (2012)	27	Bilateral PPC (P3/P4), LAlRC, LC/RA, S	1.5 mA, 13 min, active/sham	Verbal STM (1-back) and WM (2-back)	1-back: LA/RC tDCS abolished practice-dependent improvement in RT as compared to sham (9% vs. 0.65%). 2-back: LC/RA tDCS abolished practice-dependent improvement in RT (9.8% vs. 0.45%) as compared to sham. No impact on error rates.
Meiron and Lavidor (2013)	41	A /S, R/L DLPFC	2 mA, 15 min, during task, ref Cz, active/sham	Verbal n-back (4 levels of WM load), during and after stim	During online stimulation at highest WM loads males benefited from stim over L DLPFC as compared to sham, while females improved after stim over R DLPFC. No impact on RT. Online accuracy scores at the highest WM level was related to post-tDCS recall.

tDCS in general learning and memory					
Kincses et al. (2004)	22	A/C/S, L DLPFC (N = 14) and V1 ($n = 8$)	1 mA, 10 min, 5 min before and during learning, ref Cz, active/sham,	Probabilistic classification learning	A-tDCS over L DLPFC improved learning compared to sham. No effect after C-stim or stim over V1.
Marshall et al. (2004)	30 (males)	Bilateral RA/LA DLPFC (F3/F4)	0.26 mA/cm^2, intermittent on/off 15 s over 30 min, during sleep, active/sham	Declarative and procedural learning (paired associate word lists and mirror tracing), PANAS/EWL (mood)	Bilateral anodal tDCS during sleep enhanced word retention compared to sham (35.7 vs. 34.5). No impact when applied during wakefulness and no impact on procedural memory. After active but not sham tDCS positive affect decreased less and feelings of depression decreased.
Vines et al. (2006)	11	C/S, L SMG (TP3), R SMG (control)	1.2 mA, 20 min, offline, ref SOA, active/sham/control	Pitch matching (6/7 tones)	C-tDCS to L SMG affected short-term pitch memory performance (9%) compared to R SMG and sham.
Elmer et al. (2009)	20	A/C/S, R/L DLPFC (F3/F4)	1.5 mA, 5 min, during learning, ref mastoid, active/sham	Verbal LTM (VLMT)	C-tDCS to L DLPFC decreased number of words recalled after 25 min compared to sham (12%). No effects on long-term retrieval were found.
Boggio et al. (2009)	30	Bilateral ATL (T3/T4), (LA/RC), unilateral ATL (LA/RC enlarged electrode), S	2 mA, 10 min, during encoding and retrieval, active/sham	False memory (within word categories)	Bilateral and unilateral tDCS reduced false memories (73%) compared to sham. Bilateral tDCS decreased the number of false memories compared to unilateral stim (~1 vs. ~2 errors) and compared to sham (~1 vs. ~3.7 errors).
Kirov et al. (2009)	28	Bilateral RA/LA, DLPFC (F3/F4)	Five 5 min epochs of transcranial slow oscillation stimulation (tSOS, 0.75 Hz), 1 min ISI, 0.517 mA/cm_2, ref mastoid, active/sham	Verbal and non-verbal paired association, verbal memory (VLMT), number list learning, procedural memory (mirror tracing, finger sequence tapping), control tasks	TSOS during wakefulness induced a local increase in endogenous EEG slow oscillations (0.4-1.2 Hz) and a widespread increase in EEG theta and beta activity. TSOS during learning improved verbal encoding, but not consolidation as assessed 7 h after learning.

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Table 55.1

Continued

Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Clark et al. (2012)	96 (divided in diff. stim groups)	Exp. 1–3: A, R inferior PFC (F10) Exp. 4: A, R PC (P4)	0.6 mA or 2 mA, 30 min, during learning, ref arm, active/control (0.1 mA)	Detection of cues indicative of covert threats	Exp. 1–3: A-tDCS at 2 mA over R inferior PFC improved threat detection sign. more (26.6%) as compared to control (0.1 mA, 14.2%), while forgetting rate over 1 h was similar. Intermediate current strength (0.6 mA) was associated with an intermediate improvement (16.8%). Exp. 4: A-tDCS at 2 mA over R PC improved accuracy sign. more (22.5%) as compared to control (0.1 mA over F10).
Chi et al. (2010)	36 (12 each condition)	Bilateral ATL, LA/RC, RA/LC, S	2 mA, 13 min, during task, active/sham	Visual memory (geometric shapes)	LC/RA-tDCS resulted in a improved visual memory (accuracy) by 110% as compared to sham. No change after LA/RC-tDCS.
Cohen Kadosh et al. (2010)	15	Bilateral PC, RA/LC, RC/LA, S	1 mA, 20 min, 6 days, during learning, active/sham	Numerical learning (pseudo-number paired association), changes assessed by numerical tasks (Stroop, number-to-space task)	6 days of RA/LC-tDCS improved RT in Stroop compared to sham. RC/LA-tDCS impaired performance compared to sham
Penolazzi et al. (2010)	12	Bilateral frontotemporal stim between F3/4 and C3/4, LA/RC, RA/LC	1 mA, 20 min, during encodig, active/sham	Visual memory (free recall of images differing in affective arousal and valence)	Bilateral RA/LC-tDCS improved recall of pleasant images compared to unpleasant/neutral images, while bilateral LA/RC-tDCS improved recall of unpleasant images compared to pleasant and neutral images.
Javadi et al. (2012)	13	A/C, L DLPFC (F3)	1.5 mA, 1.6 sc, during encoding or delay, ref SOA, active/no stim	Word memorization	A-tDCS during encoding improved accuracy and RT compared to late A-tDCS or no tDCS. C-tDCS during encoding impaired accuracy and RT compared to late C-tDCS or no tDCS. Stim during delay had no effect.

Javadi and Walsh (2012)	32	A/C/S, L DLPFC (F3), M1 (C3, control)	1.5 mA, 20 s A, 30 s C, during encoding or recognition, ref SOA, active/sham	Word memorization	During encoding A-tDCS over DLPFC improved accuracy, while C-tDCS impaired accuracy compared to sham. M1-tDCS had no impact. During recognition C-tDCS impaired recognition compared to sham, while A-tDCS showed a trend towards improvement.
Hammer et al. (2011)	36 (A/S = 18, C/S = 18)	A/C/S, L DLPFC (F3)	1 mA, 30 min, 10 min before and during learning, ref SOA, active/sham	Errorless/errorfull learning (word stem completion)	C-tDCS impaired encoding and retrieval after errorful learning compared to errorless learning and sham. No impact of anodal stimulation.
Bullard et al. (2011)	34 (control = 14, early = 11, late = 9)	A, R Inferior PFC (F8)	2 mA, 30 min, early/late during learning, ref arm, active/control (0.1 mA)	Detection of cues indicative of covert threats	A-tDCS (2 mA) improved threat detection compared to control (0.1 mA). A-tDCS was more effective when applied during early learning.
Marshall et al. (2011)	16	Bilateral RA/LA, DLPFC, (F3, F4)	Theta-tDCS at 5 Hz, 0.517 mA/cm^2, 5 min, 1 min ISI, during REM or non-REM sleep, ref mastoid, active/sham	Verbal paired association, procedural memory (mirror tracing, finger sequence tapping), mood (PANAS)	Theta-tDCS during non-REM impaired consolidation of verbal memory compared to sham. No effect on consolidation in procedural memory. Stim during REM led to an increase of negative affect.
Jacobson et al. (2012)	24	Bilateral L IPS/SPL (P3), R IPL (P6), LA/RC, RA/LC (control)	1 mA, 10 min, active/control stim/control group	Verbal memory (discrimination of familiar/unfamiliar words)	LA/RC-tDCS improved accuracy, but not RT as compared to control stim. No effect after LC/RA-tDCS.
TMS and tDCS in memory studies with elderly subjects					
Rossi et al. (2004)	66 (<45 and >50 y)	R/L DLPFC (F3/F4)	500 ms of 20 Hz at 90% rMT, during encoding and retrieval, active/sham/baseline	Visuospatial memory (old/new discrimination of images)	Stim over R DLPFC in younger subjects interfered with retrieval more than stim over L DLPFC. This asymmetrical effect dissipated with age as indicated by bilateral interference effects on recognition. Stim of left DLPFC during encoding had a disruptive effect on all subjects which would not comply with the HAROLD model.

Continued

Table 55.1

Continued

Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
Solé-Padullés et al. (2006)	39 (>50 y with 1+ y memory complaints)	Bilateral R/L DLPFC combined with baseline and post-TMS fMRI	10 trains of 10 s rTMS at 5 Hz, ITI 30 s, 80% rMT, offline, active/sham	Face–name association	Stim improved associative memory compared to sham (rate of change: 1.60 vs. -0.63). TMS led to an increase in activation of the right IFG and MFG and occipital areas.
Manenti et al. (2011)	31 (60–81 y), HP and LP	R/L DLPFC	450 ms of 20 Hz rTMS (ISI 7–8 s), total of 640 pulses, 90% rMT, during encoding or retrieval, active/sham/baseline	Verbal memory (associated/non-associated word pairs)	The high-performing (HP) group performed better in the experimental task than the low-performing group (LP) (92.0% vs. 78.9%). Stim over L DLPFC affected accuracy more during encoding than during retrieval, but only for unrelated word-pairs in the LP group. No significant differences in RT. Asymmetry as predicted by the HERA model was observed only in LP.
Flöel et al. (2012)	20 (50–80 y, mean 62 y)	A, R TPC	1 mA, 20 min, during learning, active/sham	Object location learning, immediate and delayed (1 week later) free-recall	Anodal stim improved delayed correct free-recall responses compared to sham (24% vs. 8.5%), but not immediate recall (34% vs. 28.8%). No significant differences in RT.
TMS and tDCS in memory studies with Alzheimer's patients					
Cotelli et al. (2006)	15	R/L DLPFC (btw F3/F4 and F/7/F8), 1 session	600 ms of 20 Hz TMS at 90% rMT, during encoding, active/sham	Visuoverbal object and action naming	Stimulation over L and R DLPFC improved accuracy in action naming as compared to sham stimulation. Object naming did not improve significantly.
Cotelli et al. (2008)	24	R/L DLPFC, 1 session	500 ms of 20 Hz TMS at 90% rMT, during encoding, active/sham	Visuoverbal object and action naming	Stimulation over L and R DLPFC improved accuracy in action naming but not object naming as compared to sham stimulation in the mild AD group. Improved naming accuracy for both classes of stimuli was only found in moderate-to-severely impaired patients.

Ferrucci et al. (2008)	10	A/C/S, bilateral TPC (LA/RA, LC/RC, S), 1 session per condition	1.5 mA, 15 min, offline, active/sham/baseline	Verbal memory and visual attention	A-tDCS improved accuracy, while C-tDCS decreased performance as compared to baseline. No impact on visual attention.
Boggio et al. (2009)	10	A/S, L DLPFC (F3), L temporal cortex (T7)	2 mA, 30 min, A/S, during task, ref SOA, active/sham	Visual STM, WM (digit span backward), Stroop	Accuracy in visual memory improved during A-tDCS over L DLPFC (18%) and temporal cortex (14%) as compared to sham. No effect on WM and Stroop.
Cotell et al. (2011)	10	L DLPFC, 20 sessions without training vs. 10 sessions placebo	25 min, 2 s of 20 Hz (ITI 28 s) at 100% rMT, offline, active/sham/baseline	Various tests for memory, executive functions, and language	Improvement of auditory sentence comprehension as compared to baseline and placebo training; no effect on other cognitive or langauge functions.
Bentwich et al. (2011)	8	6 regions, 3 per day (Broca, Wernicke, R DLPFC and R-pSAC, L-pSAC, l-DLPFC), (30 sessions with training)	20 2-s trains of 10 Hz per area (=1200 pulses per day), 90% MT (frontal areas), 110% MT (other areas), active/ baseline	Training tasks: attention, memory, language	ADAS-cog improved by approx. 4 points after training and was maintained at 4.5 months follow-up. CGIC improved by 1.0 and 1.6 points, respectively. MMSE, ADAS-ADL, Hamilton improved, but not significantly. No change in NPI.
Boggio et al. (2012)	15	A/S, bilateral (RA/LA) temporal cortex (T3/ T4), 5 sessions	30 min, 2 mA, ref deltoid, offline, active/sham	Visual STM, visual attention, MMSE, ADAS-Cog	A-tDCS improved memory performance by 8.99% from baseline compared to sham (−2.62%). No impact on visual attention or other cognitive measures.
Haffen et al. (2011)	1	L DLPFC, 10 sessions	20 min of 5-s trains of 10 Hz (ITI 25 s), 100% rMT, offline, active	Verbal memory (Memory Impairment Screen, free and cued recall), Isaacs Set Test, TMT, picture naming, copying, MMSE	Stimulation improved episodic memory task performance and speed performance. Improvements were still seen 1 month later, however scores returned to baseline by 5 months. ADL improvements reported by wife.
Ahmed et al. (2012)	45	R/L DLPFC, 5 sessions without training	Group 1: ∼10 min of 5-s trains of 20 Hz (ITI 25 s), 90% rMT per DLPFC Group 2: ∼ 16 min of 1 Hz rTMS, 100% rMT, ∼16 min per DLPFC (2000 p)	MMSE, IADL, GDS	Mild to moderate AD patients (20 Hz) showed improved scores on all rating scales as compared to the 1-Hz and sham groups. Although improvements were present at 1 month, scores returned to near baseline level by 3 months.

Continued

Table 55.1

Continued

Reference	*n*	Regions stimulated	Stimulation protocol	Task	Results
TMS and tDCS in memory studies with Parkinson's patients					
Boggio et al. (2005)	25 (PD & depression)	L DLPFC, 10 sessions without training	40 trains of 5 s of 15 Hz, 110% rMT and fluoxetine (20 mg/day), offline, active/sham/baseline	NP (TMT, WCST, Stroop, HVOT, CPM, WM): before treatment, after 2 and 8 weeks	Both the fluoxetine and rTMS groups showed significant improvement in Stroop (colored words), Hooper, and WCST (perseverative errors), and in depression rates. No significant effects on other cognitive functions.
Boggio et al. (2006)	18	A/S, L DLPFC, M1 (control), 1 session per protocol	20 min, 1 or 2 mA, 20 min, during task, ref SOA, active/sham/control	Verbal 3-back	Accuracy in 3-back task after stimulation with 2 mA (20.1%) as well as error frequency (35.3%) improved significantly more as compared to stim with 1 mA, stim over M1, or baseline.
TMS and tDCS in memory studies with stroke patients					
Jo et al. (2009)	10 (RH stroke), 1–4 months poststroke	A/S, L DLPFC (F3), 1 to session per protocol	30 min of 2 mA, online (25 min after starting stimulation), ref SOA, active/sham/baseline	Verbal 2-back before and at 25 min tDCS onset	A-tDCS improved recognition accuracy as compared to sham. No impact on RT.

A, C, S, anodal, cathodal, sham; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; aMT, active motor threshold; ATL, anterior temporal lobe; BA, Brodmann's area; BBR, brain–behavior relationship; Cb, cerebellum; CGIC, Clinical Global Impression of Change; CPM, colored progressive matrices; cTBS, continuous theta-burst stimulation; Cz, vertex; DLPFC, dorsolateral prefrontal cortex; DMS, delayed match-to-sample; DMPFC, dorsomedial prefrontal cortex; DR, discrimination rate; EF, executive functions; ERP, event-related potential; Exp., experiment; FEF, frontal eye fields; FL, frontal lobe; fO, frontal operculum; Fz, frontal midline; GDS, Geriatric Depression Scale; HF, high frequency; HVOT, Hooper Visual Organization Test; IADL, Instrumental Activities of Daily Living; IFG, inferior frontal gyrus; IFJ, inferior frontal junction; IPL, inferior parietal lobule; IPS, intraparietal sulcus; ITI, intertrain interval; L, left; LA/RA, left anodal/right anodal; LC/RC, left cathodal/right cathodal; LF, low frequency; LH, left hemisphere; LOC, lateral occipital cortex; M1, primary motor cortex; MFG, middle frontal gyrus; MMSE, Mini Mental State Examination; MSO, maximum stimulator output; NP, neuropsychological; NPI, neuropsychiatric inventory; OC, occipital cortex; OFC, orbitofrontal cortex; p, pulse; PANAS, positive and negative symptoms scale; PC, parietal cortex; PCG, postcentral gyrus; PD, Parkinson's disease; PFC, prefrontal cortex; PL, parietal lobule; PM, prospective memory; PMC, premotor cortex; PPC, posterior parietal cortex; ppTMS, paired-pulse transcranial magnetic stimulation; R, right; RBMT, Rivermead Behavioural Memory Test; rCBF, regional cerebral blood flow; ref, reference; RH, right hemisphere; rMT, resting motor threshold; R-pSAC and L-pSAC, right and left parietal somatosensory association cortex; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory cortex; SFG, superior frontal gyrus; sign., significant; SMG, supramarginal gyrus; SOA, supraorbital area; sp, single pulse; SPL, superior parietal lobule; stim, stimulation; STM, short-term memory; T, tesla; TL, temporal lobe; TMT, trail making test; TPC, temporoparietal cortex; tRNS, transcranial random noise stimulation; TSOS, transcranial slow oscillation stimulation; VAT, visual attention task; VLPFC, ventrolateral prefrontal cortex; VPFC, ventral prefrontal cortex; VFT, verbal fluency test; VRT, visual recognition task; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WM, working memory; y, years.

NBS studies are helping address relates to the organization of information processing streams. Is processing of STM supported through a domain-specific segregation (spatial, object, verbal processing) or rather through a processing segregation (encoding, maintenance, storage)?

Processing segregation

Most studies examining this question have used a delayed match-to-sample task and applied stimulation during either the delay period or the decision period (Fig. 55.2). High-frequency TMS applied over the parietal cortex during the *delay period* can improve STM function (Kessels et al., 2000; Kirschen et al., 2006; Luber et al., 2007; Yamanaka et al., 2010), but some studies found it to impair STM (Koch et al., 2005; Postle et al., 2006). In either case, the effects seem specific to the delay period, since parietal TMS during the decision phase has not been found to impact STM (Luber et al., 2007; Hamidi et al., 2009). The question whether DLPFC also plays a role during the delay phase has not been answered yet. Although some TMS studies support DLPFC participation (Pascual-Leone and Hallett, 1994; Koch et al., 2005), others have found no impact when stimulating DLPFC during the delay phase (Herwig et al., 2003; Postle et al., 2006; Hamidi et al., 2008; Sandrini et al., 2008). On the other hand, high-frequency TMS over the DLPFC during the *decision period* impairs STM functions (Koch et al., 2005; Hamidi et al., 2009). Therefore, although further studies are needed, findings suggest a dissociation between parietal and prefrontal areas, playing primary roles in delay and decision phases, respectively. These findings are supportive of the notions of posteroanterior temporal gradient in memory processing: parietal regions coming online first and prefrontal regions contributing to later subprocesses. Chronometric TMS experimental designs enable such notions to be directly tested further.

Mottaghy et al. (2003a) conducted the first such experiment (Fig. 55.3), albeit focusing on verbal WM. They used single-pulse TMS to explore the temporal dynamics of left and right inferior parietal and DLPFC involvement in verbal WM in six healthy volunteers. TMS was applied at 10 different time points 140–500 ms into the delay period of a 2-back verbal WM task. Precise and consistent targeting of a given cortical brain region was assured by using frameless stereotactic neuronavigation. A choice reaction task was used as a

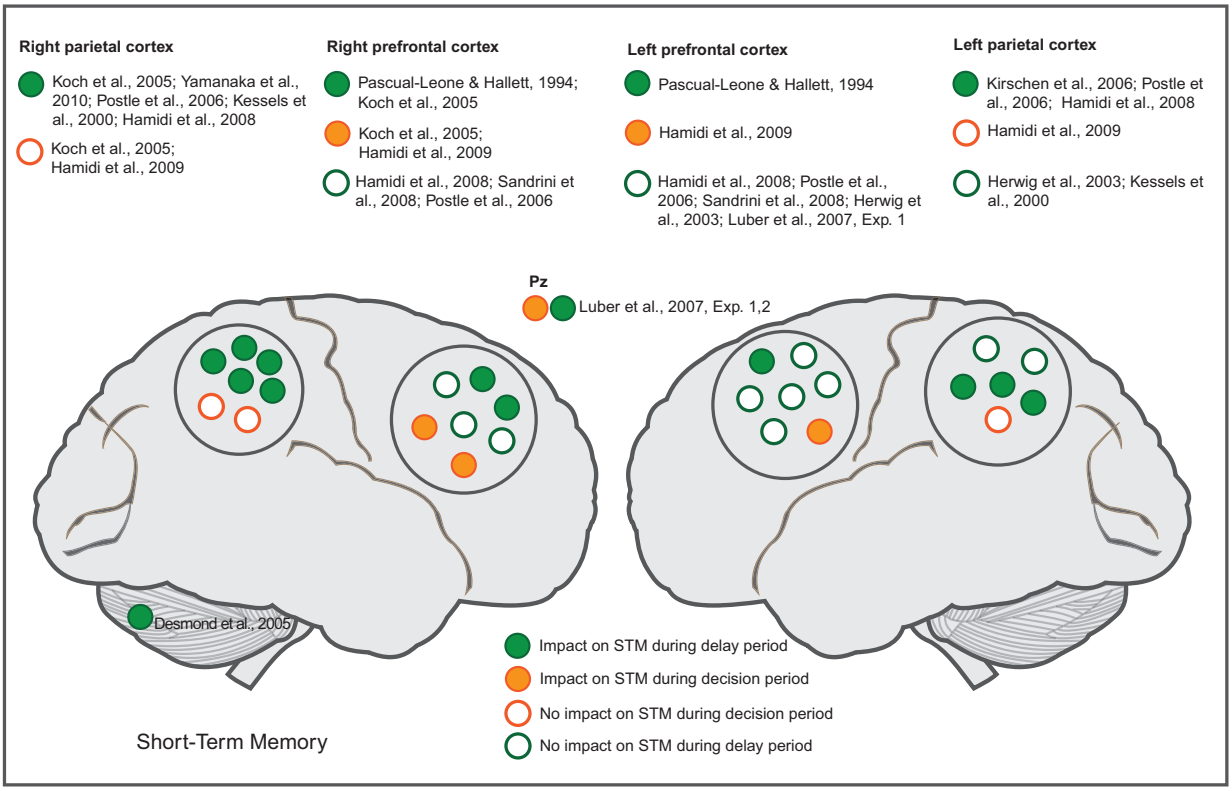

Fig. 55.2. Schematic summary of findings from studies investigating the impact on short-term memory after stimulation over the left or right prefrontal cortex, parietal areas, or the cerebellum during the delay (green) or the decision period (orange).

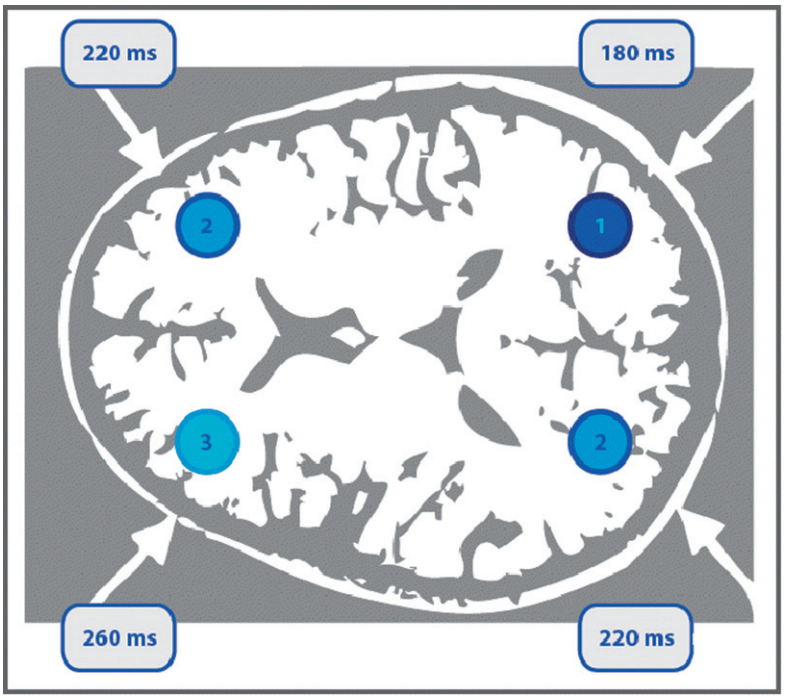

Fig. 55.3. Accuracy in the 2-back task as a function of the time of transcranial magnetic stimulation (TMS). TMS interference peaked at 180 ms at the right inferior parietal cortex, at 220 ms at the left inferior parietal cortex and right middle frontal gyrus (MFG), and at 260 ms at the left MFG (all $p < 0.05$). This study illustrates the chronometry of causal contributions of different brain regions to memory processing. (Modified from Mottaghy et al., 2003a, by permission of the authors.)

control task. Interference with task accuracy was induced by TMS earlier in the parietal cortex than in the PFC, and earlier over the right than the left hemisphere. This suggests a propagation of information flow from posterior to anterior cortical sites, converging in the left PFC. Significant interference with reaction time was observed after 180 ms with left PFC stimulation. These effects were not observed in the control task, underlining the task specificity of our results. Hamidi and colleagues (2009) also examined the roles of right and left DLPFC in recall and recognition. They found that right DLPFC stimulation impaired accuracy in delayed recall, while enhancing accuracy in delayed recognition. On the other hand, left DLPFC stimulation impaired delayed recognition. Therefore, it seems clear that TMS, in repetitive and chronometric single-pulse experimental designs, can provide valuable insights into the functional segregation of core subprocesses of STM.

Domain-specific segregation

Mottaghy et al. (2002b), in another pioneering study (Fig. 55.4) used TMS to show that functional and modality-specific segregation need not be mutually exclusive. They applied low-frequency rTMS to explore the functional organization of STM by selectively disrupting the left dorsomedial PFC (DMPFC), DLPFC, or ventral PFC (VPFC). They applied a 10-min 1-Hz rTMS train before assessing spatial or nonspatial (face recognition) delayed-response performance. Spatial task performance was impaired after rTMS to DMPFC, whereas nonspatial task performance was impaired after rTMS to VPFC. Disruption of the DLPFC affected the performance in both tasks. This finding reveals a task-related segregation of processing streams along prefrontal structures. More recent studies have confirmed the utility of TMS to offer empirical support for modality-specific segregation. For example, Soto et al. (2012) combined evidence from fMRI and rTMS to demonstrate that verbal and nonverbal memories interact with attention functions independently: whereas rTMS to the superior frontal gyrus disrupted STM effects from colored shapes, rTMS to the lateral occipital cortex disrupted effects from written words. Finally, Morgan and colleagues (2013) used TMS to reveal the neural substrates for integration of segregated features of STM processes. They investigated STM for colors, orientations, and combinations of these, and found that continuous TBS (cTBS) over the right parietal cortex or left inferior frontal gyrus selectively impaired STM for combinations but not for single features. Therefore, functional coupling between frontal and parietal areas appears to be critical to bind modality-specific segregated processes.

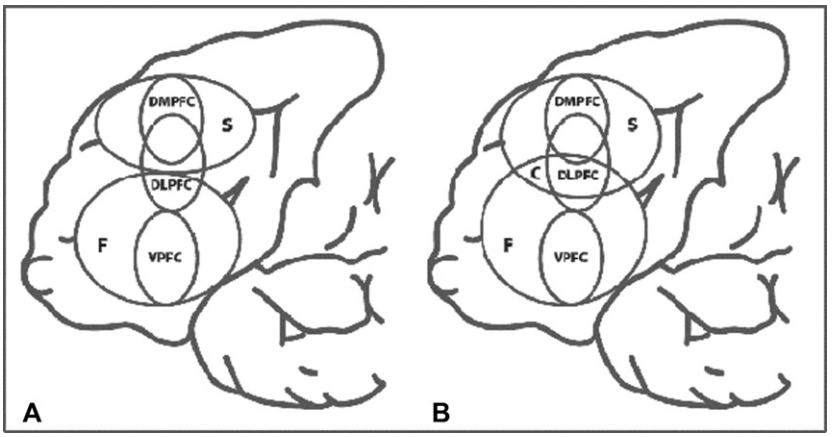

Fig. 55.4. Study exploring the segregation of memory processes in prefrontal cortex. Two alternative models were proposed based on the data. (**A**) There might be two different, nonoverlapping, functionally segregated regions within the prefrontal cortex (PFC) that are domain-specific (S, spatial domain; F, face domain). Repetitive transcranial magnetic stimulation (TMS) over the dorsomedial PFC (DMPFC) interferes only with the processing of the spatial information. Dorsolateral PFC (DLPFC) stimulation might have induced overlapping interference of two adjacent domain-specific areas, whereas the ventral PFC (VPFC) led only to interference with the processing of the face stimuli. (**B**) The DMPFC and the VPFC interference effects can be explained in the same manner as in proposal (**A**); however, the performance deterioration over the DLPFC in this model might be explained by the interference with information processing of a common module (C) that is employed during both types of stimulus. (Modified from Mottaghy et al., 2002b, by permission of the authors.)

Frontoparietal binding

Frontoparietal interactions in memory formation and maintenance appear to be dynamic and NBS studies – particularly studies combining TMS with MRI or EEG – help gaining critical insights in this regard.

In the motor domain, frontoparietal interactions seem to be particularly important in the early phase of learning, as has been shown in a recent study combining TMS and EEG (Karabanov et al., 2012). In the nonmotor domain, a recent TMS–fMRI study (Feredoes et al., 2011) found that DLPFC contribution to maintenance of stimuli in STM is highly dynamic depending on the presence or absence of distractors. In the presence of distractors, DLPFC changes its communication with posterior regions to support maintenance. These results are supported by tDCS studies that assign the DLPFC an important role in STM in the presence of distractors (Gladwin et al., 2012; Meiron and Lavidor, 2013). Zanto and colleagues (2011) combined EEG with 1-Hz rTMS to the right inferior frontal junction to investigate the contribution of the prefrontal cortex in top-down modulation of visual processing and STM in a delayed-match-to-sample task. They found that EEG patterns from posterior electrodes, which are associated with the distinction of task-relevant and -irrelevant stimuli during early encoding, were diminished after TMS, which again predicted a subsequent decrease in STM accuracy. Subjects with stronger frontoposterior functional connectivity furthermore showed greater disruption. Higo and colleagues (2011) combined offline TMS over the frontal junction with subsequent fMRI to explore the same question. They also observed a TMS-induced decrease of effects in posterior regions depending on task relevance/irrelevance. The inferior frontal junction may therefore control the causal connection between early attentional processes and subsequent STM performance, and may regulate the level of activity of representations in posterior brain areas depending on their relevance/irrelevance for response selection.

It could be hypothesized that the interaction between frontal and posterior areas during the delay period secures the maintenance of information, especially if this information needs to be protected from distracting information. These processes may be related to the regulation and reactivation of patterns that were active during encoding. Accordingly, frontal areas might recruit neuronal assemblies and regulate their activity in posterior areas in order to protect and actively maintain information. Such activations may be most prominent at the beginning of the delay period and decrease gradually.

Other brain regions involved in STM

Frontal and parietal areas are undoubtedly the most explored areas in STM. Although it has been debated in the literature, there is some evidence that the cerebellum may also be involved in STM. When Desmond and colleagues (2005) applied single-pulse TMS (at 120% resting motor threshold) over the right superior

cerebellum at the beginning of the delay phase, they found an increased reaction time but no change in accuracy for correct trials in the Sternberg task. This is in agreement with a tDCS study that probed the cerebellum and found an abolishment of practice-dependent improvements in reaction time after anodal as well as cathodal tDCS in a Sternberg task (Ferrucci et al., 2008).

Last, but not least, cortical areas implied in sensory processing are also believed to be involved in STM of sensory information, which may be guided through attentional processes. A number of TMS studies have shown a role of visual cortex with visual STM and WM (see review by Postle et al., 2006). A few studies have furthermore investigated the tactile domain. Application of TMS to the visual cortex during the delay phase of STM tasks results in a decrease of accuracy in the targeted visual field for high memory loads (Van de Ven et al., 2012) or a decrease in memory scanning rates (Beckers and Hömberg, 1991). The effect of TMS was furthermore shown to be different if applied at the beginning (inhibitory) or at the end (facilitatory) of the delay period in both a visual STM task and imagery (Cattaneo et al., 2009). This is an elegant application of state-dependency TMS experimental designs (Silvanto and Pascual-Leone, 2008). Although neurons implicated in encoding are highly active at the onset of the retention period, TMS might preferentially activate neurons not involved in encoding, thereby reducing the signal-to-noise ratio of the memory trace, and impair behavior.

In the tactile domain, a TMS study using single-pulse stimulation over the middle frontal gyrus (MFG) during the early maintenance period led to a decrease in reaction time in a tactile STM task, even in the presence of a distracting stimulus (Hannula et al., 2010). In a follow-up study, the same group investigated whether this improvement only occurs when the interference is tactile, or whether MFG creates a more general top-down suppression (Savolainen et al., 2011). Their results showed that TMS did not lead to facilitation when a visual interference was presented, but only when the interfering stimulus was also tactile.

These and other findings (e.g., Silvanto and Cattaneo, 2010) suggest that sensory brain areas involved in early, modality-specific, processing of perceptual stimuli contribute to the formation and maintenance of STM representations through an interaction with the attentional system. In this context, TMS can help elaborate the chronology of memory processes and contributions of state-dependent processes.

Working memory

WM has been investigated with NBS in a growing number of studies. As for STM, most of these studies have explored the roles of DLPFC and parietal areas, trying to find an answer to the question of whether information is separately processed with regard to domain or functional subprocess (Fig. 55.5). In addition, some studies have examined the question of whether the same areas that participate in STM are also active in WM tasks.

Verbal and nonverbal WM in DLPFC

Again building on pioneering work from Mottaghy et al. (2000), most researchers have found an impairment of verbal WM after stimulation of the left DLPFC (Mull and Seyal, 2001; Mottaghy et al., 2000, 2003a; Postle et al., 2006; Osaka et al., 2007) and after stimulation of the right DLPFC (Mottaghy et al., 2003a; Postle et al., 2006; Sandrini et al., 2008). However, some studies failed to find such effects (Mull and Seyal, 2001; Rami et al., 2003; Imm et al., 2008; Sandrini et al., 2008).

The role of DLPFC in nonverbal WM has been studied much less (Oliveri et al., 2001; Imm et al., 2008; Sandrini et al., 2008). Sandrini and colleagues (2008) tried to clarify domain- and process-specific contributions of the DLPFC. They presented physically identical stimuli (letters in different spatial locations) in a 1-back task (STM) and a 2-back task (WM). Furthermore, they presented the 2-back task with stimuli of both or just one domain. A short train of 10-Hz rTMS was applied at the end of the delay period between stimuli. They found interference only during the 2-back task, and only when stimuli from both domains were presented. Interestingly, performance in the letter task was impaired after rTMS over the right DLPFC, whereas performance in the location task was impaired after rTMS over the left DLPFC. These results were interpreted as an interference effect on control mechanisms (central executive) in the sense of the suppression of task-irrelevant information. The same hypothesis has been put forward with regard to the protection of memory contents in STM (Feredoes et al., 2011; Higo et al., 2011; Zanto et al., 2011), according to which an interaction between frontal and posterior areas during the delay period secures the maintenance of information, especially in the presence of distractors.

Further experiments have aimed at dissecting the role of DLPFC in WM in order to find out whether domain- or process-specific models should be favored, and others have examined the role of interactions between DLPFC and other brain areas. Combination of TMS with brain imaging has proven quite valuable in this context. Mottaghy and colleagues (2000) found that performance in a verbal WM (2-back) task was significantly diminished after rTMS (30-second train of 4-Hz rTMS) to the left but also the right DLPFC (F3/F4). Importantly, by combining TMS with PET, they showed that TMS-altered performance in the WM task was associated with a reduction in regional cerebral blood flow (rCBF) at the

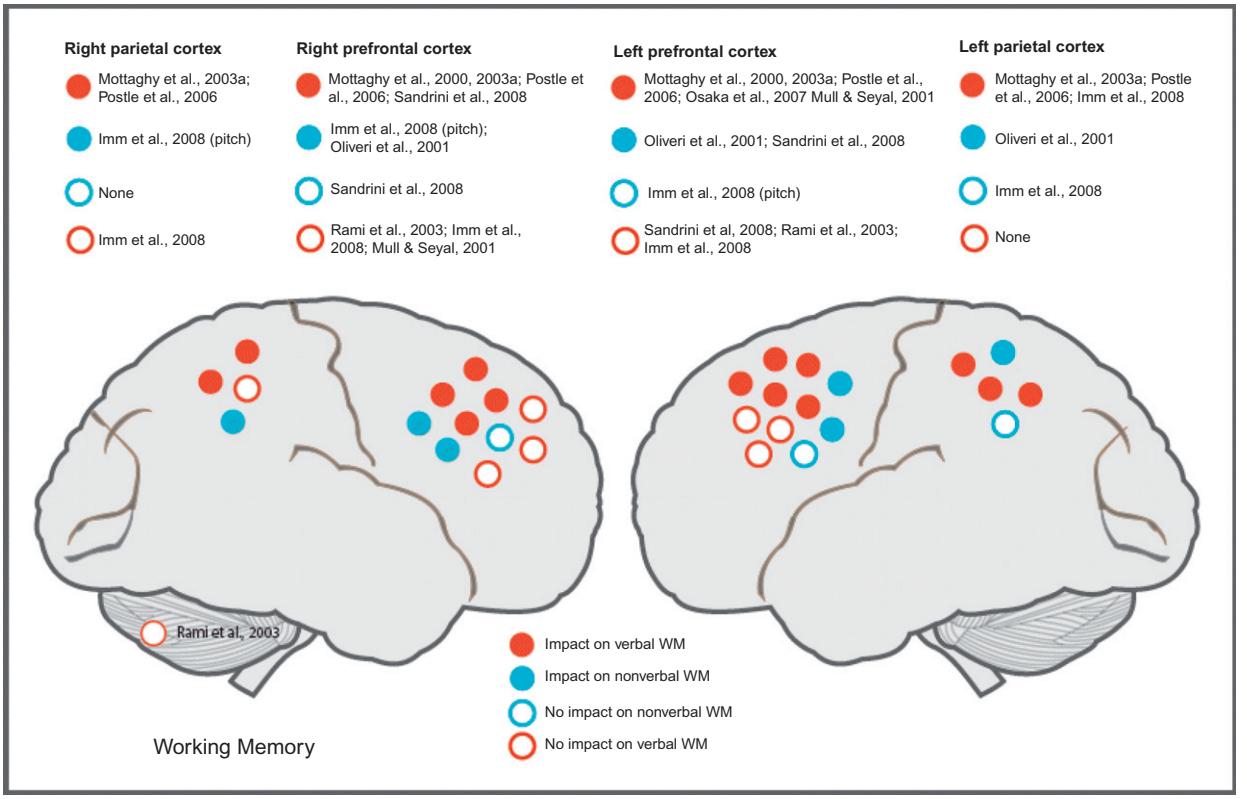

Fig. 55.5. Schematic summary of findings from studies investigating the impact on verbal (red) or nonverbal (blue) working memory (WM) after stimulation over the left or right prefrontal cortex (PFC), parietal areas, or cerebellum.

stimulation site and in distant areas as assessed with PET. In an elegant follow-up TMS–PET study, the same authors (Mottaghy et al., 2003b) showed that at baseline (in the absence of TMS) there was a negative correlation between rCBF in the left (but not the right) DLPFC and WM task performance. Application of rTMS to the left or the right DLPFC could disrupt WM performance, but appeared to do so on the basis of different distributed impact on a bihemispheric network of frontal and parietal regions: whereas rTMS over the left DLPFC led to changes in rCBF in the directly targeted left DLPFC and the contralateral right PFC, rTMS over the right DLPFC led to more distributed changes involving not only bihemispheric prefrontal, but also parietal areas (Fig. 55.6B). Regardless of the differential network impact of the right or left stimulation, the behavioral consequences of rTMS were always related to the impact onto left DLPFC rCBF. This study highlights a number of important findings of relevance for future studies on NBS in memory and learning. First, it shows that rTMS to different nodes of a given brain network can exert differential impact onto said brain network. More recently, Eldaief et al. (2011) have expanded on this line of inquiry combining resting-state fMRI with TMS to examine brain network dynamics. Second, the study shows that network dynamics are modified by behavioral engagement. In other words, it might be possible to learn about mechanisms of memory and learning by examining how the impact of TMS onto a given brain network is modulated by the behavioral state. Finally, the study illustrates that brain stimulation can affect behavior by disrupting a computation in the targeted brain region (as in the case of left DLPFC rTMS) or by disrupting function of a brain regions reached via trans-synaptic network impact (as in the case of rTMS to the right DLPFC altering left DLPFC via interhemispheric connections). This later finding is important in the interpretation of brain stimulation results in general, and illustrates the power of studies integrating brain stimulation with neuroimaging in exploring causal relations between brain activity and behavior (Fig. 55.6A). In a later study, Mottaghy and colleagues (2003a) applied single-pulse TMS at different time points after stimulus presentation to probe the temporal dynamics of parietal and prefrontal contributions in verbal WM. With this approach they were able to add chronometric information to their prior findings. They showed that single-pulse TMS could interfere with task accuracy earlier in the parietal than in the PFC, and earlier over the right than left hemisphere. This indicates an information flow from posterior to anterior converging

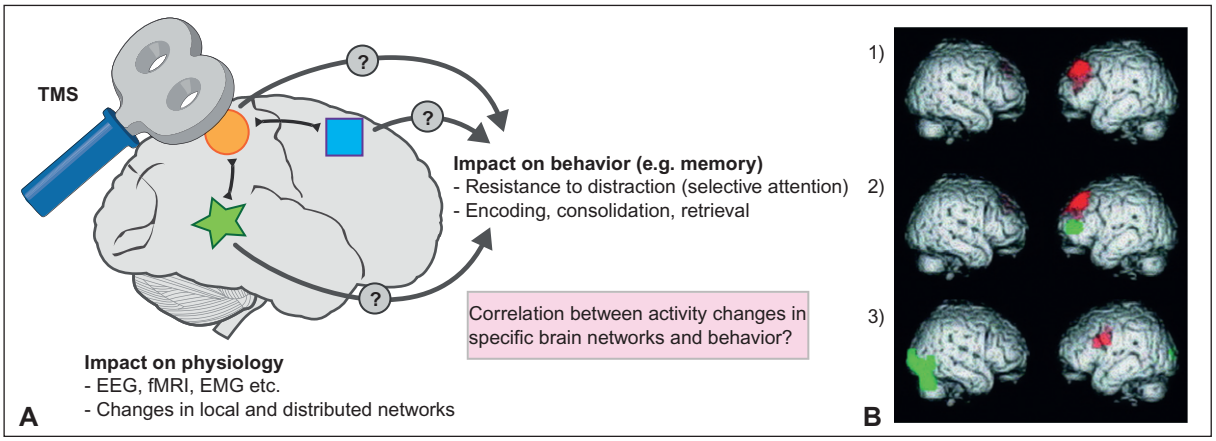

Fig. 55.6. Transcranial magnetic stimulation–positron emission tomography (TMS–PET) study of the neurobiological substrates of working memory. (**A**) The impact of TMS on behavior relies on activity changes in local and distributed brain networks. The combination of TMS with brain imaging techniques, such as EEG, fMRI, PET, and EMG, allows us to detect correlations between these activity changes and behavior. Moreover, it allows study of the impact of state dependency on stimulation outcome. (**B**) Positive (green) and negative (red) correlation between regional cerebral blood flow (rCBF) and performance in the 2-back working memory (WM) task (1) without application of repetitive TMS (rTMS), (2) with rTMS delivered over the left middle frontal gyrus (MFG), and (3) with rTMS applied over the right MFG. While rTMS over the left MFG has a local impact, which is correlated with behavior, rTMS over the right MFG has an impact on a distributed network, including homologous areas. Importantly, also in the case of stimulation over the right MFG, activity changes in the left MFG but not right MFG are correlated with behavioral output. This key finding shows that the effect of TMS can be achieved by a direct effect on underlying areas, but also through trans-synaptic effects (e.g., in homologous areas). The combination of TMS with imaging techniques is crucial in order to identify neural substrates associated with behavioral output. (Modified from Mottaghy et al., 2003b, by permission of the authors.)

in the left PFC. These series of studies reveal that both hemispheres contribute to WM, but that the computation performed by the left PFC is critical in verbal WM.

Interestingly, involvement of DLPFC, regardless of stimulus modality, has been shown in an often-cited study using bilateral single-pulse stimulation during a 2-back task (Oliveri et al., 2001). Early temporal stimulation (300 ms) increased reaction time for object-related WM, whereas early parietal stimulation and late stimulation (600 ms) over the superior frontal gyrus increased reaction time for spatial WM. However, late DLPFC stimulation interfered with both tasks and not only with RT, but also with accuracy. These results relate to the discrimination of a dorsal ("where") and ventral ("what") pathway and again information flow from parietotemporal to frontal areas. They indicate that there might not only exist a bilateral involvement of the DLPFC in verbal WM, but that DLPFC might be active irrespective of stimulus material, unlike other prefrontal regions that may be segregated (see e.g., Mottaghy et al., 2002b). Segregation in posterior areas seems to be easier to pinpoint, and is concordant with the view that both hemispheres are implicated in spatial and object WM tasks (Smith and Jonides, 1997). The research that has been done up to date generally points into the direction of favoring a process-specific model for DLPFC, whereas other areas of the prefrontal or parietal cortex may be modality-based. Possibly, WM operations relying on DLPFC, such as selective attention and other executive processes (e.g., the inhibition of task-irrelevant stimuli), are independent of modality (Smith and Jonides, 1999) and play a role in both STM and WM. The combination of fMRI and EEG with TMS may help us to disentangle further the interactions of DLPFC and other prefrontal and parietal areas to WM functions.

Prospective memory

Prospective memory is tightly connected with other memory subcomponents (see Fig. 55.1), which makes it difficult to single out its processes. Perhaps this challenge accounts for the fact that few studies to date have explored prospective memory using NBS. One study (Basso et al., 2010) investigated whether verbal WM and prospective memory are based on common or separate processes. In a first experiment participants had to accomplish tasks with low, medium, or high WM load. In the prospective condition, subjects had to react whenever a specific word appeared. In a second experiment the prospective conditions included 1 or 3 prospective words. A higher prospective memory demand interfered with the WM task only at higher loads, whereas WM activity did not affect prospective memory performance. If both processes were part of the same system one might expect

a trade-off. In a third experiment single-pulse TMS was applied to the left and right DLPFC in order to test the notion that WM and prospective memory rely on distinct systems. TMS to the DLPFC increased error rates in the prospective memory task, whereas the effect on the WM task was only marginal. No difference between hemispheres was detected. The authors concluded that WM and prospective memory may not be based on the same memory system. However, it is hard to rule out that prospective memory may require resources (including in part WM resources) and may thus be easier to disrupt with TMS. More complex TMS designs, such as input–output designs with TMS applied at various intensity and timings, seem necessary to explore this issue further.

Costa and coworkers (2011) investigated the effects of cTBS (80% active motor threshold) on prospective memory. Stimulation over left Brodmann area (BA) 10 (frontal pole) resulted in impaired accuracy as compared with stimulation over Cz. In a second experiment they did not find a significant difference after cTBS over left BA46 (DLPFC) and Cz. They concluded that the left BA10 is important for prospective memory processes. This is in accordance with a neuroimaging study (Koechlin et al., 1999) that tried to dissociate the roles of frontopolar and DLPF cortices in prospective memory. Costa and colleagues employed a fairly novel TMS paradigm (cTBS) and tackled a complicated memory construct (prospective memory). However, this important, innovative study also illustrates one important challenge for all studies using NBS in memory: it is ultimately critical to have *separate* empirical demonstration of the impact of brain stimulation on brain function, and on behavior. In fact, ideally, one would want to apply TMS, measure the behavioral impact and the impact on brain physiology, and then correlate one with the other (see Fig. 55.6A). Costa and coworkers (like most investigators using TMS or tDCS in studies of memory) placed the TMS coil over the scalp overlaying the brain regions they wanted to target (frontal pole or DLPFC). They then assumed that the TMS impact on brain activity would be maximal in the underlying cortex. They assessed the impact of TMS onto prospective memory and assumed that said impact must reflect the consequence of TMS-induced change in activity in the targeted brain region. There is a risk of circular logic in this approach: "If TMS over a given region has a predicted impact onto a given memory process, then I have shown that said brain region was affected by TMS and that it plays said role in memory." Obviously, independent empirical demonstration of these two steps would be important and the use of NBS in studies of memory, or studies of cognitive functions in general, should aim to achieve such experimental discrimination.

Encoding, consolidation, retrieval

Some studies have applied rTMS during the *encoding phase* and support the critical role of the PFC in such memory processes. Stimulation of the *left* DLPFC during the encoding phase has been found to affect both verbal (Grafman et al., 1994; Rami et al., 2003; Sandrini et al., 2003; Flöel et al., 2004; Skrdlantová et al., 2005; Blanchet et al., 2010; Gagnon et al., 2010, 2011) and nonverbal (Rossi et al., 2001, 2004; Blanchet et al., 2010; Gagnon et al., 2010, 2011) memory. However, a few studies have reported an impact on memory functions after stimulating *right* frontal areas during the *encoding phase* of verbal (Grafman et al., 1994; Sandrini et al., 2003; Kahn et al., 2005; Blanchet et al., 2010; Machizawa et al., 2010) or nonverbal (Epstein et al., 2002; Flöel et al., 2004; Blanchet et al., 2010) memory functions. Some investigators did not find any effects after stimulating right frontal cortex (Rami et al., 2003; Köhler et al., 2004). No effects have been found after stimulating parietal (Köhler et al., 2004; Rossi et al., 2006) or occipital cortex (Grafman et al., 1994). Only one study reported impairment after stimulating the temporal cortex (Grafman et al., 1994).

Fewer studies have applied TMS during the *retrieval phase* of memories. Stimulation of the *right* DLPFC during the retrieval phase appears to be associated with an impact on both verbal (Sandrini et al., 2003; Gagnon et al., 2010, 2011) and nonverbal (Rossi et al., 2001, 2004; Gagnon et al., 2010, 2011) memory. No studies have reported an effect after stimulation of the *left* hemisphere during the retrieval phase.

Several studies have used NBS to reveal the important role of the ventrolateral PFC (VLPFC) in the formation of long-term memory (Grafman et al., 1994; Flöel et al., 2004; Köhler et al., 2004; Machizawa et al., 2010), and it has been suggested that VLPFC may be material-specific whereas DLPFC is not. Further studies are needed to shed light on these mechanisms.

Recent studies by Gagnon and colleagues explicitly addressed the assumptions of the HERA model (Blanchet et al., 2010; Gagnon et al., 2010, 2011) and tried to shed light on the contribution of left and right DLPFC in encoding and retrieval of verbal as well as nonverbal information. These are particularly important studies as they illustrate the value of TMS in the systematic testing of key aspects of a well formulated cognitive conceptual model. It is this type of experimental approach that can fully leverage the advantages of TMS in studies of memory and learning. In a first study, Gagnon et al. (2010) applied paired-pulse TMS (interstimulus interval (ISI) 3 ms) over the left or right DLPFC during *encoding or retrieval* of verbal (words) and nonverbal stimuli (random shapes). They found that left and right DLPFC play

different roles in encoding and retrieval irrespective of stimulus type: stimulation of the left DLPFC during encoding resulted in discrimination deficits, whereas stimulation of the right DLFPC during retrieval resulted in a reduced hit and disrimination rate. In a follow-up study they applied paired-pulse TMS with a longer ISI (15 ms) to promote facilitation (rather than cortical suppression) to the left and right DLPFC during encoding or retrieval of verbal (words) and nonverbal stimuli (random shapes) (Gagnon et al., 2011). They found a facilitation of reaction times during encoding (left DLPFC) and retrieval (right DLPFC) regardless of the type of material presented. These results are consistent with other TMS studies (Rossi et al., 2001, 2006; Rami et al., 2003) and provide experimental support for the HERA model, which proposes that the left PFC is more involved in semantic retrieval and episodic encoding than the right PFC, whereas the right PFC is involved in episodic retrieval (Tulving et al., 1994). This hemispheric asymmetry seems to uphold for both verbal and nonverbal material (Haxby et al., 2000; Blanchet et al., 2010).

USING NONINVASIVE BRAIN STIMULATION AS A DIAGNOSTIC TOOL

In addition to uses in cognitive neuroscience, it is worth considering the potential utility of NBS in clinical neuroscience as a diagnostic tool. Diagnostic applications of NBS are appealing as they are noninvasive and can be applied safely to various patient populations across the lifespan, if appropriate precautions are taken and guidelines are followed (Rossi et al., 2009). TMS has an excellent temporal resolution and its spatial resolution is superior to tDCS, which are important advantages in diagnostic applications and make TMS a superior tool to probe brain reactivity and brain connectivity.

To date, TMS has not been established as a diagnostic tool. However, if we define carefully the areas of need in specific patient populations, we may be able to complement currently used test measures, which rely mainly on behavioral assessments (Rost et al., 2008; Sigurdardottir et al., 2009; Gialanella, 2011; Wagle et al., 2011).

As for motor dysfunctions, nonmotor memory functions could be characterized by changes in the excitation/inhibition (E/I) balance and cortical plasticity in specific brain areas, which could be assessed with TMS–EEG measures (Thut and Pascual-Leone, 2010). Changes of such neurophysiological measures over the time-course of cognitive rehabilitation, during normal and pathological aging, or in response to treatment of disease could help us establishing neurophysiological biomarkers indicative of functional improvements. Such measures could not only be helpful to differentiate across pathological entities, but may also disentangle underlying causes of memory dysfunctions on an individual level. Finally, this information could help develop novel and improve existing interventions in order to improve memory functions.

In the memory domain there are several questions worth exploring with TMS as a diagnostic tool: (1) What is the pathogenesis of present memory problems? (2) Who is at risk of developing memory problems and what kind of memory problems? (3) Who is likely to benefit from a given behavioral/physiologic/pharmacological intervention?

Identify the pathogenesis of memory problems

Depending on the etiology, the pathogenesis of an individual patient's memory problem can be vastly different and be affected by many factors including age, environmental, and genetic predispositions. Regardless of etiology, though, one can also aim to identify the proximal, neural dysfunction that accounts for a given memory deficit. TMS can be applied to gain insights at both these levels of inquiry.

Single- and paired-pulse TMS measures may reveal changes in connectivity or altered network dynamics and link those to specific memory functions. Advanced combined technologies such as TMS–EEG or TMS–MRI allow us to utilize TMS-induced cortical evoked potentials or TMS-induced blood oxygen level-dependent (BOLD) fMRI changes as neural measures of brain activity in specific brain regions or networks to relate to behavioral memory measures.

rTMS paradigms, for example intermittent and continuous TBS stimulation (iTBS and cTBS), can be used to obtain indices of cortical plasticity that appear related to long-term potentiation and depression (LTP and LTD)-like induction of synaptic plasticity. Such paradigms can be used to evaluate cortical plasticity in neural structures thought to support memory processes and may allow us to draw conclusions regarding the pathogenesis of a memory problem. For example, a cortical lesion within a widespread memory network could not only have a direct impact on memory functions caused by this particular lesion but could also lead to indirect deficits due to disconnection of the lesioned area with another memory hub. TMS measures could inform us about acute processes as well as adaptive or maladaptive changes characteristic of chronic processes that lead to memory dysfunctions (Pascual-Leone et al., 2011).

Identify risk for developing memory problems

Another major area of interest lies in the possible use of TMS as a physiological biomarker, which could indicate

the individual risk of developing memory dysfunctions with age and predict what kind of memory problems could be expected in certain populations. Cognitive decline including memory functions presents a critical hallmark of aging (Morrison and Baxter, 2012). Early changes in neuroplasticity and neurophysiological circuits indicated by TMS measures, such as short-latency afferent inhibition (SAI), could constitute biomarkers for the development of neurodegenerative disorders (Freitas et al., 2011b). Risk identification with this approach requires the integration of numerous factors associated with causal and formal pathomechanisms, including age-related changes, but also, for example, changes related to systemic diseases, such as diabetes mellitus, that may indirectly have an impact on brain physiology and plasticity. TMS could be a valuable tool to identify these factors and consequently help guide and implement early interventions in populations at risk.

Another approach is using TMS measures to identify risks related to interventions that could result in brain lesions or dysfunctions. For example, consider neurosurgical interventions: presurgical detailed knowledge about functional contributions of brain areas to be resected can critically inform surgical approaches and minimize the risk. In this context, the Wada test can be used to determine hemispheric language dominance prior to brain surgery (Wada and Rasmussen, 1960). However, this test has a non-negligible risk of complications and discomfort for the patient and does not allow precise functional localization. Neuronavigated TMS can provide detailed information regarding functional anatomy of the targeted brain area and is potentially valuable for presurgical planning not only in regard to language dominance (Pascual-Leone et al., 1991; Devlin and Watkins, 2007), but also in regard to memory (Grafman et al., 1994). Such noninvasive neuronavigated TMS cortical mapping appears to correlate well with direct cortical stimulation (DCS) results and seems to be more precise than fMRI, which is the most widely used technique today (Krieg et al., 2012). As DCS is limited to intraoperative use, presurgical TMS might also save operation time by guiding intraoperative DCS.

Predicting benefit from a given intervention/medication

Cognitive rehabilitation consists in assessment-based therapeutic interventions aiming to reduce disability and promote functional recovery. Functional changes are achieved through various intervention methods targeting restitution, compensation, and adaptation (Cicerone et al., 2000). But how can we determine whether a given therapeutic intervention will have a beneficial effect for an individual patient?

TMS measures may be used not only to track but also to predict intervention-related neuroplastic changes within memory networks. Moreover, TMS measures can inform us about the functionality of specific neurophysiological circuits implicated in memory functions and may be indicative of how well an individual will profit from a given pharmacological intervention. For instance, acetylcholine (ACh) is a neurotransmitter that plays a crucial role in synaptic plasticity and memory functions, and ACh imbalances have been associated with memory deficits in patients with Alzheimer's disease (AD) (Davies and Maloney, 1976; Coyle et al., 1983). Deficits in cholinergic circuits can be counteracted with pharmacological interventions involving acetylcholine esterase (AChE) inhibitors. SAI is a TMS measure that is indicative of cholinergic circuits in the motor cortex (Di Lazzaro et al., 2000) and is altered in patients with AD (for a review see Freitas et al., 2011a). SAI may even be useful to differentiate dementia subtypes (Di Lazzaro et al., 2006, 2008) and may be used as an indicator of who will profit from AChE inhibitors. Short-latency intracortical inhibition (SICI) and the cortical silent period (cSP) are thought to reflect the excitability of inhibitory γ-aminobutyric acid (GABA)ergic circuits (Hallett, 2000) and were also found to be abnormal in patients with AD. However, the relationship of these TMS measures with specific memory dysfunctions is less clear (Freitas et al., 2011a). Notably, studies up to date have relied on TMS measures from the motor cortex. However, the combination of TMS with EEG may enable us to find more precise TMS biomarkers by exploring neurophysiological changes outside the motor cortex.

MODULATING LEARNING AND MEMORY

The interest in the augmentation of cognitive functions reaches far back into the history of modern humanity. The use of memory techniques, for instance in order to improve rhetorical skills, was already promoted by Marcus Tullius Cicero ("De Oratore", Book II, 55 BC). One of these methods, the "Cicero Memory Method" (Method of loci), a simple memory enhancement method that uses visualization to structure information, is still in use today. The pursuit of cognitive augmentation has since led researchers to take advantage of technical developments in order to achieve a better outcome. In the past decade, scientists have therefore started investigating the impact of various NBS techniques on memory functions.

Learning is a prerequisite for the formation of memory traces and is thought to be dependent on synaptic plasticity mediated by LTP and LTD, which also represent key mechanisms in the effects of NBS on brain

functions. This has not only rendered NBS valuable for the investigation of neuroplastic processes associated with learning and memory but also promotes it as a valuable tool to enhance memory functions.

Although TMS is used mostly for diagnostic purposes and the investigation of brain structures contributing to specific functions, tDCS is more often applied to enhance brain functions.

Healthy subjects

Working memory

In the past decade, researchers have begun examining the effects of WM training on neural correlates and concomitant performance (Jaeggi et al., 2008). These studies have shown that not only can WM capacity be increased via constructive training but also that said training increases the density of cortical D1 dopamine receptors in prefrontal regions (McNab et al., 2009). The neurobiological substrate of WM is an ongoing topic of research; however, prefrontal regions are believed to be critically involved. Consistent with such notions, studies exploring the potential for NBS to enhance WM have focused on the prefrontal cortex, generally the DLPFC, and the majority have used verbal WM tasks. In most studies subjects were asked to practice STM or WM tasks concurrently to tDCS, and their WM abilities were assessed either during or afterwards.

Compared with sham stimulation, tDCS with the anode over the left DLPFC (and the cathode right supraorbitally) has been repeatedly reported to enhance WM in healthy subjects (Fregni et al., 2005; Ohn et al., 2008; Mulquiney et al., 2011; Teo et al., 2011; Zaehle et al., 2011). Some researchers have suggested that increasing stimulation intensity (Teo et al., 2011) or duration (Ohn et al., 2008) might lead to more robust effects. Only one study has reported no memory improvement following tDCS with the anode over the left DLPFC (Mylius et al., 2012), and one study reported improvement in STM but not in WM (Andrews et al., 2011). The only study applying tDCS with the anode over the right DLPFC showed no WM effect (Mylius et al., 2012). On the other hand, tDCS with the cathode over the left DLPFC (and the anode right supraorbitally) yielded diverse results in different studies, ranging from memory benefits (Mylius et al., 2012), to no effects (Fregni et al., 2005), and even negative effects (Zaehle et al., 2011). The study by Zaehle et al. (2011) is of particular interest as the authors reported that the negative effects of tDCS with the cathode over the left DLPFC were associated with decreased electroencephalographic power in theta and alpha bands over posterior (parietal) regions. On the other hand, the authors found that improved WM following tDCS with the anode over the left DLPFC was associated with increased power in alpha and theta EEG bands over parietal regions. This study illustrates the potential of studies combining behavioral and neurophysiological outcome measures, and suggests the critical role of corticocortical interactions in memory enhancement. It has been proposed that a more distributed network may subserve WM functions with the posterior parietal cortex (PPC) playing an important role (Mottaghy et al., 2002a; Collette et al., 2006). Stimulation might disrupt activity in a given cortical region and thus release activity in a distant connected node, resulting in paradoxical facilitation (Najib and Pascual-Leone, 2011). The specific nature of the stimulation seems important, although, for example, random noise stimulation over the left DLPFC showed no effects (Mulquiney et al., 2011).

In order to explore further the role of parietal structures in WM, Sandrini and colleagues (2012) applied bilateral stimulation over the PPC during a 1-back (STM) or a 2-back (WM) task. They found a double dissociation, with STM being impaired after left-anodal/right-cathodal and WM being impaired after left-cathodal/right-anodal stimulation. They concluded that this dissociation might be due to differential processing strategies in STM and WM. However, the effects might have been mediated by impact on attentional (rather than memory) processes given the fact that only response time, and not accuracy, was affected. Future studies will need to investigate further the contribution of parietal areas and their interaction with prefrontal areas to WM enhancement.

Further studies could examine the duration of effects, the likely synergistic effect of cognitive training with tDCS, or the applicability of tDCS or other NBS methods to enhance WM across the age span, from children to elderly. However, all such studies need carefully to weigh risk–benefit considerations, and should be informed by a thoughtful discussion of the ethical connotations of such enhancement approaches (Rossi et al., 2009; Hamilton et al, 2011; Horvath et al., 2011).

Short-term memory

Whether NBS can enhance STM in normal subjects is less clear. Studies show less consistent results. This could in part be due to the fact that basic STM tasks are easy for healthy subjects, which leads to ceiling effects. More recent studies have applied adapted tasks, which, however, makes it difficult to compare across studies. Most studies, similar to the literature on WM, have targeted the DLPFC. Two recent studies reported beneficial effects of tDCS with the anode over the DLPFC for an STM task with additional distractors (Gladwin et al., 2012; Meiron and Lavidor, 2013). One study found a gender-dependent improvement in accuracy, with male subjects

profiting more from left DLPFC stimulation and female subjects profiting more from right DLPFC stimulation, but only if distractor loads were high (Meiron and Lavidor, 2013). The other study used a modified Sternberg task, which introduced additional distractor stimuli during the delay period (Gladwin et al., 2012). These workers found significant reaction time improvements after stimulation of the left DLPFC. Compared with these studies, Marshall et al. (2005) applied tDCS with either two anodes or two cathodes over DLPFC, with the reference electrodes positioned over the mastoids, and found deleterious effects of STM. This may indicate that the introduction of distractors to an STM task changes underlying neurobiological processes and enables enhancement effects. Improvements after tDCS may be due to either improved selective attention or more successful inhibition of distracting information. Indeed, a recent TMS study has shown that the role of the DLPFC in STM tasks seems to be dependent on the presence of distractors. The stronger the distraction, the more prominent the frontoparietal interactions become, in order to protect relevant memory representations (Feredoes et al., 2011).

Studies in which investigators stimulated parietal areas have yielded partly opposing results. This is true of studies using tDCS and those employing TMS. Regarding TMS experiments, some show worsened STM (Koch et al., 2005; Postle et al, 2006), while the other report improved STM (Hamidi et al., 2008; Yamanaka et al., 2010) after high-frequency parietal stimulation during the delay period. As for tDCS experiments, Berryhill et al. (2010) found impairment in recognition, but not free recall, after tDCS with the cathode over the right parietal cortex (and the anode over the left cheek), whereas Heimrath and coworkers (2012), positioning the cathode over the right parietal cortex (and the anode over the contralateral homologous area), found an improved capacity in a delayed match-to-sample task after tDCS when stimuli were presented in the left visual hemifield (STM for stimuli presented in the left hemifield decreased). Interestingly, Heimrath et al. used concurrent tDCS and EEG, and found a decrease in oscillatory power in the alpha band after cathodal stimulation. As alpha activity is assumed to reflect inhibition of distractors (Klimesch, 1999), the authors suggested that this measure might indicate memory performance. This study again illustrates the potential of experiments combining behavioral and neurophysiological outcome measures with NBS.

Finally, one study probed the cerebellum and found an abolishment of practice-dependent improvements in response time in a Sternberg task, regardless of whether the anode or the cathode was placed over the cerebellum (and the other electrode over the vertex) (Ferrucci et al., 2008). The contribution of the cerebellum to STM was also probed with single-pulse TMS by Desmond and colleagues (2005), who also found a negative effect on response time in the Sternberg task. Whether other cerebellar stimulation paradigms can induce an enhancement of STM remains unexplored.

General memory and learning

Researchers attempting to enhance learning processes have targeted various neural regions. Such diverse approaches again render it difficult to single out a pattern regarding stimulatory condition, mechanisms, and outcome. Most studies have applied tDCS during the learning phase, and most have targeted the left DLPFC or other left prefrontal areas. Generally, studies report memory improvement following tDCS with the anode over DLPFC (Kincses et al., 2004; Javadi and Walsh, 2012; Javadi et al., 2012) or other prefrontal areas (De Vries et al., 2010), and worsening memory after tDCS with the cathode over DLPFC (Elmer et al., 2009; Hammer et al., 2011; Javadi and Walsh, 2012; Javadi et al., 2012) or other prefrontal areas (Vines et al., 2006). However, in interpreting their results, investigators have often made the overly simplistic assumption that the effects of tDCS can be accounted for by the neurobiological effect of one of the electrodes, the anode enhancing and the cathode suppressing activity in the brain area under them. Yet, it is important to remember that tDCS is not monopolar and that all electrodes are active. Thus the brain is exposed to a flow of current with opposite faradizing effects of the anode and the cathode. Therefore, to speak of anodal tDCS or cathodal tDCS is inaccurate.

Few studies have targeted right prefrontal areas. One study reported no effects in an episodic verbal memory task after tDCS with either anode or cathode over the right prefrontal region (Elmer et al., 2009). Two studies showed that the learning process of threat detection in a virtual reality environment and the time required to learn this skill can be improved following tDCS with the anode over the right prefrontal (Bullard et al., 2011; Clark et al., 2012) or right parietal region (Clark et al., 2012). Furthermore, Bullard and colleagues (2011) found that applying tDCS at the beginning of the learning phase significantly enhanced learning in comparison with findings in experienced learners (after 1 hour of training).

Bilateral stimulation (anode and cathode over homologous areas of either hemisphere) has been applied in a few studies (Marshall et al., 2004, 2011; Boggio et al., 2009; Chi et al., 2010; Cohen Kadosh et al., 2010; Penolazzi et al., 2010; Jacobson et al., 2012). Jacobson and coworkers (2012) applied bilateral tDCS (anodal left, cathodal right, or vice versa) over the parietal lobe during encoding. They found improved verbal memory only

when the anode was placed over the left hemisphere and the cathode over the right hemisphere. Another study investigating the contribution of the parietal cortex to numerical learning applied bilateral tDCS during a training phase of 6 days (Cohen Kadosh et al., 2010). While right-anodal/left-cathodal stimulation improved learning significantly, right-cathodal/left-anodal stimulation decreased learning compared with sham tDCS.

Penolazzi and colleagues (2010) applied bilateral tDCS (anode left and cathode right, or vice versa) over the frontotemporal cortex during encoding and found facilitated recall of pleasant images after right-anodal/left-cathodal tDCS, whereas left-anodal/right-cathodal tDCS facilitated recall of unpleasant images. These results support a theoretical model (specific valence hypothesis) according to which the right and left hemispheres are specialized in the processing of unpleasant and pleasant stimuli respectively. Another group applying bilateral stimulation (anodal left, cathodal right, or vice versa) over the anterior temporal lobe assessed visual memory (Chi et al., 2010) and also reported an improvement in memorizing different types of shape after right-anodal/left-cathodal stimulation, but no effects when applying an inverse stimulation pattern.

One set of studies has investigated effects of bilateral anodal stimulation over DLPFC during sleep and wakefulness. In their first study, Marshall and colleagues (2004) reported an improvement of memory consolidation when applying intermittent (on/off 15 seconds) anodal tDCS simultaneously over both DLPFCs during slow-wave (nonrapid eye movement, non-REM) sleep but not during wakefulness. In a second study they investigated state-dependent effects, and found enhanced theta activity when transcranial slow oscillation stimulation (tSOS) was applied during wakefulness (Kirov et al., 2009). Memory enhancement occurred only when tSOS was applied during learning, but not after learning. In their third study, Marshall and colleagues (2011) applied anodal theta-tDCS (tDCS oscillating at 5 Hz) during REM sleep and non-REM sleep, which led to increased gamma-band activity and decreased memory consolidation respectively. The data from these studies illustrate the potential of transcranial current stimulation at specific stimulation frequencies selectively to modulate specific brain oscillations. This NBS method provides an interesting approach for investigating the relation between cortical brain rhythms, sleep-related processes, and memory functions.

Some studies have reported apparently contradictory results, highlighting the need for further investigation of the mechanisms of action underlying tDCS and TMS. Boggio et al. (2009) found decreased "false memories" utilizing anodal tDCS over the left anterior temporal lobe, or bilateral (left-anodal/right-cathodal) tDCS. However, the same researchers reported a nearly identical effect after applying 1-Hz rTMS over the same region, a protocol that is believed to suppress activity of the targeted brain area (Gallate et al., 2009). Of course, it is possible that the behavioral effect might be related to trans-synaptic network effects, rather than being mediated by the targeted brain region. Indeed, a study using single-pulse TMS reported a facilitatory effect on verbal memory after stimulating the *right* inferior PFC (Kahn et al., 2005), presumably due to interhemispheric paradoxical facilitation effects. This would be consistent with another study that found an improvement in verbal memory after stimulating the *left* inferior PFC with 7-Hz rTMS bursts (Köhler et al., 2004). Furthermore, a paired-pulse protocol known to induce facilitatory effects led to memory improvements after stimulation of the left and right DLPFC in verbal as well as nonverbal episodic memory. The combination of stimulation techniques and other methods, such as EEG and fMRI, allows their inherent advantages to be combined to help answer these open questions.

Elderly healthy subjects

Basic memory research includes mostly young and healthy subjects. However, one of the key topics in the domain of NBS research concerns the changes of interhemispheric balance and the increased compensatory recruitment of brain areas with aging. As memory represents an overarching topic for the elderly, it is crucial to promote research that investigates these changes and provides information as to how to enhance memory functions. Furthermore, research with healthy elderly subjects is vital if we want to translate it into the clinical setting, as patients with memory deficits are mostly older. A newly emerging field has started to investigate memory enhancement in elderly subjects and underlying models (Rossi et al., 2004; Solé-Padullés et al., 2006; Manenti et al., 2011; Flöel et al., 2012).

The "Hemispheric Asymmetry Reduction in Older Adults" (HAROLD) model states that prefrontal activity during cognitive performance becomes less lateralized with advancing age (Cabeza, 2002). Manenti and colleagues investigated the differential assumptions of the HERA model (young subjects) and the HAROLD model (elderly subjects), suggesting that hemispheric asymmetry is reduced with age. Interestingly, they could show that low-performing elderly subjects continue showing prefrontal asymmetry, whereas high-performing elderly individuals show reduced asymmetry indicative of compensatory mechanisms (Manenti et al., 2011).

Although lateralized activations within the PFC can be observed in younger subjects during episodic memory tasks (Rossi et al., 2001), this asymmetry vanishes

progressively with advancing age, as indicated by bilateral interference effects (Rossi et al., 2004).

Conversely, the predominance of left DLPFC effect during encoding was not abolished in older subjects, indicating its causal role for encoding along the lifespan. However, this study did not differentiate between high- and low-performing subjects. Another study supported the assumption that higher performance is associated with more bilateral recruitment of brain areas and that stimulation may be able to promote the recruitment of additional brain areas to compensate for age-related decline. Solé-Padullés and colleagues (2006) found improved performance in associative learning after 5-Hz offline rTMS, which was accompanied by additional recruitment of right prefrontal and bilateral posterior brain regions.

A tDCS study showed improvements in spatial learning and memory in elderly subjects (mean 62 years) when stimulating during encoding (Flöel et al., 2012). Anodal stimulation over the right temporoparietal cortex improved free recall 1 week later compared with sham stimulation. No immediate learning differences were observed, which indicates that retention (less decay) rather than encoding was affected by the stimulation.

To summarize, several studies have found different results following the stimulation of the DLPFC in young and elderly healthy subjects in accordance with the HAROLD model (Cabeza, 2002). These differences could be due to changes in interhemispheric balance and recruitment of different brain areas for the same tasks, which could arise due to compensatory mechanisms. It remains to be further elucidated whether these changes reflect local or distributed mechanisms, whether compensatory recruitment of additional brain areas is associated with higher performance levels and could be enhanced by NBS.

Patients

Compared with the wealth of studies that have been done with healthy and mostly young subjects, studies on patients are rather sparse (see Table 55.1). The evidence is encouraging and calls for further investigation of the combined application of NBS and neuropsychological therapy. Besides behavioral measures, these studies should ideally include other measurements, such as assessment of brain plasticity or memory-specific neurophysiological outcomes. The work on patients with stroke is very preliminary, and more studies with larger patient numbers and better control of lesion location are needed. In one crossover, sham-controlled study, Jo et al. (2009) applied tDCS with the anode over the left DLPFC (and the cathode over the contralateral supraorbital area) in a 2-back task to 10 patients with unilateral, right-hemispheric, ischemic, or hemorrhagic strokes (1–4 months poststroke). After a single stimulation session, performance accuracy but not reaction time improved significantly. Enhancement of memory functions has been more extensively investigated in patients with AD and Parkinson's disease (PD). These findings provide evidence that NBS could be a safe and useful tool in restoring/compensating brain functions through activation of primary and compensatory networks that underlie memory functions.

Alzheimer's disease

A few studies have demonstrated effects of NBS on cognitive functions in AD (6 TMS, 3 tDCS). The first studies that used NBS in AD looked primarily at language and not memory functions. Cotelli and colleagues used rTMS (20 Hz) over the left and right DLPFC and reported positive effects for both hemispheres. They applied a single online session of rTMS in two crossover, sham-controlled studies (Cotelli et al., 2006, 2008). In the first study they reported improved accuracy in action naming, but not object naming, for all patients (Cotelli et al., 2006). In the second study they could replicate the positive results for action naming; however, object naming also improved significantly, although only in moderately to severely impaired patients (Cotelli et al., 2008). The authors hypothesized that the lack of improvement in object naming may be due to a ceiling effect. Furthermore, the bilateral effect could have been due to compensatory activation of right hemispheric resources.

In a third placebo-controlled study the same authors tested various functions, including memory, executive functions, and language in patients with moderate AD (Cotelli et al., 2011). This study entailed 4 weeks of daily sessions of 20-Hz rTMS to the left DLPFC. Although they found significant improvements in sentence comprehension after 10 sessions (with no further improvement after 20 sessions), they did not find any improvements in memory and executive functions (Cotelli et al., 2011). This lack of improvement could be due to the fact that the patients were not doing any specific concomitant cognitive training. Alternatively, the lack of memory effects could be related to the targeted brain region.

Bentwich and colleagues (2011) interleaved cognitive training and rTMS (10 Hz) during 30 sessions while stimulating six different brain regions (Broca, Wernicke, right and left DLPFC and parietal cortices). During each session three of these regions were stimulated while patients did cognitive tasks that were developed to fit each of these regions. Improvements in cognitive functions were significant, as measured using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), and were maintained for 4.5 months after the training. A case report (Haffen et al., 2012) showed an improvement in episodic memory (free recall) and

processing speed following 10 sessions of rTMS (10 Hz) over the left DLPFC. These are open trials and, obviously, sham-controlled interventions are needed. However, the results are promising and warrant follow-up. In a sham-controlled trial, Ahmed and colleagues (2012) assigned 45 patients with AD to three different treatment groups to study the effects of high- or low-frequency rTMS (20 Hz, 1 Hz), or sham stimulation. Patients received treatment on 5 consecutive days without combined cognitive training. Mildly to moderately impaired patients receiving high-frequency rTMS improved significantly on all scales (Mini Mental State Examination (MMSE), Instrumental Daily Living Activity Scale, Geriatric Depression Scale), and maintained these improvements for 3 months. However, severely impaired patients did not respond to the treatment.

Two crossover studies applied tDCS for one session and reported improvements in visual recognition memory following stimulation of the left DLPFC and temporoparietal cortex (TPC) (Boggio et al., 2009), and in word recognition following stimulation of the bilateral TPC (Ferrucci et al., 2008). In the first study, the authors applied 15 minutes of anodal, cathodal, and sham stimulation over bilateral TPC on three different sessions in patients with mild AD. While anodal tDCS led to an improvement, cathodal stimulation led to impairments in word recognition. No effects were observed in a visual attention task (Ferrucci et al., 2008). In the second study, mildly to moderately impaired AD patients received anodal tDCS over the left DLPFC, the left TPC, or sham stimulation. Stimulation over both DLFPC and TPC resulted in a significant improvement in visual recognition. No effects were observed on selective attention or a visual delayed match-to-sample task.

Possibly, tDCS-induced changes in cholinergic activity contributed to these improvements. A recent study reported a significant change of SAI (ISI 2 ms) in the motor cortex of healthy subjects after anodal stimulation, while the resting motor threshold and amplitudes of motor evoked potentials did not change (Scelzo et al., 2011). This could explain the positive impact of tDCS on memory functions in the above-mentioned studies. Future studies measuring behavioral along with neurophysiological effects and exploring correlations between them would be desirable.

Parkinson's disease

Two studies have applied TMS or tDCS with the aim of improving cognitive functioning in PD. The first study compared the effects of active or sham rTMS and fluoxetine or placebo in patients with PD with concurrent depression (Boggio et al., 2005). The authors applied 15-Hz rTMS over the left DLPFC for 10 daily sessions, and assessed cognitive functions at baseline, and 2 and 8 weeks after the treatment. Treatments were not combined with cognitive training or psychotherapy. After 2 weeks both interventions led to similar improvements in the Stroop Test and the Wisconsin Card Sorting Test (executive functions), and the Hooper (visuospatial functions). Furthermore, depression rates improved significantly in both groups. However, no improvements were reported in STM or WM (digits forward and backward). Eight weeks after treatment, these improvements declined slightly but remained significant.

The second study found improved accuracy in a 3-back task during a single session of anodal tDCS over the left DLPFC. Improvement was significant at a stimulation intensity of 2 mA but not at 1 mA (Boggio et al., 2006).

Cognitive impairments in PD are often associated with depression symptoms, which occur in about 35% of patients. Furthermore, dementia is common in these patients with a point prevalence of 30% (Aarsland and Kurz, 2010). Further studies are needed to investigate underlying processes leading to cognitive impairments. Moreover, studies should evaluate the efficacy of repetitive NBS in combination with cognitive training for this patient population.

CONCLUSION

A quickly growing number of studies is using NBS applications to study the underlying neurobiological substrates of memory functions, to investigate the use of TMS as a diagnostic tool, and the application of NBS to enhance memory functions. To date, most studies have used TMS to probe underlying memory processes and their causal and temporal relationships, whereas TMS, tDCS, and other forms of transcranial current stimulation are being used to enhance memory functions in healthy as well as patient populations. The combination of NBS with other methods, such as EEG and fMRI, enables the measurement of behavioral along with neurophysiological effects; the exploration of correlations between them is desirable to advance our neurobiological understanding and optimize future interventions.

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