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Transcranial magnetic stimulation can measure and modulate learning and memory

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Abstract

The potential uses for Transcranial Magnetic Stimulation (TMS) in the study of learning and memory range from a method to map the topography and intensity of motor output maps during visuomotor learning to inducing reversible lesions that allow for the precise temporal and spatial dissection of the brain processes underlying learning and remembering. Single-pulse TMS appears to be adequate to examine motor output maps but repetitive TMS (rTMS) appears necessary to affect most cognitive processes in measurable ways. The results we have reviewed in this article indicate that rTMS may have a potential clinical application in patients with epilepsy in whom it is important to identify the lateralization of verbal memory. Single-pulse TMS can help identify changes in motor output maps during training, that may indicate improved or diminished learning and memory processes following a stroke or other neurological insult. Other evidence indicates that rTMS may even have the capability of facilitating various aspects of memory performance. From a research perspective, rTMS has demonstrated site- and time-specific effects primarily in interfering with explicit retrieval of episodic information from long-term memory. rTMS may also be able to modulate retrieval from semantic memory as evidenced by response-time and accuracy changes after rTMS. All these findings suggest that the use of transcranial magnetic stimulation in the study of learning and memory will increase in the future and that it is already a valuable tool in the cognitive neuroscientists' belt. © 1999 Published by Elsevier Science Ltd.

Keywords: Transcranial magnetic stimulation; Learning; Memory

1. Introduction

Although first used as a technique to measure motor pathway conduction times, transcranial magnetic stimulation (TMS) has potential applications that exceed the initial expectations of its utility. For example, TMS has become an important tool in the study of motor output maps, neuroplasticity and perception. Given the precision in the timing of TMS, investigators have been able to demonstrate not only precisely mapped errors in visual detection, but the fractionation of various forms of visual perception using interference paradigms in conjunction with precise timing of stimulation. The realization that TMS could interfere with ongoing information processing led to its application for the purposes of language lateralization. In this case, the aim was to provide a non-invasive tool, compared to the Wada test or electrical stimulation applied directly to cerebral cortex, for identification of the language dominant hemisphere in patients who were candidates for temporal lobectomy. This progression from an interest in its use with patients who have motor conduction problems to its application in studying cognitive processes has been rapid and exciting [1]. There may also be a potential use for rTMS in the facilitation of those same cognitive processes. The purpose of this article is to review recent research using TMS in the study of learning and memory and to suggest further potential applications of TMS in this area of research. While a complete understanding of the physics and neurophysiology of TMS has not yet been achieved, staying within the published safety guidelines will greatly diminish any untoward side effects resulting from its use in studying memory. Since our focus in this review is on memory, we first present what is known about the persistent effects of TMS on memory in the context of safety studies. We then review studies using both single-pulse

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and repetitive TMS to map, interfere with, or facilitate learning and memory processes. We conclude this article with some comments about the potential application and limitations of TMS in learning and memory research.

2. Safety and persistent effects of TMS on learning and memory

Because TMS is capable of producing readily detectable brain activation, there has been a concern from its earliest use that the effects of the stimulation be temporary and safe. TMS safety guidelines restrict the pulse-train length and inter-train interval that a subject may receive during an experiment [2]. Since early studies were primarily concerned with measuring motor conduction times after stimulation over the primary motor area of the cortex, little attention was paid to whether there would be any cognitive consequences of rTMS. As the use of rTMS expanded to include other areas of cortex, the potential long-term effects of rTMS on memory began to be studied. Short-term effects on memory were considered to be any immediate and transient effects desired by the experimenter (e.g. impairment of visual memory). Long-term effects were considered to be any undesired effects on learning and memory that were present after the experiment was concluded.

Across a number of safety studies, no negative long-term effects on memory have been noted following single-pulse TMS or rTMS. In fact, in some safety studies, a trend towards improved memory functioning has been noted [3, 4]. Recently, however, two studies by our group have demonstrated changes in cognition for up to one 1 h post-rTMS. In a recently published study by Flitman et al. [5], normal subjects tested approximately 1 h after rTMS showed a significant decline in story recall compared to their pre-rTMS baseline. The rTMS intensity and duration used in this study were unusually high and might have led to this adverse effect (see Flitman et al. [5] for details; also Wassermann et al. [6] for additional comments). Since rTMS was applied to a number of different scalp sites between memory tests in this study, it is impossible to determine if the memory decrement was additive across sites or due to stimulation at a particular site or set of sites. In another study [7], depressed patients receiving rTMS over the right or left frontal lobes and occipital lobes were tested 1 h later on a task-switching paradigm. In this study subjects received stimulation limited to one scalp site per day. Preliminary results have indicated that right frontal rTMS leads to a significant increase in response times during task switching but not single task conditions.

Thus, the effects of rTMS on memory and cognition can last at least 1 h after rTMS. Given that persistent post-rTMS effects can occur, it enlarges the scope of what kind of experimental designs can be used in conjunction with rTMS. In particular, when a single site is stimulated with rTMS and there are persistent neural effects of the stimulation, complex experimental designs can be administered to the subject post-stimulation with the prediction that subjects will perform more poorly (or better) in the conditions designed to examine cognitive functions that depend on the stimulated cortical region.

3. Learning and memory

Both single-pulse and repetitive TMS have been used in conjunction with learning and memory tasks. As noted above, there are at least three types of paradigms that can be used with TMS to study learning and memory:

(1) Mapping which can indicate the topography of local cortical representational (e.g. motor output) maps following performance of a task.
(2) Interference where the stimulation impairs an aspect of learning and memory.
(3) Facilitation where the stimulation enhances an aspect of learning and memory.

Studies representing each of these paradigms are discussed below.

4. Mapping studies

Pascual-Leone et al. [8] studied the excitability of the motor cortex during the development of implicit and declarative knowledge on a visuomotor learning paradigm modeled after the Serial Reaction Time Task (SRTT). In this study, asterisks were presented in one of four positions on a computer monitor and subjects had to press a key that was underneath the position of the asterisk on the monitor whenever one appeared. Both random and repeated sequences of asterisks were presented. Subjects were regularly probed verbally about their knowledge of the repeated sequence. Initially, subjects were unaware that the asterisks were presented in a repeating, 12-item sequence. Development of implicit knowledge of the sequence was reflected by decreasing response times. Eventually explicit knowledge of the actual sequence was achieved and subjects began anticipating the position of the next asterisk in the sequence. Motor cortex mapping was performed with TMS at the beginning of the experiment and at regular intervals while subjects were resting between blocks of trials. Initially, the cortical motor output maps of the muscles involved in the task became progressively larger, while those of control muscles remained unchanged. The enlargement of these maps continued until explicit knowledge was achieved. Thereafter, the cortical maps returned to their baseline topography despite continued improvement in performance. A group of control subjects, who performed the same task, but with the cues presented in

random order, failed to show a significant improvement in their response times or a modulation in their cortical motor output maps. While the size of TMS motor maps is now generally acknowledged to be essentially a function of threshold rather than true cortical extent [9], these results illustrated the rapid functional plasticity of motor output associated with visuomotor learning and the cortical response to transfer of knowledge from an implicit to explicit state. Using a similar experimental design and adapting methods for detecting event-related brain electrical activity desynchronization, Zhuang et al. [10] were able to replicate the observation of apparent motor output map enlargement during implicit learning and reduction when explicit knowledge of the task was gained.

Pascual-Leone et al. [11] used TMS to study the role of plastic changes of the human motor system in the learning of new fine motor skills. They mapped the cortical motor areas targeting the contralateral long finger flexor and extensor muscles in subjects learning a one-handed, five-finger exercise on the piano. In a second experiment, they studied the different effects of mental and physical practice of the same five finger exercise on the modulation of the cortical motor areas targeting muscles involved in the task. Over the course of 5 days, as subjects learned the exercise through daily 2 h practice sessions, the cortical motor areas targeting the long finger flexor and extensor muscles enlarged and their activation threshold decreased. These changes were limited to the cortical representation of the hand used in the exercise. No changes of cortical motor outputs occurred in control subjects who underwent daily TMS mapping but did not practice on the piano at all. They also studied the effect of increased hand use without specific skill learning in subjects who played the piano at will for 2 h each day using only the right hand, but who were not taught the five-finger exercise and who did not practice any specific task. In these control subjects, the changes in cortical motor output maps were similar but significantly less prominent than in those occuring in the test subjects who learned a new skill. The excitability of the human motor cortex during the development of implicit and explicit knowledge of a motor task had already been examined by Pascual-Leone et al. [8]. Together with the results of the piano playing experiment, these two studies illustrate the rapid functional plasticity of cortical outputs associated with learning and the transfer of knowledge from an implicit to an explicit state. These findings provide some of the first evidence in humans of the apparent topographic flexibility of regional cortical maps in response to learning contributing to a growing literature on this topic [12, 13].

Other studies have used single-pulse TMS to reveal changes in cortical topography during learning or memory on tasks such as Braille reading [14, 15]. Single-pulse TMS mapping appears to be safe in normal subjects and patients without cortical lesions and holds much promise for charting the time course and plasticity of selected learning and memory processes-in particular, those that require visuomotor processing.

5. Interference studies

The purpose of TMS interference studies has been to selectively disrupt ongoing learning and memory processes—in effect, creating a 'reversible lesion'. In these studies, either single-pulse or repetitive TMS has been used during subject performance on learning and memory tasks. The site of delivery and the TMS settings used across these studies has been variable (Table 1). A few studies have tested learning and memory after a TMS study whose major purpose was to examine other processes (e.g. as in safety studies that tested for changes in memory following the use of TMS over motor areas to affect motor control processes), but in most studies, the location and timing of TMS were specifically designed to examine its direct effect on learning and memory. Both kinds of studies are described below. Finally, even though TMS penetrates no deeper than 2 cm from the surface of the scalp and, therefore, stimulates only the area of cortex directly underneath the coil [16, 17], Paus et al. [18] have shown that by combining rTMS with 0^{15} positron emission tomography it is possible to see both local and distant effects with rTMS. The local effects may represent a disruption to, or a heightening of, activity in the cortical network that is underneath the site of stimulation while the distant effects represents a transmission of neural activity to other brain sites anatomically connected to the site of stimulation. Ilmoniemi et al. [19] examined the electrophysiological response in motor and visual cortices of normal volunteers who received transcranial magnetic stimulation. The electrical brain activity resulting from the brief electromagnetic pulse was recorded with high-resolution electroencephalography (HR-EEG) and located using inversion algorithms. TMS of the left sensorimotor hand area elicited an immediate response at the stimulated site. The activation spread to adjacent ipsilateral motor areas within 5–10 ms and to homologous regions in the opposite hemisphere within 20 ms. Similar activation patterns were generated by TMS of the visual cortex. Whether the TMS-induced transmission of activity to distant brain regions has functional value has not yet been determined [20].

Whether TMS of the motor cortex has an influence on memory was investigated by Ferbert et al. [21]. In a first experiment with 21 healthy volunteers, six pronounceable nonsense words were presented visually, immediately followed by a magnetic stimulus. There were three blocks of stimulation with field intensities of 60, 80 and 100% (referring to a maximal intensity of 2 Tesla). Each block comprised six magnetic stimuli and six nonsense words.

Table 1
TMS parameters used in a selection of the studies described in this article

Study ref. & lead author	Frequency Hz	Intensity as percentage of motor threshold or tesla strength	Duration	Intertrain interval	Location	Effect on L & M
[22] Hufnagel	50	1 Tesla	550 ms	approx 4 s	Temporal–parietal	None
[21] Ferbert	1	60, 80 & 100% of 2 Tesla	?	approx 8 s	Motor cortex	None
[27] Pascual-Leone	5	110% of motor threshold	5 s	>400 ms	Pre-frontal, motor cortex	Yes
[44] Pascual-Leone	5	90% of motor threshold	up > 2 min	several min	Motor cortex	Yes
[32] Grafman	20	120% of motor threshold	500 ms	750 ms	Prefrontal, Temporal, Parietal, Occipital	Yes
[23] Düzel	0.25 Hz	120% of motor threshold	<400 ms	> 250 ms	Temporal, Frontal	Yes
[34] Pascual-Leone	5 Hz	115% of motor threshold	up to 60 s	up to 300 ms	Prefrontal, SMA	Yes
[5] Flitman	15 Hz	120% of motor threshold	750 ms	250 ms	Frontal, Parietal	Yes
[7] Greenberg	20 Hz	80% of motor threshold	2 s	28 s	Frontal, Occipital	Yes

Frequency = the number of TMS pulses/s; Intensity = percentage of motor threshold or in some cases absolute tesla; Duration = length of each pulse train; Intertrain Interval = duration between TMS; Location = scalp areas where TMS took place.
For effect on L&M, the word yes indicates that there was a clear effect on learning and memory performance from TMS applied at one or more of the sites listed.

After each block there was a free recall test and at the end of the experiment, they administered another free recall trial as well as a multiple-choice recognition test for all 18 words. Eighteen subjects served as controls, undergoing the same procedure, except that the magnetic field intensity was zero (and the loud click generated by the discharging coil was absent). A significant but small reduction in short-term memory performance was observed only for the block using 100% field intensity (where the click was loudest). In a second experiment with 16 subjects who had not participated in Experiment 1, the effect of 100% intensity TMS was compared with a control stimulation over the cervical spine. There was no difference in free recall or in the multiple-choice test between the sites of stimulation, suggesting that the diminished recall in the 100% intensity block in Experiment 1 was not due to a specific cortical effect of the TMS on memory function. This latter finding demonstrates the importance of using sham and other control conditions in TMS research on learning and memory.

5.1. Short-term/working memory

The effect of rTMS on immediate verbal and visuo–spatial memory span was assessed by computerized neuropsychological testing in 11 healthy volunteers by Hufnagel et al. [22]. The subjects had to memorize series of numbers (Digit-Span test) or the position of cubes (Corsi-Block test) shown to them on a computer monitor and actively reproduce them immediately after the presentation. Synchronous with the appearance of each item, an rTMS train of 550 ms duration was delivered to the left or right anterolateral parietal as well as superior and posterior temporal regions at 50 Hz and with approximately 1.0 tesla stimulation intensity (50–67% of the maximum of most magnetic stimulators). Statistical comparison of memory performance during rTMS and baseline testings without stimulation revealed no significant changes. No adverse effects were observed. Thus, rTMS (using these settings) over posterior lateral temporal cortex or anterior lateral parietal cortex did not affect short-term memory performance in healthy individuals.

Düzel et al. [23] investigated whether single-pulse TMS could be used to identify the lateralization of verbal and non-verbal memory functions in candidates for epilepsy surgery by inducing focal, material-specific memory deficits. Twenty patients who underwent presurgical epilepsy evaluation with chronically implanted subdural strip electrodes received focal TMS over the temporal lobes and vertex while the sequence of items of the Digit Span or Corsi Block tests were presented on a computer monitor. TMS pulses were applied synchronously or 200 ms following the presentation of each item. The effects of TMS on memory span and the serial position curve were analysed in comparison to baseline levels. There was no significant effect of TMS on verbal (Digit Span) or non-verbal (Corsi Blocks) memory span, but there were significant qualitative effects on the serial position curve. In the group of six patients with left temporal lobe epilepsy, TMS over the left temporal lobe induced a significant recency effect on the Digit Span test (i.e. improved recency), while TMS over the vertex significantly increased errors in the recency portion of the serial position curve. The absolute number of errors on the task remained unchanged. No such effects were observed in the patients with right temporal lobe epilepsy. These results suggest that in the presence of a left temporal lobe epileptic focus, TMS can induce qualitative,

material-specific changes in verbal working memory (phonological loop) which becomes apparent only when recall of portions of the serial position curve are considered. The dissociation of TMS effects for temporal and vertex stimulation implies that TMS could selectively influence specific phonological loop components and that the phonological loop has a functionally and neuroanatomically multimodular structure. This finding converges nicely with current views on the structure of the phonological loop based on patient data and functional neuroimaging [24].

Beckers and Hömberg [25] applied single-pulse TMS over the occipital cortex (using a stimulator with a maximum output of 2 Tesla) in 24 normal volunteers. The identification of letter trigrams, presented for 14 ms in horizontal or vertical arrays was significantly impaired when the visual stimulus preceded the occipital magnetic stimulus by 40–120 ms. The extent of the effect was related to TMS intensity. The latency of perceptual impairment was shorter for more intense TMS. No perceptual impairment was obtained by 'sham' stimulation when TMS was applied to the upper cervical region rather than the occipital region to rule out non-specific startle reactions affecting attention. Occipital TMS did not evoke eye movements except for blink responses at latencies beyond 40 ms which were too late to interfere with visual input. Perceptual impairment was more marked for the second and third letters. This could be interpreted as evidence that TMS interferes with the serial processing of visual input. In a second experiment, TMS was used during a Sternberg Short-Term Visual Memory Scanning Task. In this task, TMS caused a marked decrease in memory scanning rates, whereas visual stimulus encoding and storage appeared unaffected. The authors concluded that TMS appears to be a useful method to study the role of occipital cortex in perceptual and short-term visual memory processes. Gabrieli et al. [26] have shown that patients with lesions to occipital cortex may have perceptual and/or implicit memory deficits. TMS applied to posterior cortex may become a useful tool in teasing apart perceptual and implicit memory processes.

Pascual-Leone and Hallett [27] used rTMS to study the functional contribution of the dorsolateral frontal cortex to performance on a delayed response task in 10 normal volunteers. The volunteers sat in front of a response pad with four buttons. The cues were presented on a computer screen. An instruction cue was presented for 200 ms (one of the four squares on the monitor was filled in green whereas the others were open squares). Each square on the monitor corresponded to a button on the response pad. Subjects were required to push the appropriate button that corresponded to the green square. Then there was a delay period of 5 s during which the filled color randomly appeared in each of the four squares. At the end of the delay period, all four squares turned solid red which was the cue to the subject to again press the button that corresponded with the square that was filled in green prior to the delay period. Unilateral stimulation of the right or left prefrontal cortex during the delay period between the instruction and execution cues led to a significantly greater number of response errors than were present with stimulation of the primary motor area or in unstimulated trials.

Muri et al. [28] used single-pulse transcranial magnetic stimulation (TMS) to explore the temporal organization of the cortical control of memory-guided saccades in eight humans. The posterior parietal cortex (PPC) or the dorsolateral prefrontal cortex (DPFC) were stimulated on the right side at different time intervals after the presentation of a flashed lateral visual target. The memorization delay was 2000 ms. Single pulses were applied at 160, 260 and 360 ms after the flashed target, during the period of 700 and 1500 ms, and finally at 2100 ms, i.e. 100 ms after the extinguishing of the central fixation point. The effects of TMS were evaluated by calculating the percentage of error in amplitude (PEA) and latency of memory-guided saccades. After PPC stimulation, a significant increase in the PEA of the primary saccade and final eye position was present for contralateral saccades, compared with the PEA without stimulation, when stimulation was applied 260 ms after target presentation (but not at other time intervals). There was no significant effect on ipsilateral saccades. Latency was significantly increased bilaterally when stimulation was performed 2100 ms after target presentation. After DPFC stimulation, a significant increase in the PEA of the primary saccade and final eye position existed for contralateral saccades, when stimulation was applied between 700 and 1500 ms after target presentation, but not at other time intervals. There was no significant effect on ipsilateral saccades. Latency was not affected by DPFC TMS at any stimulation times. Occipital stimulation resulted in no significant effect on the PEA and latency of ipsilateral or contralateral saccades. Muri et al. [28] concluded that the observed effects of TMS on saccade accuracy were specific to the stimulated region and specific to the stimulation time. The PPC seems to be involved in the preparation of saccade amplitude whereas the DPFC played a role in spatial working memory processes. Thus, TMS research supports the cognitive neuroscience literature on the frontal lobe contribution to holding information in working memory [29–31] and indicates that rTMS of appropriate intensity and frequency delivered to the prefrontal cortex has the potential through its interference effect to provide unique evidence about the timing and the mechanisms involved in working memory.

5.2. *Long-term/episodic memory*

Grafman et al. [32] used rTMS to see if they could selectively interfere with verbal recall depending on the site and timing of the stimulation. Five right-handed nor-

mal subjects were studied. Recall was tested immediately after presentation of a 12-word list. rTMS was applied following the onset of each word with a figure-eight coil in trains of 500 ms duration to the 10–20 International System EEG electrode positions: F7, F8, T5, T6, P3, P4 or O1 and O2 at delays of 0, 250, 500 or 1000 ms after the onset of the word stimulus. Subjects were able to repeat each word shown to them despite rTMS. Recall was significantly diminished only after T5 (left mid-temporal) or F7/F8 (dorsofrontal) rTMS at both 0 (primarily T5) and 250 (primarily dorsofrontal) ms delays.

This study, along with those described above, indicates that rTMS may be useful as a non-invasive probe for the study of both short- and long-term verbal memory processes. In particular, it may allow investigators to tease apart the independent contribution of various cortical regions to encoding and remembering-a major goal of contemporary cognitive neuroscience research [33].

5.3. Visuomotor procedural learning

Pascual-Leone et al. [34] examined the role of dorsolateral prefrontal cortex in learning a new motor sequence. Normal subjects completed several blocks of a serial reaction time task using only one hand with or without concurrent rTMS. In an attempt to disrupt visuomotor learning, rTMS was applied at low intensity over the supplementary motor area or over dorsolateral prefrontal cortex contralateral or ipsilateral to the hand used in the experiment. Stimulation of the contralateral dorsolateral prefrontal cortex markedly impaired implicit learning of the visuomotor sequence as measured by a lack of significant change in response times during the task. Stimulation over other cortical sites did not interfere with implicit learning of the sequence. These results support the hypothesis that the contralateral dorsolateral prefrontal cortex plays a particularly important role in the encoding of new visuomotor sequences (also see [35–37] for a similar perspective from lesion data and functional neuroimaging).

In the Pascual-Leone et al. [34] study, it appeared that the dorsolateral prefrontal cortex was critical for implicit learning of a motor sequence. Gerloff et al. [38] used high-frequency (15–20 Hz) rTMS to study the specific role of the mesial frontocentral cortex (including the supplementary motor area) in the organization of sequential finger movements of different complexity in humans. In fifteen subjects, rTMS was applied to the scalp overlying the region of the supplementary motor area and over other sites, including the contralateral primary motor cortex (hand area) during the performance of three overlearned finger sequences on an electric piano. In all trials, rTMS started 2 s after the first key press and lasted for approximately 2 s. All sequences were metronome-paced at 2 Hz and explicitly retrieved from memory. The 'simple' sequence consisted of 16 repeated index finger key presses, the 'scale' sequence consisted of four times four sequential key processes of the little, ring, middle and index fingers, and the 'complex' sequence consisted of a much less systematic and, therefore, more difficult series of 16 key presses. To measure the effect of rTMS interference on regional cortical function, they analysed rTMS-induced errors in performing the movement sequences. Stimulation over the supplementary motor area caused errors only in the complex sequence, while stimulation over the primary motor area caused errors in both the scale and complex sequences, and stimulation over other positions (e.g. 10–20 positions: F3, F4, FCz, P3 or P4) did not interfere with overlearned sequence performance at all. Stimulation over the supplementary motor area interfered with the organization of elements in the complex sequence of movements that followed the stimulus, with error induction occuring approximately 1 s later than with stimulation over primary motor cortex. These findings are in keeping with recent results in non-human primates [39] indicating a critical role of the supplementary motor area in the organization of forthcoming movements in complex motor sequences that are rehearsed from memory and fit into a precise timing plan. The results of the Pascual-Leone et al. [34] and Gerloff et al. [38] studies indicate that the prefrontal cortex appears to be important (relative to the supplementary motor area) for the implicit encoding of a sequence of movements, but once the movement sequence becomes overlearned and can be explicitly retrieved, the supplementary motor area appears to play a more important role in the retrieval and production of the same sequence.

A large number of studies, reviewed elsewhere in this issue of Neuropsychologia, have demonstrated TMS modulation of memorized sequences of saccades and point to another form of visuomotor procedural memory which is susceptible to TMS manipulation [28, 40, 41].

5.4. Semantic memory

A recent study by Flitman et al. [5] indicates that aspects of semantic memory can also be studied using rTMS. In this study, subjects received rTMS over frontal and parietal sites in both hemispheres during picture-word verification and feature-detection tasks. Subjects were required to press one key if the word matched the picture or another key if it didn't. Applying rTMS over either left hemisphere site significantly impaired accuracy in the picture-word verification condition. Word frequency data indicated that retrieving words of lowest frequency was more likely to be interfered with by rTMS. This finding suggests that selected cognitive architecture parameters such as frequency of item exposure can be systematically interfered with by rTMS application which points to its potential usefulness in uncovering the organizing principles of semantic memory at a local cortical level. Using rTMS in this manner can complement func-

tional neuroimaging and lesion studies that have as their goal a description of the network of local regions contributing to semantic knowledge representation and access [42, 43].

6. Facilitatory effects and therapeutic studies

Pascual-Leone et al. [44] studied the effects of rTMS applied to motor cortex on performance on the serial reaction time task, a measure of visuomotor learning which was administered to six medicated patients with Parkinson's disease (PD) and 10 age-matched controls. In normal subjects, subthreshold 5 Hz rTMS did not significantly change choice reaction time, slightly shortened movement time, but increased the error rate. In the PD patients, rTMS significantly shortened choice reaction time and movement time without affecting the error rate. These tantalizing results suggest that subthreshold rTMS over motor cortex may improve certain aspects of motor learning performance in PD patients and might be a useful adjunctive therapy.

Studies of the effect of rTMS at different frequencies on the excitability of the motor cortex suggest the possibility of manipulating neural activity in ways that might prove beneficial in some conditions. For instance, Chen et al. [45] have shown that 15 min of rTMS at 1 Hz produces long-lasting depression of motor-evoked potentials. In contrast, others have produced increases in excitability with very brief periods of 5-25 Hz rTMS. Advantage of these differential effects has been taken in treatments aimed at correcting imbalances of cortical activity. McCann et al. [46] have successfully employed 1 Hz stimulation to treat post-traumatic stress disorder where compulsive retrieving of traumatic memories is accompanied by evidence of medial frontal and mesial temporal hyperactivity on PET scanning. Others have used high-frequency rTMS to improve mood in depression where prefrontal activity is reduced [7]. These studies suggest a possible role for rTMS in the treatment of learning and memory disorders—perhaps by modulating cortical networks to increase item accessibility.

7. Animal studies

Recent animal research using TMS has attempted to identify the direct neuronal effects of rTMS on learning and memory. Wang et al. [47] used a system capable of recording relatively localized rTMS evoked trains of complex spikes in rodent auditory cortex. Low rate rTMS from 1–10 Hz produced a frequency dependent increase in spike rate. Iterations of rTMS resulted in long-term potentiation (LTP)-like, and more durable long-term depression (LTD)-like, changes in evoked spike rate. These findings suggest that the effects of rTMS on human learning and memory have a basis in well-studied basic neuronal processes. Likewise, Kling et al. [48] studied rats who were allowed to drink distinctively flavored water and later received an IP injection of LiCl. In phase 1, between drinking and the onset of mild malaise, the experimental group of rats received TMS of the head while controls received an equivalent amount of stimulation of the back. Later, when the flavored water was again presented, the experimental rats exposed to TMS drank 10–15% more indicating that they had forgotten to some extent that the flavor was associated with illness. In phase 2, the procedure was repeated with a different distinctive flavor and again the experimental rats drank more on the test day. In phase 3, all rats received stimulations of the back between tasting and the illness which did not interfere with the establishment of a new taste aversion. Histological examinations revealed no visible pathology. The results indicated that TMS can cause a mild retrograde memory disruption, but there was no evidence for any TMS-induced gross structural change in the brain causing such a memory deficit. On the other hand, Yamada et al. [49] found no effects of rTMS in three monkeys performing a delayed response task which required spatial short-term memory.

8. Summary

Repetitive TMS has a modest, but reversible, negative effect on all components of memory depending on the site, timing and intensity of stimulation. The site effects are compatible with what was previously known about the location of memory processes in the brain. The effects of timing of stimulation have been little studied but Grafman et al.'s [32] study demonstrated that temporal lobe rTMS was more effective in diminishing long term memory when applied at the 0 ms latency whereas the effects of frontal lobe stimulation appeared at longer rTMS latencies indicating that timing can help dissociate the temporal versus frontal lobe contributions to learning and memory. At least in some cases of visuomotor learning, single-pulse TMS can help chart the time course and cortical topography of neuroplastic cortical map changes that correspond to learning. There is little evidence of the facilitating effects of rTMS on learning and memory to date. However, data from the treatment of psychiatric disorders suggest that appropriately targeted rTMS at the right settings might have beneficial effects upon learning and memory in some neurological disorders.

9. Discussion

Validation of the clinical and scientific usefulness of using TMS to study learning and memory processes will come when its use can be shown either to advance basic knowledge about the neuropsychology of learning and memory processes or to have a significant impact upon

the clinical care of patients with learning and memory disorders. The results we have reviewed in this article indicates that rTMS may have potential clinical application in patients with epilepsy in whom it is relevant to identify the lateralization of verbal memory. Another clinical application may be in the use of single-pulse TMS to identify changes in motor output maps during training to improve visuomotor learning and memory processes following a stroke or other neurological insult. Another potential clinical application may come from attempts to use rTMS to facilitate various aspects of memory performance. From a research perspective, TMS has demonstrated site and time-specific effects primarily in interfering with explicit retrieval of episodic information from long-term memory. This observation suggests that TMS can be used to help plot the 'cortical' time course of processes concerned with encoding information into long-term storage [32]. Since rTMS has both local cortical and some distant cortical and subcortical effects [18, 50], it may even be possible to transiently modulate the functions of the hippocampus and related structures during memory performance. There is some evidence that rTMS may also have a role in modulating retrieval from semantic memory as evidenced by response-time and accuracy changes post-rTMS [5, 51]. To date there has been no published study investigating the effects of rTMS on implicit memory or priming processes.

Given these findings and promising new avenues of research, the introduction of TMS as an additional tool of cognitive neuroscientists is complete. It remains for subsequent studies to determine the precision of its effect on learning and memory and whether it will lead to new clinical applications or aid in the effort to conceptualize the basic cognitive and neural processes involved in learning and memory.

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