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Transcranial magnetic stimulation and neuroplasticity

Alvaro Pascual-Leone[a,b,*], Francisco Tarazona[b], Julian Keenan[a], Jose M. Tormos[b], Roy Hamilton[a], Maria D. Catala[b]

[a] *Laboratory for Magnetic Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA, USA*

[b] *Unidad de Neurobiologia, Departamento de Fisiologia, Universidad de Valencia and Instituto Cajal, Consejo Superior de Investigaciones Cientifica, Spain*

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Abstract

We review past results and present novel data to illustrate different ways in which TMS can be used to study neural plasticity. Procedural learning during the serial reaction time task (SRTT) is used as a model of neural plasticity to illustrate the applications of TMS. These different applications of TMS represent principles of use that we believe are applicable to studies of cognitive neuroscience in general and exemplify the great potential of TMS in the study of brain and behavior. We review the use of TMS for (1) cortical output mapping using focal, single-pulse TMS; (2) identification of the mechanisms underlying neuroplasticity using paired-pulse TMS techniques; (3) enhancement of the information of other neuroimaging techniques by transient disruption of cortical function using repetitive TMS; and finally (4) modulation of cortical function with repetitive TMS to influence behavior and guide plasticity.

1. Introduction

A growing body of evidence from animal models and neurophysiologic and neuroimaging studies in humans, supports the notion that the central nervous system is capable of change and adaptation throughout life (for recent reviews see [4, 16]. While the developing nervous system seems more capable of modification, dynamic, plastic changes can be documented in the adult nervous system as well. Unmasking of existing connections, shifting synaptic weighting, even sprouting of new dendritic connections and formation of new synapses seem possible [16]. The central nervous system is a rapidly adapting, dynamically changing system in which modification is driven by afferent input, efferent demand, environmental and behavioral influences, and functional significance. Plastic changes seem to underlay the acquisition of new skills, the adaptation to new contexts and the recovery of function after injury. However, if plasticity is indeed a fundamental property of the central nervous system throughout life, then plastic changes may not necessarily represent a behavioral benefit for a given subject and our challenge is to modulate neural plasticity for the optimal behavioral gain. The picture of the nervous system that is emerging is rather close to the intuitions of Santiago Ramón y Cajal who in 1904, in the 'Textura del sistema nervioso del hombre y de los vertebrados' wrote:

> "...the work of a pianist...is inaccessible for the untrained human, as the acquisition of new abilities requires many years of mental and physical practice. In order to fully understand this complicated phenomenon it is necessary to admit, in addition to the strengthening of pre-established organic pathways, the establishment of new ones, through ramification and progressive growth of dendritic arborizations and nervous terminals... Such a development takes place in response to exercise, while it stops and may be reversed in brain spheres that are not cultivated."[1]

Transcranial magnetic stimulation (TMS) can be used in different ways for studies of neuroplasticity [4, 11–13, 21, 30]. These different applications relate to four principal types of studies: (1) demonstration of plastic changes; (2) elucidation of mechanisms underlying plasticity; (3) providing functional information to findings of neuroplasticity with other neuroimaging techniques; and (4) modulating neuroplasticity to enhance it or reduce it in order to influence behavioral consequences.

TMS can be applied in single, focal pulses to different

* Corresponding author. Tel.: 001 617 667 02 03; fax: 001 617 975 53 22; e-mail: apleone@bidmc.harvard.edu.

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scalp positions over the motor cortex while recording motor evoked potentials or force pulses [11, 39]. This methodology allows the generation of cortical output maps serially in the same subject and the correlation with measures of functional capacity. This can be used to demonstrate the reorganization of cortical motor outputs following transient immobilization, acquisition of new motor skills, amputation, or recovery from CNS injury [4, 18, 22, 26, 27].

Short trains of repetitive TMS (rTMS) at frequencies of up to 25 Hz can be used to disrupt naming or speech output, generate maps of language function and determine hemispheric language dominance [6, 20]. Applied to stroke patients, this technique might be useful to demonstrate patterns of recovery from aphasia. Similarly, rTMS can be used to study plastic reorganization in other cortical areas following injury, such as the functional reorganization of the occipital cortex following peripheral blindness [14].

Paired-pulse TMS techniques [17] can be used to study intracortical excitability and the level of activity of different cortico-cortical connections and neurotransmitter systems. Such studies can illuminate the mechanisms of modulation of motor cortical representation during the acquisition of new skills or transient deafferentation [44].

Repetitive TMS can be used to transiently disrupt areas of activation on neuroimaging studies in order to establish their functional significance. For example, early blind subjects show activation of the occipital cortex in PET and fMRI during tactile Braille reading [34]. This finding suggests cross-modal plasticity. Transient disruption of the occipital cortex with rTMS results in profound worsening of the Braille reading skill, thus providing a true functional insight to the neuroimaging findings [5]. This combination of TMS with other neuroimaging modalities promises to enhance the information from PET, fMRI, or EEG mapping studies as it may provide causal information between a pattern of brain activation and a given behavior (see Paus in this issue).

Finally, rTMS can enhance or decrease cortical excitability and thus potentiate or reduce neuroplastic processes [29]. This application of rTMS might be capable of speeding up recovery from stroke, reducing the consequences of immobilization, or enhancing acquisition of new skills.

In the present paper we will use studies on the neural substrates of implicit motor learning in the serial reaction time task (SRTT) to illustrate these different applications of TMS in the study of neuroplasticity.

2. Serial reaction time task (SRTT)

The SRTT (Fig. 1) is a test of procedural learning in which both implicit and explicit learning strategies can be explored. We have used a variation of the SRTT originally introduced by Nissen, Bullemer and Willingham [19, 41]. The subject sits in front of a computer screen and a keyboard with four clearly marked response keys. The subject is asked to rest the index, middle, ring, and little fingers of the hand to use on the appropriate response keys in preparation for the task. An asterisk appears in one of four positions that are horizontally spaced on the screen and aligned above the response keys. The subject has to push with one finger, as fast as possible, the key aligned with the asterisk that appears. The asterisk does not disappear until the correct button has been pushed, upon which the next stimulus appears.

The test is ordered in blocks of trials. First, the subject completes a series of practice blocks that are discarded from further analysis but serve to familiarize the subject with the task. Then, the subject completes one or more blocks, in which the visual cues appear in pseudo-random order, and performance is recorded as baseline. Thereafter, depending on the specific experiment, the subject completes a series of additional blocks in which the cues are presented in a repeating sequence (Fig. 1). The length of the repeating sequence may vary depending on the experiment. In each block the sequence is generally repeated 10 times. The subject is not told about the repeating character of the sequence and does in fact not recognize it until having completed a number of blocks. Nevertheless, despite the lack of conscious recognition of the repeating character of the trials, the subject's response times show a progressive shortening. This shortening in response time is an indirect measure of implicit, procedural learning. Eventually the subject becomes aware of the repeating sequence of the trials and continues to improve the response times, though now presumably driven by explicit learning strategies. Finally, the subject completes one final block in which the visual stimuli are again presented in pseudo-random order. The difference in response time between the last repeating block and this final random block provides a second measure of procedural learning.

3. Mapping plastic changes

Maps of motor cortical output to different hand and forearm muscles can be obtained using single pulse, focal TMS serially during the performance of the SRTT [22]. Performance in the task can then be compared with the modulation of the cortical output maps to muscles involved in the task and to uninvolved, neighboring muscles.

Motor cortical output maps to the forearm flexor muscles of the (right) hand were generated using a small 8-shaped coil (each wing 4 cm in diameter) and a Cadwell magnetic stimulator (Cadwell Inc., Kennewick, WA, U.S.A.). Stimuli were applied to a 5×5 grid of scalp

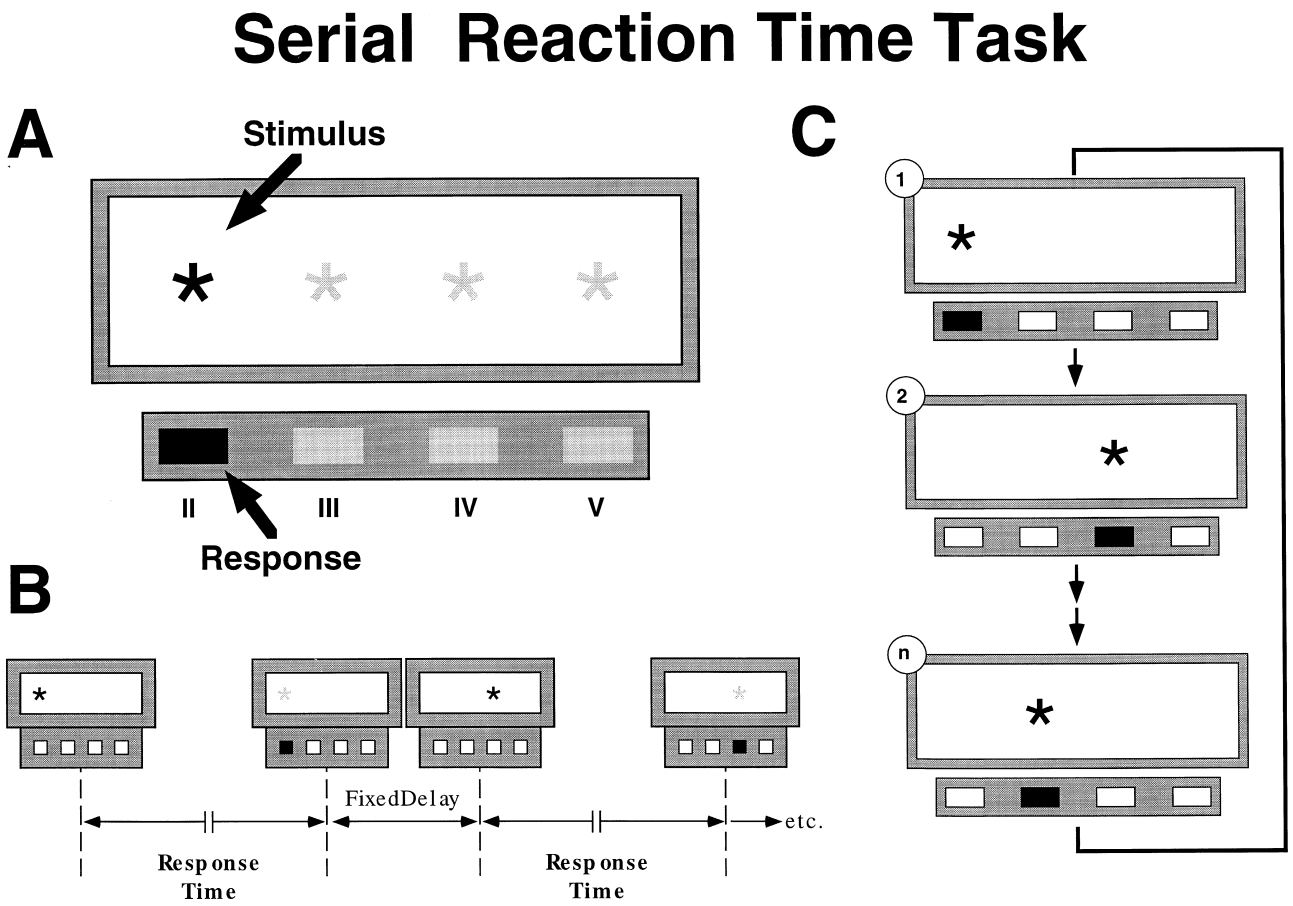

Fig. 1. Schematic summary of the serial reaction time task (SRTT). A visual stimulus is presented on the computer screen and the subject has to respond as fast as possible by pushing the appropriate response key using the appropriate digit (A). Upon correct response the visual stimulus disappears and the next visual stimulus appears, often after a predefined delay (B). If the subject pushes the incorrect response key, the visual stimulus does not disappear and the subject has to self-correct. Unknowingly to the subject the visual stimuli are presented in a repeating sequence (C). Despite lack of awareness of this repeating sequence, the subject's response times shorten providing an indirect measure of implicit procedure learning.

positions 1 cm apart over the left sensorimotor cortex. The coil orientation was held constant, the coil was applied to the different scalp positions, and each scalp position was stimulated five times. Stimulation intensity was kept at 10% above the subject's motor threshold intensity. Motor evoked potentials (MEPs) induced by TMS were recorded using surface EMG electrodes taped to the skin over the muscle. The mean amplitude for the MEPs induced by TMS from each scalp position was calculated and plotted against the scalp position as a contour map. Shown in Fig. 2 is a thresholded bubble map with the scalp positions projected onto the subject's 3-dimensional reconstructed MRI brain image (Fig. 2).

This TMS mapping study [22] demonstrates an enlargement of the motor cortical output map to the contralateral muscles involved in the task during the phase of implicit learning. The enlargement of the motor cortical output to the involved muscles cannot be demonstrated for uninvolved muscles. For example, the forearm finger flexors (Fig. 2) or the first dorsal interosseus muscle that participates in the movement of the index finger and are required for the SRTT task reveal the modulation of the output maps. However, the motor cortical output map to the abductor muscle of the thumb, which is not used for the SRTT, task does not change.

As mentioned, when the subject becomes aware of the repeating nature of the stimuli an explicit search strategy is likely to be engaged. During this time in which both, implicit and explicit learning is probably taking place, the response times continue to shorten but the cortical output maps tend to plateau. Eventually, as the subject learns the full repeating sequence of stimuli, the performance becomes primarily driven by the explicit knowledge. At this point, there is a rapid reduction of the motor cortical output maps towards the baseline topography (Fig. 2). This return of the maps towards their baseline topography suggests that as a motor sequence is explicitly learned, the contribution of the motor cortex is attenuated and other brain structures assume more active roles in the execution of the task. It seems that flexible short-term modulation of cortical outputs takes place during skill acquisition that might in fact be critical in the event-

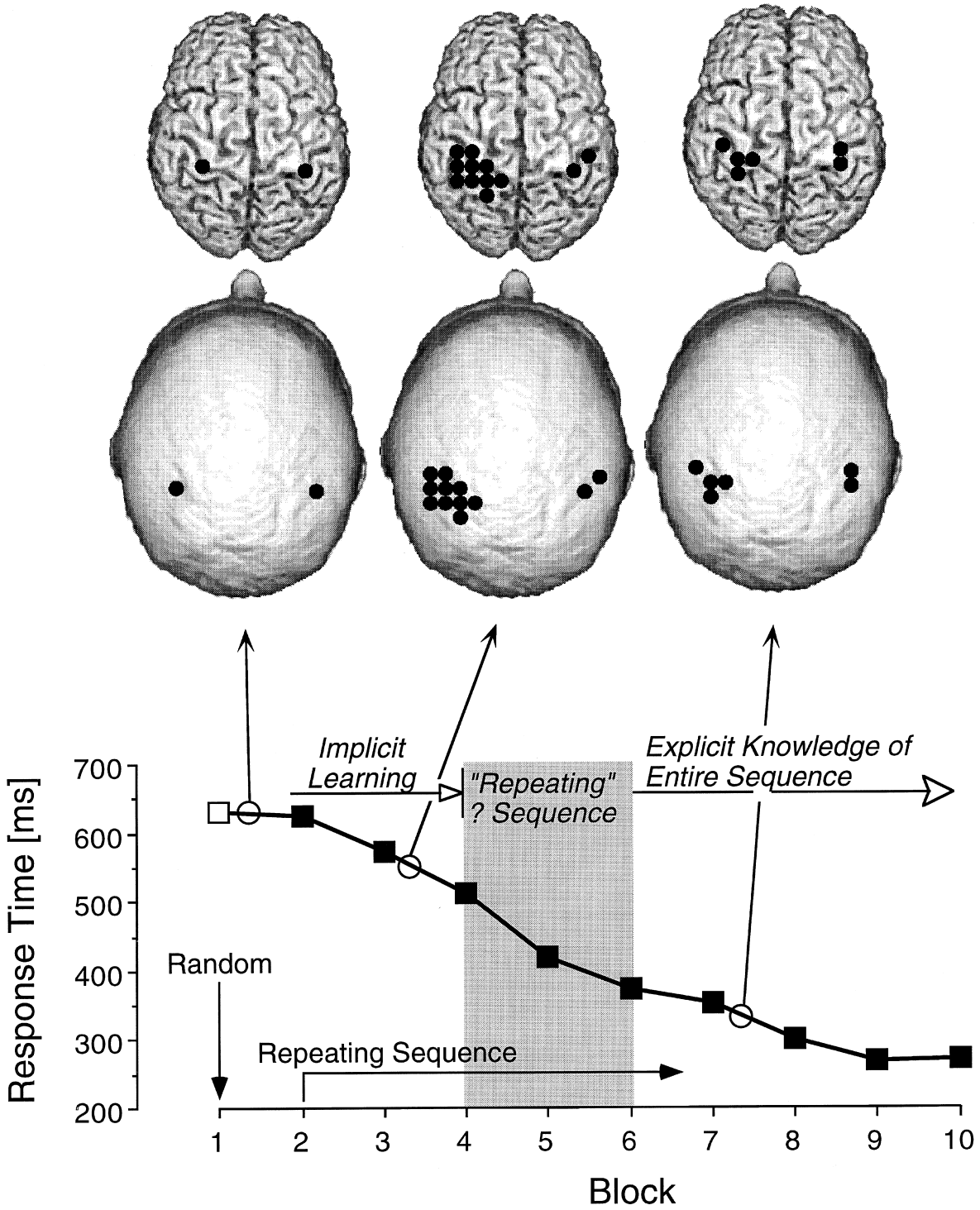

Fig. 2. Modulation of the cortical motor output maps in the course of the serial reaction time task (modified from [23]). The subject completes 10 blocks of the task. During blocks of repeating presentation of the visual stimuli (blocks 2–10), the subject shows a progressive reduction in response time (learning). Initially the subject is unaware of the repeating nature of the stimuli (blocks 2–4, 'implicit learning'). During this time there is a marked increase in the cortical motor output map for the forearm finger flexors on the right hand used in the task. In blocks 4–6 the subject knows that there is a sequence but does not know what. Presumably the subject uses both implicit and explicit learning strategies at that point. After block 6, the subject the entire sequence ('explicit knowledge'), performance is likely driven by explicit learning, but there is continued performance improvement. However, at this point, the cortical output maps show a rapid return to baseline.

ual development of more permanent structural changes in the intracortical and subcortical networks as the skill becomes more and more overlearned and automatic. These findings with TMS are in agreement with similar motor learning studies using other brain imaging techniques such as fMRI or PET [8–10, 15, 35, 36, 42].

This type of TMS mapping study can be applied to the identification of neuroplasticity also in the context of other forms of motor learning [26], adjustment to blindness and acquisition of the Braille reading skill [14], or recovery from peripheral or central nervous system injury [4].

4. Studying the physiology underlying plastic changes

Rapid modulation of motor cortical outputs in the context of skill acquisition is likely the result of unmasking of existing connections [2, 3, 16]. Decreased inhibition or increased synaptic efficacy of existing neural circuits might be considered as possible mechanisms for this rapid plasticity. In either case, it is hypothesized, that this kind of rapid cortical plasticity ought to result in changes in intracortical excitability that might be demonstrable using the paired-pulse TMS technique [17].

A first, conditioning stimulus is applied, followed at a variable interval, by a second, test stimulus. The intensity of both stimuli influences the effects as different circuits are recruited by different intensities of stimulation. The interstimulus interval (ISI) influences the results as the time constant of each activated circuit may differ. At very short ISIs (< 1 ms) it is possible to study neural time constants of the stimulated elements; at ISIs of 1–4 ms it is possible to investigate interactions between I-wave inputs to cortico–spinal neurons, and at ISIs of 1–20 ms it is possible to investigate cortico–cortical inhibitory and facilitatory circuits. All these effects appear to be cortically mediated [17, 38] and intracortical inhibition and facilitation appear dependent on the activation of separate circuits [46]. Medications that enhance GABAergic activity have been shown to markedly decrease the degree of cortico–cortical facilitation evoked by paired TMS stimuli at ISIs of approximately 8–12 ms [45]. In Parkinson's disease, the dopamine deficiency is associated with reduced cortico–cortical inhibition at short ISIs (< 5 ms) [1, 33], while dopaminergic drugs enhance cortico–cortical inhibition [1, 32, 33, 43].

Ziemann et al. [44] have recently elegantly demonstrated the utility of the paired-pulse TMS technique in the study of the mechanisms of short-term cortical plasticity in a deafferentation paradigm [2, 3]. In addition, their study illustrates the possibility of modulating cortical excitability and thus neuroplasticity with rTMS. Transient forearm deafferentation was induced by ischemic nerve block in healthy volunteers. Plastic changes in the motor cortex contralateral to the deafferented forearm were probed with paired-pulse TMS to the biceps brachii muscle proximal to the level of deafferentation. Ischaemic nerve block alone induced a moderate increase in the size of the motor evoked potentials in the biceps, but no changes in intracortical inhibition or facilitation. However, rTMS at 0.1 Hz to the motor cortex contralateral to the ischaemic nerve block reduced intracortical inhibition and increased intracortical facilitation markedly potentiating the plastic changes induced by the ischemic nerve block alone. These findings indicate that the deafferented motor cortex becomes modifiable by inputs that are normally subthreshold for inducing changes in excitability. The deafferentation-induced plastic changes can be up-regulated by direct stimulation of the 'plastic' cortex and down-regulated by stimulation of the opposite cortex, probably through inhibitory transcallosal connections [44].

Following the example of Ziemann et al. [44], in the setting of the SRTT, repeated studies of intracortical excitability with the paired-pulse TMS technique may enhance our understanding about the intracortical mechanisms responsible for the modulation of motor cortical outputs described above.

5. Adding function significance to neuroimaging studies

Functional neuroimaging studies do not define the role of a given structure for a specific behavior, they simply establish an association between activity in a given neural structure or network and the performance of a task. Repetitive TMS can transiently block the function of a specific cortical structure and thereby allows the definition of a causal link between behavior and regional brain function [24]. This form of TMS application generates 'virtual lesion patients'. The study of subjects with such transient and reversible 'lesions' has advantages over the study of patients with brain injuries. First, the study can be repeated and its subject can therefore be retested and serve as its own control. Second, reversible, transient lesions limit the influence of adaptative changes and functional readjustments that take place following structural brain injuries.

In this form of application, rTMS might be viewed as a noninvasive counterpart for human studies of cortical faradization or of local cortical cooling in animals. Cohen et al. [5] have recently illustrated this form of applying rTMS in cognitive neuroscience in the study of cross-modal plasticity in early blind Braille readers (Fig. 3A). Studies with short trains of rTMS can be viewed as first steps in the exploration of causal links between cortical activation and behavior addressing topographical questions and eliminating questions regarding temporal variables. Follow-up studies can then explore the question of the timing of the contribution of a given cortical area to a given behavior. Hamilton and Pascual-Leone [14] have

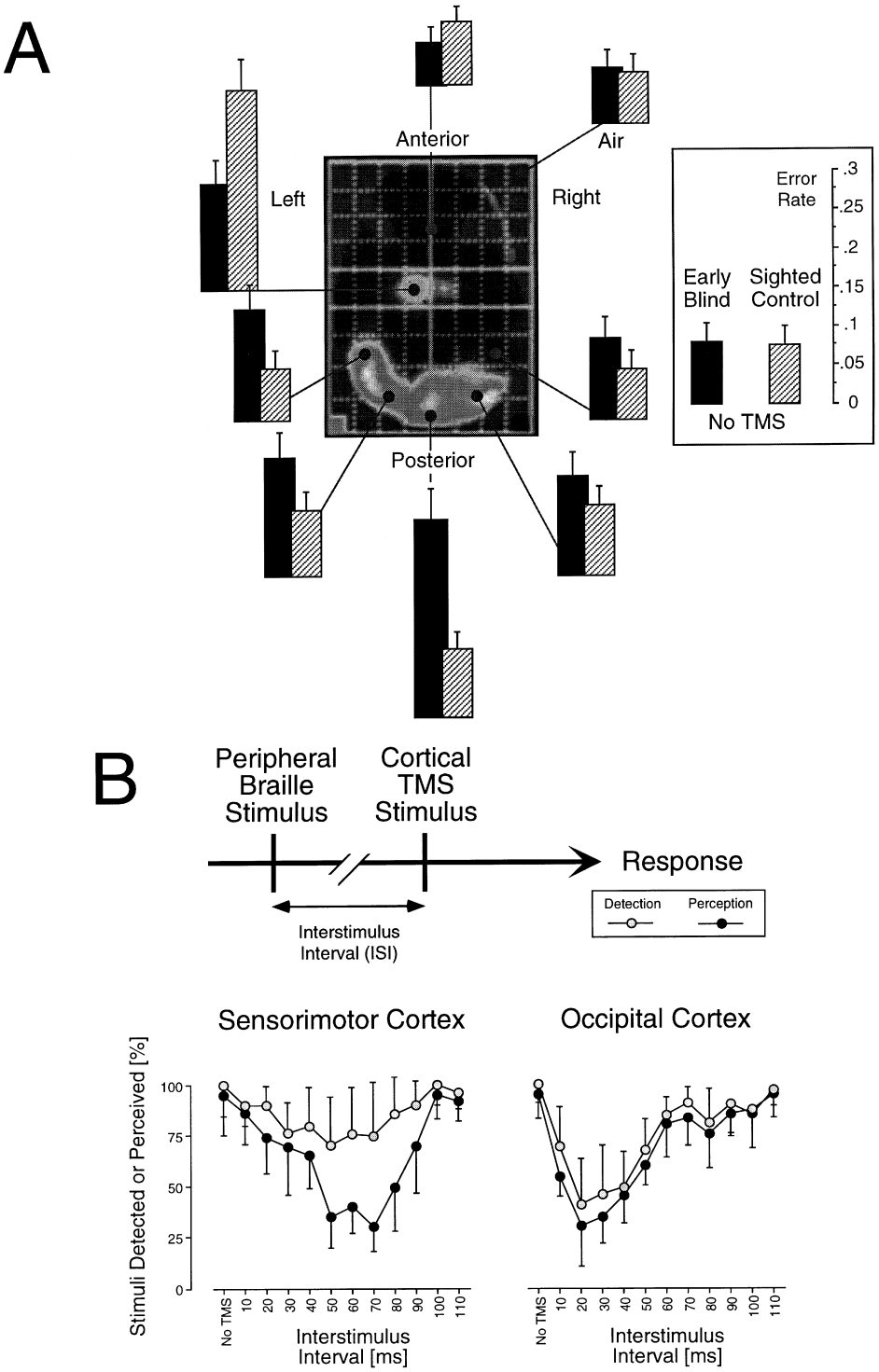

Fig. 3. Effects of TMS on tactile Braille reading ability in sighted control and early blind subjects. Effects of trains of repetitive TMS inducing errors in tactile Braille reading depending on cortical target expand the information derived from PET studies showing activation of sensorimotor and occipital cortex during Braille reading (A, modified from [5, 35]). Effects of single TMS stimuli to occipital or sensorimotor cortex on tactile Braille symbol discrimination depending on the interval between the peripheral Braille stimulus to the right index finger pad and the cortical stimulus (B, modified from [14]).

illustrated this possibility in the study of the occipital cortical contribution to tactile Braille reading in early blind subjects (Fig. 3B).

Using this approach of 'induction of virtual patients' with rTMS, we have studied the role of the dorsolateral prefrontal cortex in the SRTT [31]. Functional neuroimaging studies of the pattern of neural activation during studies of procedural learning suggest that among

other cortical regions, the dorsolateral prefrontal cortex is critical [8–10, 15, 35, 36]. However, such studies cannot resolve the specific role of the dorsolateral prefrontal cortex. For example, activity of the dorsolateral prefrontal cortex might be related to the acquisition of the explicit knowledge or participate in implicit components of procedural learning.

Normal subjects completed several blocks of the SRTT using only one hand with or without concurrent rTMS. In this version of the SRTT subjects were not specifically asked whether the cues were presented in a random or repeating order at any point during the task. Blocks consisted of 120 trials, 10 repetitions of a 12-item repeating sequence. In order to transiently disrupt their function, rTMS was applied over the supplementary motor area or over the dorsolateral prefrontal contralateral or ipsilateral to the hand used for the test. TMS was delivered with a Cadwell High Frequency Magnetic Stimulator (Cadwell Inc., Kennewick, WA, U.S.A.) equipped with a water-cooled, eight-shaped coil. Each loop of the coil measures approximately 7.5 cm inner diameter and the intersection of the two loops measures 3.5×1.5 cm. For stimulation of the dorsolateral prefrontal cortex the coil was centered on the lateral convexity, 5 cm rostral to the optimal scalp position for the abductor pollicis brevis muscle. The optimal scalp position was taken to represent the localization of the primary motor cortex [40]. For stimulation of the supplementary motor cortex the stimulation coil was centered, along the mid-sagittal line, 5 cm rostral to the optimal scalp position for activation of the anterior tibialis muscles. For stimulation of the dorsolateral prefrontal cortex, the stimulation coil was held tangentially to the scalp with the current following parallel to the sagittal axis. For stimulation of the supplementary motor area, the coil was oriented so that current flow was perpendicular to the head's sagittal axis. Stimulation was delivered in trains of 5 Hz frequency that started at the beginning of each block of trials and continued for a maximum of 60 s according to the safety recommendation [25, 38]. In all cases, this was sufficient to assure stimulation from the beginning until completion of the block. In order to guarantee that this was the case, we varied the SRTT eliminating the delay between subject's response and appearance of the subsequent stimulus.

In the no-TMS condition all subjects showed a progressive decrease in response time during the four blocks with a repeating sequence and a significant increase in response time from the last block with a repeating sequence to the block with randomly presented cues. Both of these changes are measures of procedural learning [19, 41]. During the different rTMS conditions, we found no significant differences in response time and error rate in the last block of each set in which visual cues were randomly ordered. This ruled out a rTMS effect on response execution regardless of stimulation site. However, rTMS had profound, position specific effects on task performance during the blocks in which visual cues were presented in a repeating sequence. Stimulation to the contralateral dorsolateral prefrontal cortex markedly impaired procedural, implicit learning, as documented by the lack of significant change in response times during the task (Fig. 4). Stimulation over the other areas did not interfere with learning (Fig. 4).

These results support the notion of a critical role of dorsolateral prefrontal structures in learning of motor sequences and are in agreement with results of patients with traumatic or cerebrovascular lesions of the dorsolateral prefrontal cortex [23]. Of note, is the fact that blocking of the contralateral prefrontal cortex affected the reduction in response time during blocks of repeating visual stimuli while the subjects were unaware of the repeating nature of the trials. Therefore, the inference is that the dorsolateral prefrontal cortex is needed for implicit procedural learning.

6. Modulating neuroplasticity and behavior with rTMS

During the implicit, procedural learning phase, cortical excitability increases in the motor cortex for the motor outputs to muscles involved in the SRTT task. Honda et al. (unpublished data) found in a recent PET study of implicit learning during the SRTT a correlation between response time shortening and motor cortical activity. Results of electroencephalographic coherence studies [42] and of the TMS mapping study presented above [22] support the same notion. This increase in cortical excitability might be necessary for skill acquisition. If this is so, external modulation of motor cortical excitability might influence the rate of procedural learning. In the present, previously unpublished experiment, we investigated whether modulation of motor cortical excitability with rTMS prior to performance of the SRTT can influence implicit motor learning.[2]

rTMS can increase or decrease cortical excitability depending on the stimulation parameters [29]. These modulatory effects of cortical excitability can be documented by combining TMS with a variety of neuroimaging and neurophysiologic techniques. There seems to be substantial interindividual variability on the effects of different rTMS parameters, such that the same rTMS settings might result in opposite modulation of cortical excitability in different subjects. On the other hand though, there seems to be a fair amount of intraindividual stability of the effects.

Subjects completed three SRTT blocks in each of which a 12-item sequence was repeated 10 times. Then, they

[2] These data are part of the doctoral thesis work of Francisco Tarazona, M.D. presented during June 1998 at the University of Valencia, Spain.

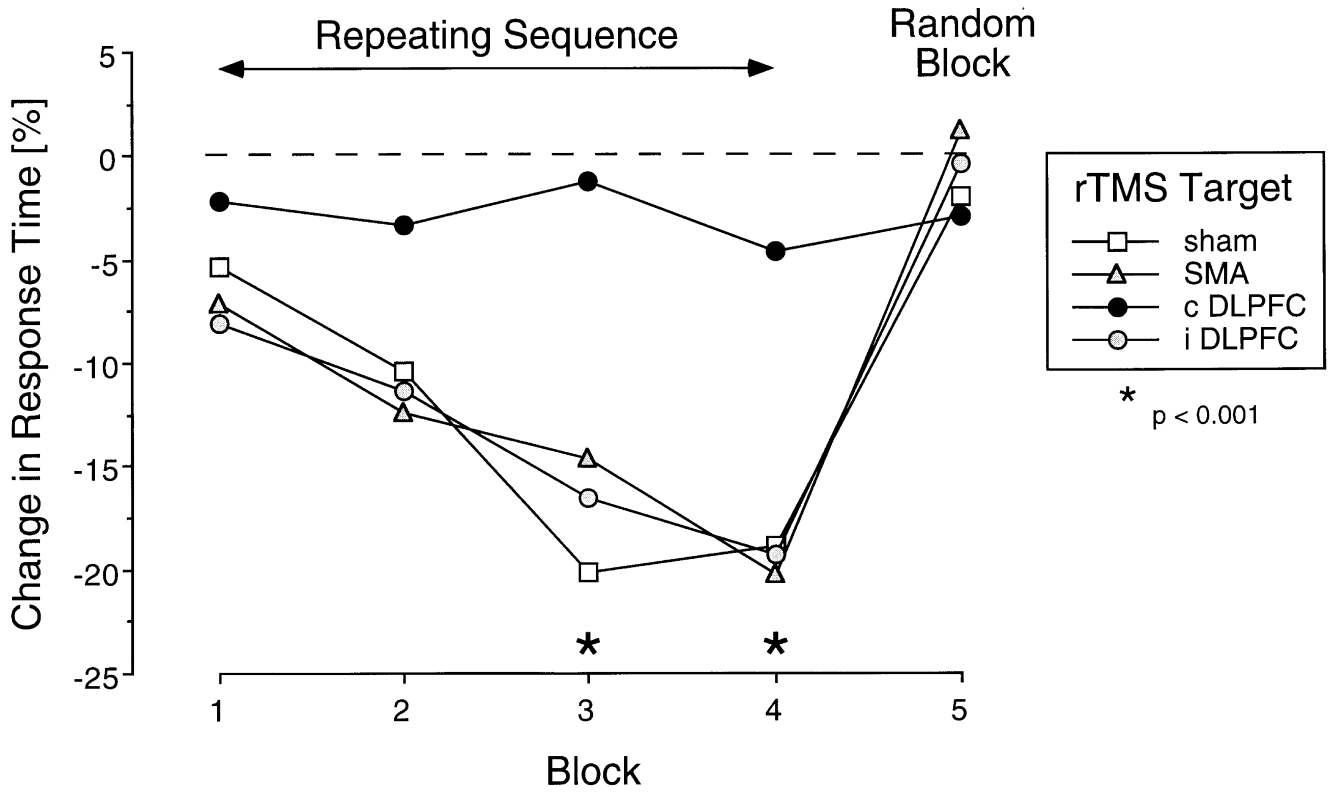

Fig. 4. Effects of repetitive TMS to different cortical targets on the shortening of response time in the serial reaction time task (modified from [32]). Graph displays the average response time in all subjects during 4 blocks of a repeating sequence (blocks 1–4) and a final block of random presentation of visual stimuli (block 5). Response times are expressed as percentage change from a previous, baseline block of the task in which stimuli were presented in random order. Note the lack of change in response time during rTMS to the contralateral dorsolateral prefrontal cortex (c DLPFC). Targets of rTMS 'sham' = coil angulated away from the head at 90°; 'SMA' = supplementary motor area; 'c DLPFC' = contralateral dorsolateral prefrontal cortex; 'iDLPFC' = ipsilateral dorsolateral prefrontal cortex.

underwent either sham, 1 Hz, or 10 Hz rTMS at subthreshold intensity. Finally, they completed three more SRTT blocks with a different repeating sequence. Both 12-item sequences were equivocal and their order (before or after rTMS) was random and counterbalanced across subjects. In one of the SRTT versions the stimuli were numbers (1, 2, 3, or 4) presented in the middle of the screen. In the second SRTT version the sequence was different and in addition stimuli were circles presented in one of four horizontally spaced positions on the computer screen. We elected to use two different types of stimuli in order to minimize transfer of learning from one SRTT version to the next.

We studied 21 normal, right-handed subjects (12 men and 9 women, mean age 26.3 years) randomly assigned to receive either 1 Hz, 10 Hz, or sham rTMS. The effects of rTMS on cortical excitability were tested in all subjects prior to their participation in the study by applying rTMS to the motor cortex and measuring cortical excitability before and after the rTMS trains. In all subjects recruited for the study, sham rTMS did not affect motor cortical excitability, while 1 Hz rTMS reduced it and 10 Hz rTMs enhanced it [29]. We do not know if rTMS to the dorsolateral prefrontal cortex exerts the same effects on cortical excitability as in motor cortex. Nevertheless, we assume a correlation between the rTMS effects on cortical excitability of different cortical areas.

TMS was applied with a Dantec Magpro magnetic stimulator (Dantec Medical Inc., Denmark) and a focal, 8-shaped coil. All subjects were studied on two different days separated at least by one week. On one of the days, rTMS was applied to the motor cortex while on the other day it was applied to the dorsolateral prefrontal cortex. The position of the stimulation coil on the scalp was marked in all subjects with a vitamin A capsule and thereafter all underwent an anatomical MRI study in order to localize the site of stimulation in their brain. The motor cortex position did indeed target the central sulcus with a maximal error of less than 1 cm. The dorsolateral prefrontal cortical position targeted the dorsolateral prefrontal cortex in all subjects, being centered over the border between areas 9 and 46 and affecting both.

Figure 5 summarizes the results. RT in Block 1 was analyzed to determine if there was a baseline difference between the groups. A two-way factorial (rTMS condition (3) by region of stimulation (2)) was performed on

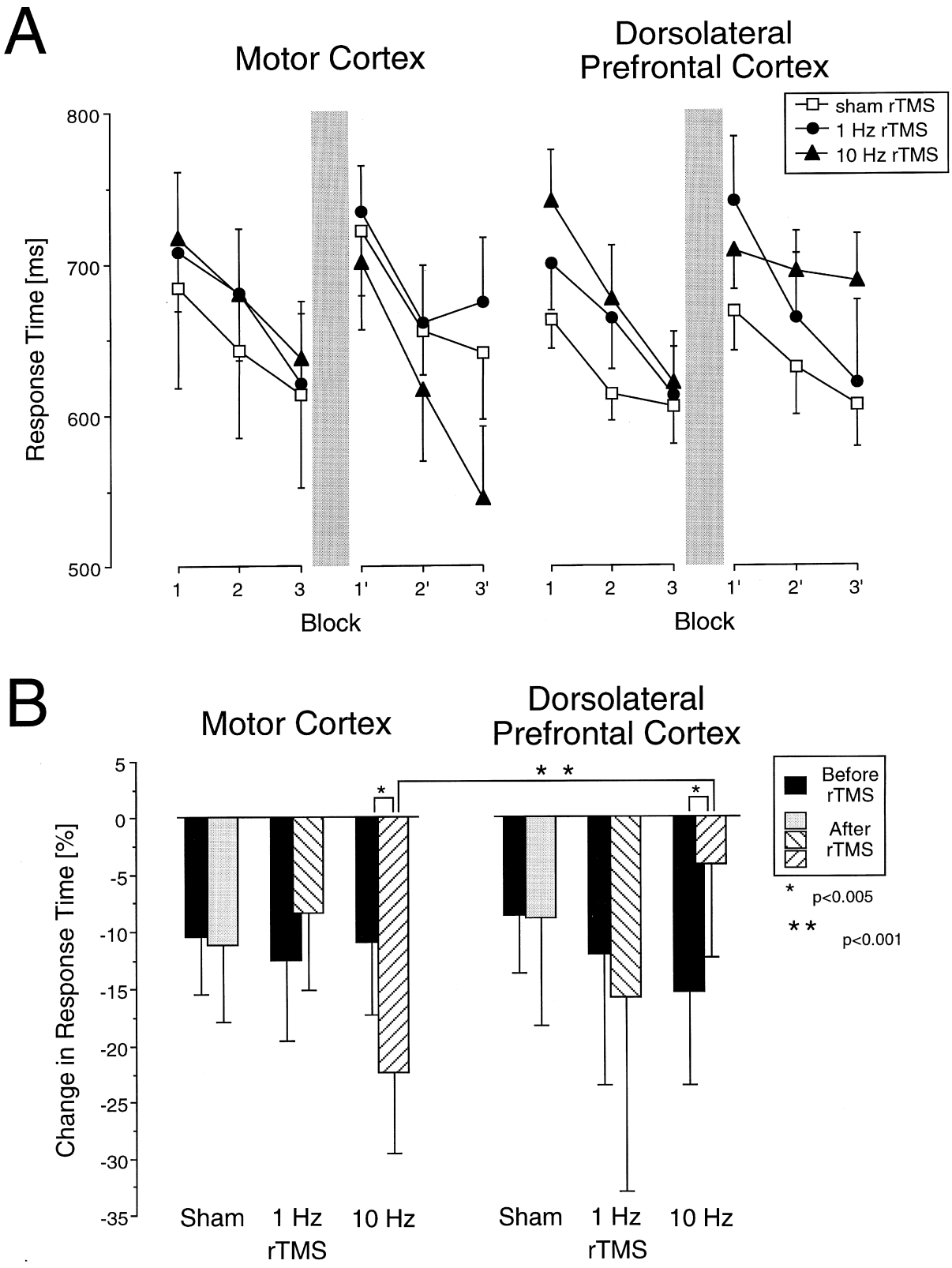

Fig. 5. Effects of modulation of excitability of motor or contralateral dorsolateral prefrontal cortex by repetitive TMS on procedural learning in the serial reaction time task. Graph A shows the average response times for all subjects during the three block before (1, 2, and 3) and after (1′, 2′, and 3′) rTMS (gray bar). The visual stimuli in all blocks were presented in a repeating sequence unknowingly to the subjects, none of which became aware of the sequential nature of the task. Repetitive TMS was applied either at 1 Hz, 10 Hz, or with the coil angulated away from the head (90°, sham). Graph B shows the change in response time from block 1 (or 1′) to 3 (or 3′) as an index of procedural implicit learning. Solid bars display the mean (±standard deviation) change in response time before rTMS. Pattern bars express the change in response time (mean ±s.d.) following rTMS (1 Hz, 10 Hz or sham) to motor or dorsolateral prefrontal cortex.

the RT scores. We found no significant interaction (F $2, 10) = 0.46, P > 0.05$) or main effects for rTMS condition (F $(2, 30) = 0.53, P > 0.05$) or region of stimulation ($F(2, 30) = 0.18, P > 0.05$). A similar analysis was performed for the error rates and no significant interaction or main effects were found. The rate of learning prior to rTMS exposure was assessed by examining the change scores from Block 1 to Block 3. We found that these scores did not differ ($F(5) = 0.43, P > 0.05$), thus ruling out baseline differences in task performance across study groups. A further analysis was performed for the first block pre-rTMS and the first block post-rTMS (Blocks 1 and 1′) in order to rule out effects of rTMS on response time independent of implicit learning. No significant difference was found between these two Blocks ($t(35) = -0.62, P > 0.05$).

Changes in RT across blocks 1 to 3 and 1′ to 3′ provide a measure of implicit learning pre- and post-rTMS respectively. To determine the effects of rTMS on changes in RT, we tested for overall differences in RT across all blocks with a three-way factorial analysis of rTMS frequency, stimulation site, and pre vs post condition. We found a significant interaction ($F(2, 10) = 5.50$, $P < 0.005$). A series of planned comparisons were then performed to determine the various effects of rTMS on RT.

First, the change scores in RT across blocks 1 (1′) to 3 (3′) were compared pre- and post-rTMS to the motor cortex. A one-way ANOVA comparing pre- and post-rTMS scores depending on rTMS condition (sham, 1 Hz or 10 Hz) revealed an overall significant interaction(F $(5, 30) = 3.55, P < 0.01$). Corrected post-hoc Bonferroni tests demonstrated that in the 10 Hz group the changes in response time were significantly greater post-rTMS than pre-rTMS ($t(10) = 2.99, P < 0.01$). The other two rTMS conditions (sham and 1 Hz rTMS) did not yield significant results.

Second, similar comparisons were carried out for the dorsolateral prefrontal rTMS group. While we found no overall significant difference, the planned post-hoc analysis revealed that the 10 Hz condition had a significantly smaller reduction in reaction time across the three SRTT blocks post-rTMS than pre ($t(10) = -2.36$, $P < 0.05$). The other two rTMS conditions were found to induce no significant differences.

A final planned comparison was then carried out comparing the motor and dorsolateral prefrontal rTMS groups and we found a significant overall interaction ($F(5, 30) = 3.62$, $P < 0.01$). A post-hoc comparison revealed that the 10 Hz group differed significantly as a function of stimulation site ($t(10) = 4.02, P < 0.005$), while the other rTMS conditions did not yield significant differences.

Error rates were analyzed in a likewise manner. All of the planned comparisons and interactions described for analysis of the RT results were completed also for the error rates and no significant differences were found in either the overall comparisons or the planned specific tests.

This experiment demonstrates that modulation of cortical excitability with rTMS can indeed influence behavior. Enhancement of excitability of the motor cortex seemed to speed up procedural learning. On the other hand, reduction of motor cortical excitability slowed down procedural learning (though this effect did not reach statistical significance). Contrary to the effects over the motor cortex, enhancement of excitability of the dorsolateral prefrontal cortex actually interfered with procedural learning suggesting that a specific level of activation is needed to obtain maximal behavioral benefit.

This experiment suggests the possibility of using rTMS in conjunction with physical, occupational, behavioral or other rehabilitative therapies in order to enhance their beneficial effects for patients recovering from brain injury. 'Preactivation' of a given cortical region prior to more traditional therapeutic interventions might help enhance their effect. Similarly, modulation of cortical excitability as an adjunct to medication treatment might offer therapeutic advantages in neuropsychiatric illnesses [7, 28, 30].

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