Interference of Left and Right Cerebellar rTMS with Procedural Learning

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Abstract

■ Increasing evidence suggests cerebellar involvement in procedural learning. To further analyze its role and to assess whether it has a lateralized influence, in the present study we used a repetitive transcranial magnetic stimulation interference approach in a group of normal subjects performing a serial reaction time task.

We studied 36 normal volunteers: 13 subjects underwent repetitive transcranial magnetic stimulation on the left cerebellum and performed the task with the right (6 subjects) or left (7 subjects) hand; 10 subjects underwent repetitive transcranial magnetic stimulation on the right cerebellum and performed the task with the hand ipsilateral (5 subjects) or contralateral (5 subjects) to the stimulation; another 13 subjects served as controls and were not submitted to repetitive transcranial magnetic stimulation; 7 of them performed the task with the right hand and 6 with the left hand. The main results show that interference with the activity of the lateral cerebellum induces a significant decrease of procedural learning: Interference with the right cerebellar hemisphere activity induces a significant decrease in procedural learning regardless of the hand used to perform the serial reaction time task, whereas left cerebellar hemisphere activity seems more linked with procedural learning through the ipsilateral hand.

In conclusion, the present study shows for the first time that a transient interference with the functions of the cerebellar cortex results in an impairment of procedural learning in normal subjects and it provides new evidences for interhemispheric differences in the lateral cerebellum. ■

INTRODUCTION

Animal models as well as neurophysiological studies in humans support the notion that the cerebellum is involved in procedural learning (i.e., the process by which repeated practice of a task results in improved performcance of that task). Neuroimaging studies have provided controversial results in this field. A PET analysis studying the modifications of regional blood flow during learning of a complex sequence of movements demonstrated a significant increment of blood flow in the anterior regions of the right cerebellar hemisphere. This activation was not directly correlated with the motor components of the task, such as frequency or speed of finger movements, supporting the hypothesis that it is specifically related to motor learning (Seitz, Roland, Bohm, Greitz, & Stone-Elanders, 1990). In a motor task very difficult to learn, in which the executive responses were not automatic, an fMRI study reported a high cerebellar activation inversely proportional to the ability in performing the task: Once learned, the task provoked a very low activation of the same cerebellar regions (Ellerman et al., 1994). In a study devoted to analyze the neural network responsible of learning of a motor sequence, Jenkins, Brooks, Nixon, Frackowiak, and Passingham (1994) showed an increase in parietal associative cortex and cerebellum PET activity during learning of new sequences. This result indicates a role of the cerebellum in those processes that make automatic a motor skill. In another PET study, changes in blood flow related to implicit learning revealed the involvement of the right ventral striatum and dentate nucleus of the cerebellum (Doyon, Owen, Petrides, Sziklas, & Evans, 1996).

On the other hand, other studies failed to reveal learning-related activations in the cerebellum (Honda et al., 1998). Seidler et al. (2002), trying to separate the effects of motor learning from changes in performance, found no cerebellar activation during the learning phase of a motor sequence-learning task. They concluded that, during the acquisition of a motor skill, the cerebellum does not contribute to sequence learning per se but rather to its expression.

The serial reaction time task (SRTT; Nissen & Bullemer, 1987) is one of the most commonly used tests to study procedural learning. In this task, the subject has to give a motor response to visual stimuli presented in random order or in sequence: The difference between

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the reaction times (RTs) recorded in the two conditions represents an index of procedural learning.

Pascual-Leone et al. (1993) reported that patients with cortical cerebellar atrophy show impairment in procedural learning analyzed through the SRTT. Using the same task, Molinari et al. (1997) demonstrated that also focal cerebellar lesions impair the ability to learn the visuomotor procedure regardless of the side of the lesion. In these patients, the impairment in procedural learning was not related to a deficit in the acquisition of declarative knowledge of the sequences, even if they could use this knowledge, acquired before the task, to improve their performance.

In another study, patients with focal cerebellar lesions did not acquire procedural learning when performing the task with the hand ipsilateral to the lesion, but showed normal learning with the contralateral hand (Gómez-Beldarrain, García-Moncó, Rubio, & Pascual-Leone, 1998).

To further analyze the role of the cerebellum in procedural learning and to assess whether it has a lateralized effect, in the present study we used a repetitive transcranial magnetic stimulation (rTMS) interference approach in a group of normal subjects performing the SRTT. We applied 1 Hz rTMS trains to the lateral (right and left) cerebellar hemisphere immediately before performing the SRTT with the hand ipsilateral or contralateral to the stimulated cerebellar hemisphere. The resultant RTs were compared to those of a group of subjects during control conditions (without rTMS).

RESULTS

The mean duration of the SRTT after the TMS was 354.7 ± 33.7 msec.

Table 1 shows the average RTs across the five blocks of SRTT in the different subject groups.

A first analysis was run to compare subjects submitted to rTMS over the left and right cerebellar hemisphere with all control subjects, regardless of the hand used to perform the task. ANOVA revealed a significant main effect of block [$F(4,132) = 25.68$, $p < .0001$] and a significant interaction Group × Block [$F(8,132) = 2.02$, $p < .05$]. The RTs increase observed in control group between blocks 4 and 5 was significantly different from the one observed in rTMS groups, both for the right and for the left cerebellar rTMS groups [lCB vs. controls: $F(1,33) = 6.38$, $p = .016$; rCB vs. controls: $F(1,33) = 12.69$, $p = .001$]. These results show that cerebellar rTMS interferes with sequence learning: In fact, controls showed a larger increase of RTs compared with subjects submitted to rTMS. On the contrary, the comparison between left and right rTMS did not reveal significant differences in RTs increase between blocks 4 and 5.

Each rTMS group was then analyzed separately in comparison with the control groups, matched for the hand used for the task. Because the main index of procedural learning in SRTT is the RT rebound across blocks 4–5, the analysis was limited to these blocks (Figure 1). The ANOVA between rCB-rh and Cont-rh revealed a significant main effect of group [$F(1,10) = 53.08$, $p < .0001$] and a significant interaction [$F(1,10) = 9.32$, $p = .012$] (Figure 1A). The comparison between rCB-lh and Cont-lh revealed a significant main effect of block [$F(1,9) = 33.74$, $p = .0003$] and a significant Group × Block interaction [$F(1,9) = 7.79$, $p = .021$] (Figure 1B). Comparing lCB-lh and Cont-lh, the analysis revealed a significant main effect of block [$F(1,11) = 62.91$, $p < .0001$] and a significant interaction Group × Block [$F(1,11) = 8.61$, $p = .014$] (Figure 1C). On the contrary, the analysis of lCB-rh versus Cont-rh revealed only a significant main effect of block [$F(1,11) = 43.10$, $p < .0001$], without any significant interaction ($p = .3$) (Figure 1D).

In order to better verify whether TMS on the left side affects learning with the ipsilateral and contralateral hands differentially, a three-way ANOVA was run (see Methods). This analysis failed to show a significant interaction of Group × Hand × Block [$F(1,22) = 0.07$, $p = .8$]. Thus, although individual contrasts show that left cerebellar rTMS interferes with sequence learning

Table 1. Average RTs (in msec) across the Five Blocks of SRTT in the Different Subjects' Groups

	Mean RTs (Standard Error)				
Groups	*Block 1*	*Block 2*	*Block 3*	*Block 4*	*Block 5*
lCB-rh	464.9 (23.7)	433.2 (28.8)	436.3 (28.4)	411.2 (28.6)	484.3 (25.0)
lCB-lh	485.2 (49.6)	470.4 (43.7)	453.0 (48.2)	448.4 (40.1)	480.9 (36.3)
rCB-lh	516.1 (25.1)	484.3 (24.9)	471.8 (10.9)	480 (25.8)	504.8 (13.3)
rCB-rh	463.8 (31.5)	457.2 (36.6)	442.6 (26.1)	451.2 (27.4)	493.6 (28.7)
Cont-rh	504.2 (39.7)	468.9 (51.3)	461.6 (48.8)	427.3 (39.7)	530.8 (47.8)
Cont-lh	497.4 (36.4)	496.1 (41.4)	495.1 (44.1)	441.7 (36.2)	512.4 (30.2)

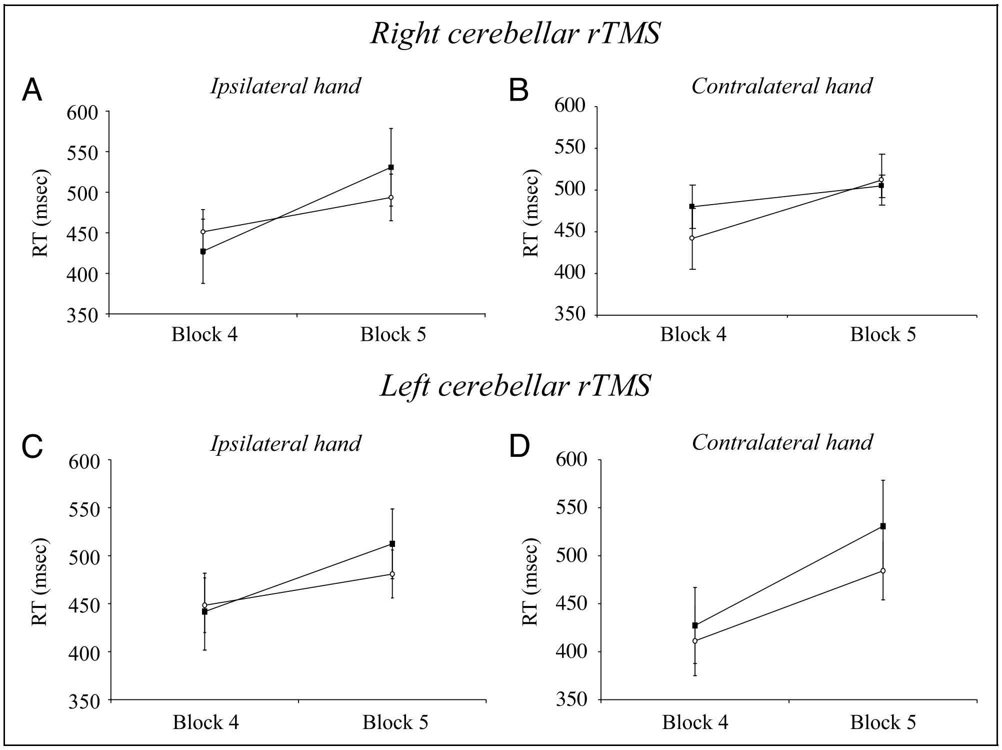

Figure 1. Reaction times across blocks 4–5 in controls and in subjects submitted to rTMS over the left and right cerebellar hemispheres, performing the SRTT with the hand ipsilateral or contralateral to the stimulation. (A) right rTMS–right hand versus Controls–right hand; (B) right rTMS–left hand versus Controls–left hand; (C) left rTMS–left hand versus Controls–left hand; (D) left rTMS–right hand versus Controls–right hand. Black squares indicate control groups and white circles indicate rTMS groups.

only when the task is performed with the left hand, the pattern of rebound increase of RTs in left TMS versus control subjects is not significantly different comparing the right versus left hand.

At the end of the five blocks, none of the subjects were able to reproduce the repeating sequence of the SRTT.

DISCUSSION

The main result of the present study is that an rTMS interference with the cerebellar hemispheres' activity disrupts procedural learning as measured with the SRTT task: rTMS of the right cerebellar hemisphere produces a significant decrease of procedural learning when the task is performed either with the ipsilateral or with the contralateral hand; rTMS of the left cerebellar hemisphere also produces a significant decrease of procedural learning, which is more evident when the task is performed with the hand ipsilateral to the stimulation, although no significant differences between the two hands emerged.

These results suggest that the cerebellar hemispheres could play a critical role in sequence implicit learning. The finding that the right cerebellum seems more involved than its twin in implicit learning of new sequences through both hands could be due to its outputs to the contralateral parietal cortex (Middleton & Strik, 1997) and this would be consistent with the well-known dominance of the left cerebral cortex for many aspects of movements. Indeed, according to Rushworth, Johansen-Berg, Göbel, and Devlin (2003), some of the neuropsychological difficulties experienced by patients with left hemisphere lesions and patients with apraxia, such as difficulty with fast movement sequences, may be related to a failure to redirect motor attention from one movement to another. Adiadokokinesia, a deficit frequently associated with cerebellar lesions, could be consistent with the difficulty of execution of fast movement sequences. On the other hand, our results do not allow to support clearly a cerebellar interhemispheric difference in procedural learning (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; van Mier et al., 1995), and further studies are needed to address this topic.

Cerebellar contribution has been for a long time considered as confined to the motor sphere, but during the last years there have been a number of demonstrations of the cerebellar involvement in cognitive processes, such as visuospatial attention (Silveri, Misciagna, & Terrezza, 2001), working memory, procedural learning, language (Eckert et al., 2003; Leggio, Silveri, Petrosini, & Molinari, 2000), planning and timing (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Akshoomoff & Courchesne, 1992; Wallesch & Horn, 1990), as well as in the emotional domain (Schmahmann & Sherman, 1998). In this context, TMS can represent a useful way to complement neuropsychological and neuroimaging studies in the study of cerebellar functions. An example of this application is provided by a recent study (Theoret, Haque, & Pascual-Leone, 2001) in which trains of rTMS at 1 Hz frequency were applied over the medial and lateral cerebellum in a group of normal subjects performing a paced finger-tapping task. rTMS of the cerebellar vermis induced a specific disruption of the performance, while rTMS of the lateral cerebellum or motor cortex did not affect subjects' performance.

By using the same approach, in the present study we induced impairment in procedural learning that could not be ascribed only to peripheral motor dysfunction. In fact, rTMS interference was not generalized across the task, but was selective for the blocks containing the repeating sequence to be implicitly learned. This finding allows ruling out an unspecific disruption of the cerebellar output toward the contralateral primary motor area in interpreting the reported results. Indeed, transsynaptic effects and spread of current towards other interconnected structures cannot be completely excluded in interpreting these results. In fact, recent studies (Gershlager, Christensen, Bestmann, & Rothwell, 2002) show that cerebellar TMS is associated with a stimulation of the brainstem that influences spinal cord excitability. However, the specific effect of interference in the sequential blocks observed in the present research makes the hypothesis of a specific cerebellar disruption more tenable.

Therefore, the present findings account for a cerebellar role in sequential procedural learning beyond the strict motor control functions attributed to this structure. Previous PET and fMRI studies have shown an activation of cerebellar structures during procedural learning (Doyon et al., 1996; Ellerman et al., 1994; Grafton, Woods, & Tyszka, 1994; Jenkins et al., 1994). Molinari et al. (1997), investigating procedural learning abilities in the presence of focal cerebellar lesions, found that focal cerebellar damage affects the detection of a sequence and the acquisition of declarative knowledge about it, regardless of the side of the cerebellar lesion. Similarly, patients with cerebellar cortical degeneration did not display any improvement with task repetition, indicating impairment both in procedural and in declarative learning with both hands (Pascual-Leone et al., 1993).

Our findings support these neuropsychological observations in a homogeneous population of normal subjects. In fact, the use of an interference technique, such as rTMS, allows reproducing the classical lesion method of neuropsychological research, with the advantage to make selective interference with specific structures and without the confounding effects of patients' heterogeneity and of plasticity associated to brain lesions.

According to Middleton and Strick (2001), the deficits in the performance of cognitive tasks following cerebellar pathology would result from an interruption of cerebellar inputs to the prefrontal cortex. It has been suggested that the cerebellum influences several areas of the prefrontal cortex via the thalamus, with separate output channels from the dentate nucleus for either cognitive or motor operations. As suggested by single-neuron recordings in primates (Funahashi, Inoue, & Kubota, 1997; Mushiake & Strick, 1993, 1995) and by neuroimaging studies in human subjects (Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Jueptner, Stephan, et al., 1997; Kim, Ugurbil, & Strick, 1994), output channels in the ventral dentate nucleus that innervate the contralateral prefrontal cortex would be involved in learning new sequences, spatial working memory, planning, and rule-based learning. According to these findings, the dentate nucleus could be an interface between the cerebellar and prefrontal cortex for monitoring of sequential behavior and retrieving of long-term procedural learning (Hikosaka, Miyashita, Miyachi, Sakai, & Lu, 1998), while other authors argue that its role is to organize the processes by which motor sequences become automatic with extended practice (Nixon & Passingham, 2000).

In this context, the cerebellum could be the epicenter of a network of anatomically interconnected structures deputed to procedural learning. This hypothesis is supported by the findings of disrupted procedural learning in the SRTT following rTMS of the prefrontal cortex contralateral to the performing hand (Pascual-Leone, Tarazona, et al., 1999; Pascual-Leone, Wassermann, Grafman, & Hallet, 1996). Moreover, in a modified version of the SRTT, patients with prefrontal cortex dysfunction due to Parkinson's disease acquire procedural learning more slowly than controls (Pascual-Leone, Grafman, & Hallet, 1995).

Lesion studies also support the cerebellar role in procedural learning. Clear deficits in procedural spatial learning have been demonstrated by analyzing the performances of hemi-cerebellectomized rats in the Morris Water Maze (Petrosini, Molinari, & Dell' Anna, 1996). The authors suggest that the cerebellum may represent not the site of storage of spatial procedural strategies, but the site of their acquisition, whereas other studies reported that it is the combination of brainstem and cerebellum dysfunctions that leads to an impairment of procedural learning (Daum et al., 1993).

In conclusion, the present study shows that a transient disruption of the cerebellar cortex leads to an impairment of procedural learning in normal subjects. These results shed further light on the role of the lateral cerebellum and on interhemispheric differences in procedural knowledge and emphasize the importance of using interference techniques in normal subjects to complement lesion and neuroimaging studies on this topic.

METHODS

We studied a group of 36 normal volunteers (14 men and 22 women). All subjects were right-handed. They provided written informed consent for participation in the study that was approved by the Santa Lucia Foundation's ethical committee.

Serial Reaction Time Task

Each subject was seated in front of a computer screen with the hands positioned upon four buttons of the keyboard (H, J, K, and L). Subjects were instructed to push one of the four buttons as soon as an asterisk appeared on the screen, respectively, in the left, middle–left, middle–right, and right position. The subjects had to maintain four fingers (except the thumb) of the left or right hand on the buttons and were asked to press the key corresponding to the position of the asterisk that appeared on the screen as quickly and accurately as possible. The target asterisks disappeared only when the correct key was pressed and the new stimulus was presented after an interval of 250 msec. In this version of the SRTT, we proposed five blocks, constituted by sequences of 12 asterisk positions repeated eight times each. In the first and the last blocks, the asterisks were presented in random order, whereas in blocks 2, 3, and 4 the asterisks were presented in a sequence of 12 stimuli (H, K, H, L, K, J, L, H, K, J, L, J); however, the subjects were not told about this repeating sequence.

At the end of the five blocks, the subjects were asked whether they had become aware of the presence of a repeating sequence during the execution of the task; in case of a positive answer, subjects were invited to reproduce the sequence on the keyboard.

The task was preceded by a practice phase composed of 24 stimuli presented in random sequence.

rTMS Protocol

rTMS over the lateral (left or right) cerebellum was applied using the same scalp coordinates as Theoret et al. (2001) (1 cm under and 3 cm left/right to the inion). TMS was delivered by means of a MagStim rapid magnetic stimulator, using a figure-of-eight coil (70 mm in diameter).

The coil was positioned tangentially to the scalp, with the handle pointing superiorly.

rTMS was applied at 1 Hz frequency for 10 min (corresponding to 600 stimuli), at an intensity of 90% of the motor threshold. Motor threshold was defined as the lowest TMS intensity (as assessed with single-pulse TMS of the contralateral motor cortex) able to induce a visible muscle twitch of the contralateral hand (i.e., ipsilateral to cerebellar stimulation) in at least 50% of a sequence of 10 consecutive trials.

The task was performed immediately after the cessation of the rTMS train; each subject performed the practice phase before the stimulation.

Participants were divided in six groups. Thirteen subjects underwent rTMS stimulation on the left cerebellum: Six of them performed the task with the right hand (lCB-rh; 3 women and 3 men; mean age 24 ± 2.4) and seven with the left hand (lCB-lh; 4 women and 3 men; mean age 23 ± 5.4); other 10 subjects underwent rTMS on the right cerebellum: Five of them performed the task with the right hand (rCB-rh; 4 women and 1 man; mean age 21 ± 0.7) and five subjects performed the task with the left hand (rCB-lh; 4 women and 1 man; mean age 23.4 ± 4.2).

Finally, 13 subjects served as controls and were not submitted to rTMS: Seven of them performed the task with the right hand (Cont-rh; 3 women and 4 men; mean age 25.1 ± 3.9) and six with the left hand (Cont-lh; 4 women and 2 men; mean age 26.2 ± 2.8).

Individual subjects could not be submitted to all experimental conditions because of the effect of learning of the repeating sequence across the different conditions and because of the limited duration of the TMS interference effect.

Data Analysis

Mean RTs of the five blocks of the SRTT were calculated in the five subjects' groups and statistical analysis was performed on mean RTs across blocks 1–5.

The RTs of subjects receiving left and right cerebellar rTMS, regardless of the hand used for the task, were compared with those of controls. The values were submitted to ANOVA, with group (three levels: right rTMS, left rTMS, controls) as a between-subjects factor, and the mean RTs in blocks 1–5 as within-subjects factor. Because the difference in RTs between blocks 4 and 5 can be considered as the main index of procedural learning in SRTT, planned comparisons (LSD test) were made to test the significance between single factors in these blocks.

Further repeated-measures ANOVAs were performed in order to compare each rTMS group to the correspondent control group in blocks 4–5 (left rTMS–left hand vs. controls–left hand; right rTMS–right hand vs. controls–right hand; left rTMS–right hand vs. controls–right hand; right rTMS–left hand vs. controls–left hand).

Finally, to further test the differential effects of left cerebellar rTMS with sequence learning performed with the left versus right hand, we performed an ANOVA with group (two levels: left rTMS, controls) and hand (two levels: left, right) as between-subject factors and block (two levels: 4, 5) as within-subject factor.

For all tests, the level of significance was set at .05.

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This experiment was undertaken with the understanding and written consent of each subject, and conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (18 July 1964).

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