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# Effect of focal cerebellar lesions on procedural learning in the serial reaction time task

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**Abstract** Prior studies have shown that procedural learning is severely impaired in patients with diffuse cerebellar damage (cortical degeneration) as measured by the serial reaction time task (SRTT). We hypothesize that focal cerebellar lesions can also have lateralized effects on procedural learning. Our objective was to assess the effects of focal cerebellar lesions in procedural learning as measured by the SRTT. We studied 14 patients with single, unilateral vascular lesions in the territory of the posterior-inferior or superior cerebellar artery, who were compared with ten age- and sex-matched controls in a one-handed version of the SRTT. Patients with lesions at any other level of the brain or posterior fossa were excluded by cranial magnetic resonance imaging. Our results show that patients do not acquire procedural knowledge when performing the task with the hand ipsilateral to the lesion, but show normal learning with the contralateral hand. No correlation was found with the side, size, or vascular territory of the lesion. We conclude that procedural learning is impaired in hemispheric cerebellar lesions and involves only the hand ipsilateral to the lesion, which suggests a critical role for the cerebellum and/or crossed cerebellar-prefrontal connections in this type of learning.

**Key words** Cerebellum · Serial reaction time task · Procedural memory · Human

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## Introduction

Procedural learning refers to the process by which repeated exposure to a task, regardless of whether the subject does or does not form a conscious memory of this exposure, results in improved performance of that task. Explicit and implicit knowledge refer to whether or not the subject has a conscious awareness of the exposure to the task or information that eventually results in improved performance. The serial reaction time task test (SRTT; Nissen and Bullemer 1987; Willingham et al. 1989) allows for the study of procedural-implicit and procedural-explicit learning (Pascual-Leone et al. 1995).

The neural basis for procedural memory has not been completely established, but it seems associated with a plastic modulation of the motor cortical outputs to the muscles involved in the task and is dependent on a neural network that receives critical contributions from the basal ganglia, cerebellum, and prefrontal cortex (Pascual-Leone et al. 1995; Ungerleider 1995). From a functional point of view, positron emission tomography (PET) and cerebral blood flow studies have shown an increase in metabolic activity and blood flow in the supplementary motor cortex, basal ganglia, and cerebellum during complex motor task learning (Grafton et al. 1994). Other authors have shown an increase in the parietal association cortex and cerebellum PET activity during procedural learning of sequences, a task similar to that performed in the SRTT (Jenkins et al. 1994).

Prior studies have shown that patients with Parkinson's disease acquire procedural knowledge more slowly than normal controls and that patients with cortical cerebellar atrophy have an impaired ability to learn the SRTT (Pascual-Leone et al. 1993b). Recent findings in single patients suggest that focal, unilateral cerebellar lesions might interfere with procedural learning in the SRTT differentially, depending on which hand is used during the task (Pascual-Leone et al. 1995).

In this study, we tested the hypothesis that procedural learning is impaired in patients with focal cerebellar le-

sions and also whether this impairment involves the hand ipsilateral or contralateral to the lesion.

## Materials and methods

### Subjects

We studied 14 patients with chronic focal cerebellar lesions limited to the right ($n = 5$) or the left ($n = 9$) cerebellar hemisphere. Ischemic cerebellar infarctions ($n = 12$) were located in the territory of the posterior-inferior cerebellar artery (PICA) in seven patients and in the territory of the superior cerebellar artery (SCA) in five patients. Two patients had cerebellar hematomas involving territories predominantly of the PICA, right-sided in one case and left-sided in the other. Enough time from the stroke (mean 29 ± 22 months, range 6–66 months) was allowed so that there was no motor impairment that precluded the proper performance of the task.

The clinical characteristics of these patients are summarized in Table 1. The mean age was 61.3 years (range 33–74 years); ten were men and four were women. All were right-handed according to the Annett Inventory (Lezak 1995). In all patients, additional ischemic lesions at any level of the brain or posterior fossa were ruled out by magnetic resonance imaging (MRI). None had preexisting neurological conditions or a history of cognitive impairment prior to their cerebellar stroke.

As part of a previous study, all patients underwent a neuropsychologic evaluation which included the following tests: Wechsler Adult Intelligence Scale (WAIS-r), cancellation test, Stroop test, controlled word association test, Boston naming test, Rey-Osterreith complex figure copy and 20-min delay-recall tests, Wechsler Memory Scale (logical memory I and II, verbal paired associates, and visual reproductions I and II), trail making A and B, Hamilton depression scale, and Purdue pegboard test (Gómez-Beldarrain et al. 1997).

A complete neurological examination was also performed on all patients by two Board-certified neurologists prior to entering the study. At the time of the study, none of the patients had significant residual neurological impairments that could interfere with performing the SRTT.

We also studied ten normal, right-handed control subjects, aged 52–72 years (mean age 62.6 years); three women and seven men. All had normal neurological, neuropsychological, and general physical examinations, no underlying neurological illnesses, and were not taking any medication. The study was approved by the Institutional Review Board. All subjects gave their written informed consent, that was obtained according to the declaration of Helsinki, prior to entering the study.

### Serial reaction time task

The subject sat in front of a computer screen at eye level behind a response pad, with four buttons numbered 1–4, and was instructed to push each button with a different finger of the right or left hand (index finger for button 1, middle finger for button 2, ring finger for button 3, and little finger for button 4). The "go" signal consisted of a number (1, 2, 3, or 4) displayed in the middle of the screen and corresponding to the numbered response buttons. Upon appearance of the go signal, the subject had to push the appropriate response button as fast as possible with the appropriate finger. When the correct response button was pushed, the go signal disappeared and the next go signal appeared 500 ms later. If an incorrect button was pushed, the go signal remained on the screen until the subject made the correct response.

The SRTT was performed in 5 blocks of 100 trials (block 1–5). In blocks 1 and 5, the go signals were presented in random order. In blocks 2–4, the go signals represented a sequence of ten cues whose order was repeated ten times in each block of trials. However, the subjects were not told about this repeating sequence.

Each patient and control subject completed two versions of the 5 blocks of the SRTT. These two versions differed in the repeating sequence used for blocks 2–4. The sequences used in both versions of the test were unpredictable. Subjects completed one version of the test with one hand and the other version with their other hand. Both patients and controls performed first with the right and then with the left hand. In this sequence, a specific number is never followed by the same one, and associations of numbers are not predictive, to assure that subjects are learning sequential information and not a "first-order conditional" type of learning (Rauch et al. 1995).

Subjects were specifically asked, upon test completion, whether they had noticed a sequence in order to assess explicit learning of the task.

### Data analysis

In each trial, response time (RT) was measured from the appearance of the go signal until the first button was pressed in response by the subject. For each block of trials, we calculated the median RT (Nissen and Bullemer 1987; Willingham et al. 1989) and expressed the median RT in blocks 2–5 as a percentage of the median RT in block 1 in order to normalize for each subject's baseline performance. In addition, we calculated an error rate (ER) to express the number of incorrect response buttons pressed as the initial response and requiring self-correction. The time until correction was also recorded but not specifically studied. For patients and controls, we calculated the mean and standard deviation RT from the individual median RTs in each block of trials. For this purpose, we separated dominant (right) from non-dominant (left) hand performance in the control subjects. In the patients, we separated performance with the hand ipsilateral and contralateral to the lesion. Two parameters represent an index of procedural learning: shortening of the RT from block 2–4 and a rebound RT increase between block 4 and 5. In all subjects, we also calculated the difference in RT and ER between blocks 4 and 5, which also represents an index of the procedural knowledge acquired during the SRTT (Pascual-Leone et al. 1993a). Statistical analysis was performed with analyses of variance (ANOVA) and post hoc Scheffé test, assuming a significance level of $P < 0.05$.

## Results

Table 1 summarizes the clinical characteristics of all patients, and Fig. 1 shows a schematic composite of the

**Table 1** Clinical characteristics of the cerebellar patients (*M* male, *F* female, *PICA* posterior-inferior cerebellar artery, *SCA* superior cerebellar artery, *R* right, *L* left)

| Patient | Age (years) | Sex | Vascular territory | Side | Time since lesion (months) |
|---|---|---|---|---|---|
| 1 | 53 | M | PICA | R | 6 |
| 2 | 58 | M | PICA | L | 66 |
| 3 | 73 | M | SCA | L | 14 |
| 4 | 55 | F | SCA | L | 10 |
| 5 | 65 | M | SCA | R | 23 |
| 6 | 58 | F | SCA | L | 58 |
| 7 | 74 | M | SCA | L | 9 |
| 8 | 68 | M | PICA | L | 6 |
| 9[a] | 65 | M | PICA[a] | L | 21 |
| 10 | 73 | F | PICA | L | 11 |
| 11[a] | 63 | M | PICA[a] | R | 43 |
| 12 | 33 | F | PICA | L | 64 |
| 13 | 53 | M | PICA | R | 26 |
| 14 | 66 | M | PICA | R | 59 |

[a] The two patients with hematomas rather than ischemic strokes and the vascular territory within which the hematoma was contained

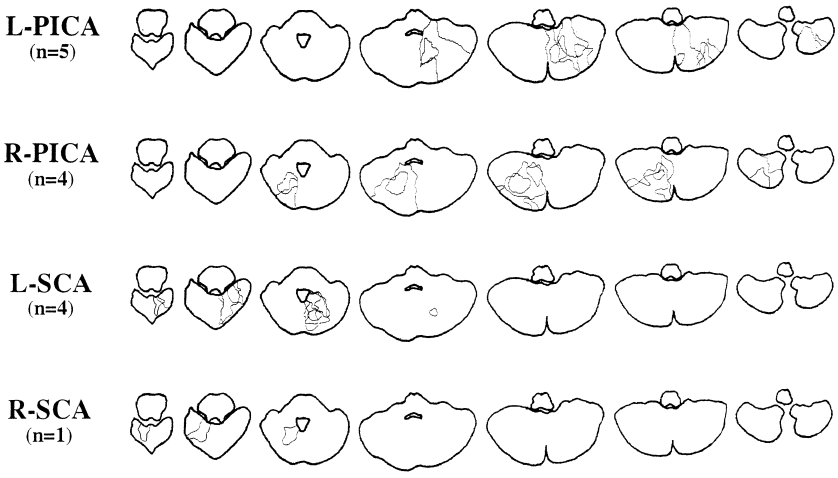


**Fig. 1** Schematic representation of the outline of the cerebellar lesion in all patients. Each *row* of cerebellar outlines shows the overlaid outlines of the lesions of all patients with lesions within the same vascular territory. The images are generated by digitizing brain magnetic resonance images (MRI) of each patient, tracing out the outline of the lesion and of the cerebellum, and fitting the cerebellar outline to the chosen template which represents the approximate cerebellar levels that were obtained in the MRI examination of each patient (*PICA* posterior-inferior cerebellar artery, *SCA* superior cerebellar artery)

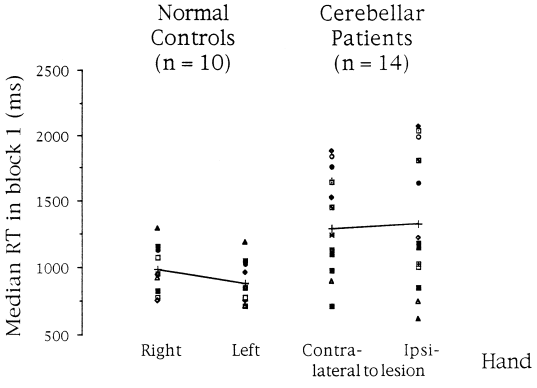


**Fig. 2** Scattergram of the median response time (*RT*) in the first block of the serial reaction time task during which the trials were presented in a random order. Each *symbol* represents a normal control or a patient. The *crosses* represent the mean within each group. Results are presented separately for the left and right hand of the controls and for the hand ipsilateral and contralateral to the lesion in the patients

brain MR images of all patients illustrating the localization of their lesions. Patients were studied in a chronic stage and hence they had recovered clinically to the point that they did not show any sensory-motor impairment that would preclude the performance of the task.

Neuropsychological evaluation with an extensive battery of tests common in clinical practice (see Materials and methods for the list of tests performed) did not disclose any relevant abnormalities(Gómez Beldarrain et al. 1997). Only the Purdue pegboard test (PPT) showed very mild impairment in this series of patients with chronic lesions (i.e., more than 6 months), in contrast to patients with recent lesions (i.e., less than 3 weeks), who showed a clearer PPT impairment and therefore were excluded from this study. Specifically, PPT values for patients and controls in this study were: controls, right hand 13.9, left hand 12; patients, right hand 12, left hand 11.

Figure 2 displays the median RTs in block 1 of the SRTT in all controls and patients. One-way ANOVA failed to find any significant RT differences between in the hands in block 1 (left or right hand in the controls, and hand ipsilateral or contralateral to the lesion in the patients). Therefore, there were no intermanual differences at baseline that could explain any eventual differences in performance between the right and left hand in the patient's group. Controls performed slightly slower with the right hand than with the left hand, despite the fact that all were right-handed, although the difference did not reach statistical significance. It should be noted, however, that all of them performed first with the right hand and then with the left, which could have led to a left-hand advantage from practice.

Our findings showed significantly less procedural learning during the SRTT in the patients when performing with the hand ipsilateral to their lesion compared with the contralateral hand and with either hand of the controls. These findings were derived from two distinct analyses of the results.

First, the shortening of RT over blocks 2–4 can be considered as an indicator of procedural implicit learning (Nissen and Bullemer 1987; Willingham 1989; Jenkins et al. 1994).

We conducted a within-group one-way ANOVA with the differences in RT values across blocks 2–4 for each hand of the patients and the controls (Fig. 3), finding significant differences ($P < 0.005$). Post hoc analysis showed a significant smaller shortening of the RT for the hand ipsilateral to the lesion ($P < 0.05$), compared with the RT shortening for the contralateral hand which was comparable with that of the controls' hands. Interesting in this analysis is the trend toward greater shortening of the RTs in blocks 2–4 in the patients when using their hand contralateral to the lesion than in the controls when using either hand (Fig. 3). This trend did not reach statistical significance and might have been the consequence of a greater benefit from practice in the cerebellar patients than in the controls.

Second, the increase in RT in block 5 (random presentation of trials) in comparison with block 4 (sequential presentation) is another useful measure of the procedural knowledge acquired during the SRTT (Nissen and Bulle-

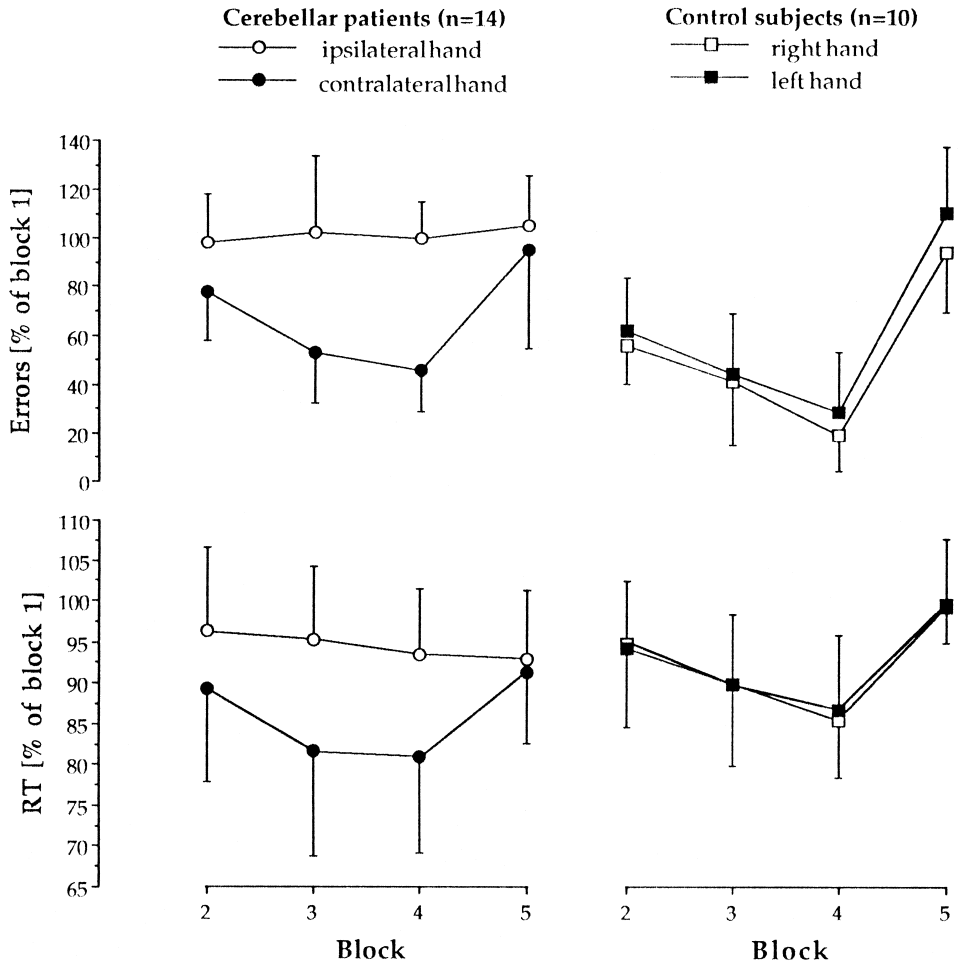


**Fig. 3** Errors (*top*) and response times (*RT*, *bottom*) across blocks 2–5 of the serial reaction time task for the patients and the controls. RT is expressed as percentage of the RT in block 1. Results are presented separately for the hand ipsilateral and contralateral to the lesion in the cerebellar patients and for the right and left hands of the controls. Note the progressive shortening of RT during blocks 2–4 (repeating sequence of trials) and the "rebound" increase in RT in block 5 (random presentation). Note that this modulation of RT is not apparent for the hand ipsilateral to the lesion in the patients. The error rates run a parallel course to the RTs

mer 1987; Willingham 1989; Pascual-Leone et al. 1993b). One-way ANOVA showed a significant difference ($P < 0.001$) between the difference in RT (∂RT) in blocks 4 and 5 and the hand tested (left or right hand of the controls and hand ipsilateral or contralateral to the lesion in the cerebellar patients). Post hoc paired comparisons (Scheffé test) showed significantly smaller ∂RT for the hand ipsilateral to the lesion in the patients than for their contralateral hand ($P < 0.005$) or either hand of the controls (Fig. 4; $P < 0.05$).

The error rate (ER), expressed as the percentage of errors relative to block 1, ran a parallel course to the procedural learning curve, with a decrease in the number of errors across block 2–4 and a rebound increase in the number of errors in the random block 5 (Figs. 3, 4). Again, this was another expression of procedural learning that only occurred with the hand contralateral to the lesion, whereas the ER did not show much variation across blocks with the ipsilateral hand, reflecting the absence of learning. None of the patients achieved explicit knowledge of the sequence and only two controls mentioned having noticed some sort of sequence, but were unable to reproduce the numbers.

We found no differences between right- and left-sided cerebellar hemisphere lesions, or between PICA versus SCA territory lesions. The results for the ERs were similar to those presented for the RTs, but, given the much larger number of errors in the patients than in the controls, comparisons yielded higher significance levels.

## Discussion

Patients with unilateral cerebellar lesions showed a significant shortening in the RT across blocks 2–4 in the SRTT and a rebound increase in the RT when presented with the random block 5 while performing with the hand contralateral to the lesion. On the contrary, there was no evidence of procedural learning when performing with the hand ipsilateral to the lesion (i.e., no shortening of RT across blocks 2–4 and no rebound RT increase in block 5). Similarly, the ER mirrored these results, supporting a strictly unilateral absence of procedural learning. These results support the critical role of the ipsilateral cerebellar hemisphere in procedural learning of the one-handed SRTT. The impairment of procedural learning cannot be ascribed to motor dysfunction in these patients, which was ruled out by the absence of abnormalities on clinical examination and by performance in the first, random block of trials of the SRTT (Fig. 2). Patients were slower than con-

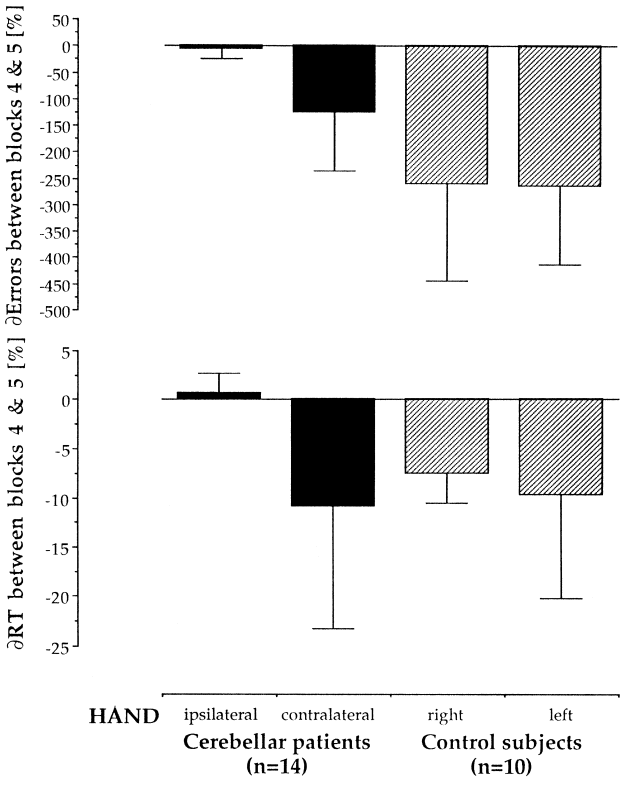


**Fig. 4** Bar histogram of the difference in errors (*top*) and response time (∂RT, *bottom*) between blocks 4 and 5 for the patients and the controls. Results are expressed in percentage change in RT across blocks 4 and 5 and presented separately for the hand ipsilateral and contralateral to the lesion in the cerebellar patients and for the right and left hands of the controls. "Rebound" increase in RT in block 5 as compared with block 4 (see Fig. 3) results in negative values of the ∂RT. Conversely, relative shortening of RT in block 5 as compared with block 4 results in positive values. Therefore, the more negative ∂RT, the more procedural knowledge can be assumed. *Bars* indicate the group mean and the SD. As in Fig. 3, the error rates show similar findings to RTs

trols, but the two hands of patients performed at a similar level initially and yet only one hand failed to achieve procedural learning.

The cerebellum, therefore, must be considered to play a role in sequential, procedural motor learning beyond the strict motor control functions. Our findings are also in agreement with prior PET and blood flow studies, which have shown an activation of the cerebellum during procedural learning, although whether or not this defect could be unilateral had not been previously addressed (Grafton et al. 1994; Jenkins et al. 1994).

Despite the demonstration of procedural learning impairment, patients did not show other neuropsychological abnormalities according to an extensive battery of tests common in clinical practice, which included the evaluation of declarative memory, executive function, visuospatial abilities, attention, or global intelligence. They only showed very mild impairment in the PPT, a test that measures motor speed, hand-eye coordination, and motor skills. That all the patients had normal results from neurological examinations and were evaluated at a chronic stage (range 6–66 months after stroke), suggests that the procedural deficit is long-lasting and independent of other cerebellar deficits. It has been suggested that it is the combination of brainstem and cerebellar lesions that lead to a procedural learning deficit (Daum et al. 1993), but in this study brainstem lesions were ruled out by cranial MRI. Therefore, procedural learning deficit in our patients is to be ascribed only to the cerebellar lesion.

In patients with cerebellar cortical degeneration, the SRTT reveals a profound alteration in procedural learning with both hands (Pascual-Leone et al. 1993b), and those patients fail to achieve explicit knowledge of the repeating sequence and show only limited use of declarative knowledge of the task to improve their performance (Pascual-Leone et al. 1993b). In our study, both patients and controls failed to achieve explicit knowledge of the sequence.

Our findings indicated that lesions in the right cerebellar hemisphere lead to impaired procedural learning in the SRTT only with the right hand, while lesions in the left cerebellar hemisphere impair selectively the procedural learning with the left hand, and this occurred regardless of the territory of the cerebellar lesion (SCA or PICA). Since the dentate nucleus is the main efferent cerebellar structure and is supplied by the SCA (Amarenco 1991; Kase et al. 1993), it might have been expected that SCA lesions would result in greater impairment of the SRTT; however, lesions to afferent or efferent pathways of the cerebellar hemispheres, supplied by PICA and SCA, respectively (Amarenco 1991; Kase et al. 1993), result in similar dysfunctions in the SRTT. Other tasks might be needed to show differential consequences.

In conclusion, impairments in procedural learning are linked to the absence of the normal modulation of motor cortical outputs to the muscles involved in the task (Pascual-Leone et al. 1993a, 1994). Several structures, including the cerebellum, basal ganglia, and prefrontal cortex, are involved in modulating the cortical motor outputs and therefore are likely to be implicated in implicit motor learning. Based on our results, it appears that the role of the cerebellum is lateralized and selective for procedural learning with the hand ipsilateral to each cerebellar hemisphere. Crossed connections between cerebellum and prefrontal cortex have been shown(Middleton and Strick 1994) that might be also important in the role of the cerebellum in this form of learning. This notion is supported by the findings of disrupted procedural learning in the SRTT by dysfunction of the dorsolateral prefrontal cortex contralateral to the performing hand (Pascual-Leone et al. 1995, 1996).

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