Transcranial Magnetic Stimulation and Motor Plasticity in Human Lateral Cerebellum: Dual Effect on Saccadic Adaptation

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Abstract: The cerebellum is a key area for movement control and sensory-motor plasticity. Its medial part is considered as the exclusive cerebellar center controlling the accuracy and adaptive calibration of saccadic eye movements. However, the contribution of other zones situated in its lateral part is unknown. We addressed this question in healthy adult volunteers by using magnetic resonance imaging (MRI)-guided transcranial magnetic stimulation (TMS). The double-step target paradigm was used to adaptively lengthen or shorten saccades. TMS pulses over the right hemisphere of the cerebellum were delivered at 0, 30, or 60 ms after saccade detection in separate recording sessions. The effects on saccadic adaptation were assessed relative to a fourth session where TMS was applied to Vertex as a control site. First, TMS applied upon saccade detection before the adaptation phase reduced saccade accuracy. Second, TMS applied during the adaptation phase had a dual effect on saccadic plasticity: adaptation after-effects revealed a potentiation of the adaptive lengthening and a depression of the adaptive shortening of saccades. For the first time, we demonstrate that TMS on lateral cerebellum can influence plasticity mechanisms underlying motor performance. These findings also provide the first evidence that the human cerebellar hemispheres are involved in the control of saccade accuracy and in saccadic adaptation, with possibly different neuronal populations concerned in adaptive lengthening and shortening. Overall, these results require a reappraisal of current models of cerebellar contribution to oculomotor plasticity. *Hum Brain Mapp* 33:1512–1525, 2012. © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Neural plasticity is crucial for successful performance of the large repertoire of cognitive and sensory-motor activities in our ever-changing world. Plasticity mechanisms are also aimed to compensate for the detrimental effects of various physical, physiological, or pathological perturbations of our body. Short-term motor adaptation is a progressive modification of motor commands that has been increasingly used to get insight into human learning and neural plasticity, and to understand the involvement of the cerebellum in these processes. Adaptation of saccadic eye movements can be induced noninvasively thanks to the double-step target paradigm eliciting a systematic error signal [McLaughlin, 1967]. Saccadic adaptation has been particularly studied in recent years but even for the cerebellum, the neural substrates underlying this process are still poorly understood [see for recent reviews: Iwamoto and Kaku, 2010; Pelisson et al., 2010]. Indeed, current models designate the medial part (vermis and fastigial nuclei) of the posterior cerebellum as the exclusive cerebellar center for controlling accuracy and adaptation mechanisms [see for reviews: Hopp and Fuchs, 2004; Pelisson et al., 2003, 2010]. In agreement with this view, a recent study reported on an inhibitory effect of repetitive transcranial magnetic stimulation (rTMS) applied to the medio-posterior cerebellum on saccadic adaptation [Jenkinson and Miall, 2010]. In contrast, only a few electrophysiological [Mano et al., 1991; Ron and Robinson, 1973] or fMRI studies [Dieterich et al., 2000; Hayakawa et al., 2002; Schraa-Tam et al., 2009] suggest an implication of other zones of the cerebellum in the control of saccades. A recent fMRI study has demonstrated that the Crus I lobule in the cerebellar hemisphere is activated in relation to saccadic error processing [Liem et al., 2010]. Moreover, a potential involvement of the lateral cerebellum in saccadic adaptation is further suggested by deficits observed in patients with lesions of the medial but also lateral part of the cerebellum [Alahyane et al., 2008; Choi et al., 2008; Golla et al., 2008; Straube et al., 2001]. However, the precise role of the cerebellar hemisphere in saccade control and in saccadic adaptation is unknown.

In addition, most studies demonstrating a contribution of the medial part of the cerebellum in saccadic plasticity have focused on the shortening of saccades induced by a backward target step (backward adaptation). In contrast, the adaptive lengthening of saccades (forward adaptation) has been much less investigated, despite its major functional significance for the compensation of saccades hypometria (i.e., saccades falling short of target) resulting from aging or neuromuscular pathologies. Only Golla et al.

[2008] studied both types of adaptation in patients with lesions of the cerebellum. They found that patients with vermal lesions have a larger impairment in forward adaptation than in backward one. Other recent indirect evidence suggests that saccade lengthening and shortening rely on separate plasticity processes [Catz et al., 2008; Golla et al., 2008; Hernandez et al., 2008; Kojima et al., 2004; Panouilleres et al., 2009; Zimmermann and Lappe, 2009]. Thus, our understanding of backward adaptation mechanisms cannot be extrapolated to forward adaptation.

In summary, there are some suggestions of an involvement of the lateral cerebellum in saccade control, but its exact role and its potential involvement in saccadic adaptation are unknown. To address these issues, we decided to test whether magnetic resonance imaging (MRI)-guided single-pulse transcranial magnetic stimulation (spTMS) over the Crus I lobule of the cerebellum could interfere with saccade control and saccadic adaptation. Both backward and forward adaptations were investigated, because they rely on separate mechanisms and possibly on different neural substrates. Another originality of our study is that the possible involvement in saccadic plasticity of Crus I has never been investigated before. Based on cerebellar physiology and on afferent/efferent projections, we hypothesized that the potential role of Crus I in saccadic adaptation could specifically involve (1) the adaptation of saccades in the ipsiversive direction, given the direction of saccades evoked by electrical stimulation of cerebellar hemispheres in monkey [Ron and Robinson, 1973], (2) the processing of error signals in the ipsiversive direction [as proposed by Pisella et al. [2005] for visuo-manual prism adaptation], or (3) the adaptive change of saccade amplitude in one direction specifically, lengthening or shortening [based on Golla et al., 2008].

MATERIALS AND METHODS

Subjects

Twenty-six subjects were included in this study (mean age: 25.1 ± 5.2 years, 12 women, 20 fully naïve volunteers). All subjects had normal or corrected to normal vision and gave their informed consent to participate. The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and all procedures were approved by the medical ethical committee of University Medical Center Utrecht (protocol number 08-148).

This study was divided in three experiments: the backward adaptation experiment, the forward adaptation

Figure 1.

Reconstructed cerebellar stimulation sites. Posterior (**A**) and lateral (**B**) view of the MNI 3D standard brain showing the location of stimulation sites (Crus I) for 23 participants. Stimulation site was determined on each subject anatomical scan by a neu-

ronavigation system. All sites were located in Crus I, slightly above the horizontal fissure and 3.5-cm lateral to the interhemispheric line (average MNI coordinates across the 23 participants [...]) (35 ± 2 , -86 ± 2 , -31 ± 2).

experiment, and the control experiment. Two participants took part in all experiments and two others performed in both the backward and control experiments. Three participants were excluded on the basis of their T1-weighted MRI scans (see “MRI-guided Transcranial Magnetic Stimulation” section). One subject was excluded because of strong neck and shoulder muscles’ contractions when stimulating the cerebellum, which precluded the stability of the head. Three more subjects were excluded after analysis because the long latency of their saccades (>300 ms) did not guarantee that reactive saccades were elicited. Thus, the data presented here are from 10 subjects for the backward experiment, 9 subjects for the forward experiment, and 6 subjects for the control experiment.

Set-up and Eye Movement Recordings

The experiments were run in the TMS laboratory of the University Medical Center in Utrecht. In a darkened room, subjects were sitting 57 cm from a 100 Hz computer screen (320×240 mm²). The movements of the participants’ head were limited with a chin rest, a forehead rest and a band at the back of the head. Eye movements were recorded using a Remote Eyelink 1000 system (SR Research, Canada). The vertical and horizontal positions of the left eye were sampled at a frequency of 1,000 Hz and a spatial resolution of 0.01° . Calibration and validation of the eye-tracking system were performed at the beginning of each experimental session by having the subjects look at nine

points of an array covering the computer screen. Software developed in C++ at the Erasmus MC (Rotterdam) allowed monitoring of eye movements, on-line detection of the primary saccade onset (as determined when the first saccade toward the target brought eye position outside a window of 1.7° around the fixation point), changes of the visual display and triggering of the TMS pulse.

MRI-Guided Transcranial Magnetic Stimulation

Before inclusion in the study, an anatomical T1-weighted scan was acquired for each participant with a 3Tesla Achieva MRI scanner (Philips Medical System, Best, The Netherlands—see Ettinger-Veenstra et al., [2009], for details about the T1-scan). The stimulation site was identified per participant on the non-normalized T1-weighted MRI scan at the level of the Crus I lobule [Schmahmann et al., 2000]. This site, located slightly above the horizontal fissure and ~ 3 – 4 cm lateral relative to the interhemispheric line, was marked in the stereotactic software (see below) prior to the experiment. Standardized coordinates of stimulation sites were obtained afterwards by normalizing each subject’s T1-weighted MRI scan to the Montreal Neurological Institute (MNI) template by using the “unified segmentation” algorithm of SPM5 [Ashburner and Friston, 2005]. The average MNI coordinate of the stimulated area across the subjects is [35 ± 2 , -86 ± 2 , -31 ± 2] (see Fig. 1 for all individual stimulation sites in MNI space). Three subjects out of 26 were excluded because the

maximal distance between Crus I and the occipital cortex was smaller than 1 cm or the minimal distance between Crus I and the surface of the scalp was larger than 2.5 cm. These exclusion criteria were used to consistently stimulate the cerebellum and to limit the possibility of interfering with occipital visual cortex.

A figure-of-eight coil (70 mm) was used for TMS stimulation. The TMS device was a Magstim Rapid² with a peak magnetic field strength of 3.5–4 Tesla. For each subject, stimulating the right motor cortex allowed identification of the motor threshold as the lowest stimulation intensity able to induce a visible twitch in the resting contralateral hand in 5 of 10 trials [Schutter and van Honk, 2006]. Then the distances between the scalp and Crus I and between the scalp and the hand motor area were measured. This allowed us to adjust stimulation intensity to compensate for the difference of depth between stimulated areas. Thus, the “distance-adjusted motor threshold” was calculated by adding to the motor threshold 3% of TMS output for every additional millimeter in the scalp to Crus I distance relative to the scalp to motor hand area distance [Stokes et al., 2005]. The intensity of stimulation was set at 90% of this distance-adjusted motor threshold, based on a previous study of cerebellar hemispheres TMS with a similar figure-of-eight coil [Theoret et al., 2001]. This intensity was used to stimulate Crus I but also the Vertex, to control for the effects of auditory and tactile stimulations associated with TMS (see below “Experimental design and procedure” section).

The stimulation spot was determined on the head of each subject with the aid of a stereotactic neural navigation software (NeNa 1.5, Rudolf Magnus Institute, Utrecht, The Netherlands, www.neuralnavigator.com) and a magnetic tracking system (miniBird, Ascension technology, Burlington, VT; Neggers et al., [2004]). The coil was then, placed on this spot tangentially over the scalp, with the handle pointing upward. It was maintained on location for the duration of the sessions with a hydrostatic arm (Manfrotto, Feltre, Italy).

Experimental Design and Procedure

Each adaptation experiment (backward and forward) consisted of four sessions. In three sessions, TMS was applied over Crus I with a different delay relative to saccade detection: 0, 30, or 60 ms (see Fig. 2A). Note that because of the 1.7° eye position threshold used for saccade detection and the delay of eye position processing, actual TMS pulse administration occurred on average ~18 ms after the aforementioned times (i.e., 18 ms after actual saccade onset, or close to actual saccade completion or about 30 ms after actual saccade completion, respectively, for the 0, 30, and 60 ms aforementioned timings). In the fourth session, TMS was applied over the Vertex as a control site, with a delay of 30 ms after saccade detection. The Vertex was chosen as a control site, because Vertex is located far

enough from saccadic areas of the cerebral cortex. Like in most TMS studies, this Vertex session was aimed to control for nonspecific factors (fatigue, TMS noise, etc.) that could have contributed to modify saccadic behavior in the Crus I sessions. Thus, the specific role of Crus I in saccadic adaptation will be inferred by comparing the data from the three Crus I sessions to the Vertex session. The order of the sessions was counterbalanced between subjects.

Each session was divided in four phases. The first phase was a preadaptation without TMS (preadapt noTMS, 30 trials). During this phase, the subjects looked at a central fixation point (size: 0.3° of visual angle) for a random duration of 500–1000 ms. Then this fixation point was switched off and replaced by a target (0.3°) randomly presented in the left or right visual field at $\pm 10^\circ$. We asked the participants to look at the target as quickly and accurately as possible. When the saccade was detected, the target was turned off. The subject could then look back at the center of the screen waiting for the fixation point to reappear, announcing the beginning of the next trial. The inter-trial duration was 2 s.

The second phase was a preadaptation with TMS (preadapt TMS, 30 trials). This phase was similar to the preadapt noTMS except that, for every trial, a TMS pulse occurred at a fixed timing after saccade detection (0, 30, or 60 ms for Crus I sessions, or 30 ms for Vertex session).

In the third phase (adaptation, 200 trials), the backward or forward adaptation was induced using a slightly modified version of the double-step target paradigm [McLaughlin, 1967]. At a beginning of a trial, the subject fixated the central fixation point. Fixation duration and target appearance were identical to preadapt but at saccade detection, the target jumped toward the fixation point in the backward experiment and away from it in the forward experiment. The size of this intrasaccadic jump was 33% of the initial target eccentricity of 10°. Then, in both experiments, the target was switched off 110 ms after saccade detection to restrict the duration of postsaccadic error encoding. Because single-pulse TMS has a short-lasting effect, we used this short duration of jumped target to avoid false negative results by making sure that the postsaccadic visual processing of error signals and TMS effect temporally match. Pilot experiments demonstrated that target durations as short as 15 ms elicit a high level of adaptation for reactive saccades [Panouilleres et al., 2011]. In addition, in both adaptation experiments, a TMS pulse occurred at a fixed timing relative to saccade detection (i.e., the same timing as in preadapt TMS). The temporal sequence of these events is schematically depicted in Figure 2A for a backward adaptation trial.

The last phase of a session consisted of a postadaptation with TMS (postadapt TMS, 30 trials), which was identical to preadapt TMS.

The control experiment was conducted to see if TMS itself could induce saccadic adaptation, knowing that adaptation-like changes of saccade amplitude have been elicited by electrical stimulation in the monkey [Kaku et al., 2009; Kojima et al., 2007; Soetedjo et al., 2009]. This

Figure 2.

Protocol of the backward adaptation experiment and example of saccades in preadaptation. **(A)** Schematics of a backward adaptation trial, with eye (black line) and target (gray bars) positions as a function of time. When the saccade is detected (eye position threshold of 1.7°), the target jumped backward (toward the fixation point to the 6.7° position) and a TMS pulse occurred at a certain time (0, 30, or 60 ms) after saccade detection (these three TMS timings were used in separate sessions). Target was switched off 110 ms after saccade detection. For the forward experiment, only the direction of the target jump (away from fixation point to the 13.3° position) differed from the backward experiment, leading to a progressive increase of gain. **(B)** Time-course of saccadic gain during the backward experiment: example of the Vertex session for subject SB. Saccadic gain is presented as a function of the number of trials in a session (290 trials) and according to the different phases: preadapt

noTMS (pre-noTMS), preadapt TMS (pre-TMS), adaptation and postadapt TMS (post-TMS). Horizontal black bars indicate the mean gain in preadapt noTMS, in preadapt TMS, in postadapt TMS and for the last 20 trials of the adaptation phase. These bars help to show the main measures of this study: comparing mean gains between pre-noTMS and pre-TMS will reveal a direct effect of TMS on saccade metrics, whereas comparisons between the pre-TMS mean gain and mean gains at the end of the adaptation and in post TMS will reveal the adaptation efficiency and after-effect, respectively (see Materials and Methods section). **(C)** and **(D)** Time-course of eye position aligned on target appearance. The preadaptation trials without TMS are represented in black whereas the preadaptation trials with TMS over Crus I at 0 ms are represented in gray. The occurrence of TMS pulse is indicated by the vertical-dashed line.

experiment was identical to the adaptation experiments, including three sessions with TMS over Crus I (0, 30, and 60 ms) and one with TMS over the Vertex (30 ms). Each session was composed of the same four phases as for ad-

aptation experiments. The only difference with these experiments was that the target remained at $\pm 10^\circ$ (i.e., there was no intrasaccadic target jump) for the 200 trials following the preadapt TMS.

Figure 2B presents for the Vertex session of the backward experiment, an example of the time-course of saccadic gain as a function of the number of trials. Saccadic gain progressively decreased during the adaptation phase and remained low in postadapt TMS relative to the preadapt phases. For the forward experiment (not shown), the gain of saccades progressively increased during the adaptation phase and for the control experiment (not shown), no modification of saccade gain was observed.

Data Analysis

Horizontal movements of the left eye were analyzed off-line with a custom program developed in the Matlab environment (The MathWorks, Natick, MA). The position and time of the beginning and end of each primary saccade (the first saccade after target appearance) were detected using the Eyelink eye movement parser (velocity threshold: 30°/s). Saccades contaminated by a blink were excluded from further analysis.

Saccade amplitude and duration were calculated as the difference between final and initial positions and times, respectively. Saccade velocity was calculated using the two-point central difference derivative [Bahill and McDonald, 1983]. For the preadaptation phases, acceleration duration (time from saccade start to velocity peak) and deceleration duration (time from velocity peak to saccade end) were also calculated. The gain of each saccade was computed as the ratio between saccade amplitude and retinal error (difference between target position and initial eye position). Mean gain values were calculated separately for the leftward and rightward saccades, for the pre- and postadaptation phases as well as for every block of 40 trials of the adaptation phase (± 20 trials in the left and right directions). Saccades with a gain outside the interval mean ± 2 SD were excluded. Gain change for the saccade of trial n was calculated as follows:

for the backward experiment:

$$\text{Gain change } (n) = \frac{\text{Mean gain preadapt TMS} - \text{gain } (n)}{\text{Mean gain preadapt TMS}} \quad (1)$$

for the forward and control experiments:

$$\text{Gain change } (n) = \frac{\text{Gain } (n) - \text{Mean gain preadapt TMS}}{\text{Mean gain preadapt TMS}} \quad (2)$$

Thus, positive values indicate gain changes in the direction of adaptation (decrease or increase for the backward and forward experiments, respectively) whereas negative values indicate changes opposite to the adaptation. For the control experiment, positive (negative) values indicate gain increases (decreases).

We calculated the three following adaptation parameters separately for each saccade direction. Initial speed of adaptation (first half of the adaptation phase) was defined as the slope of the linear relationship between the gain of the first 50 trials of the adaptation phase and the trial number. Adaptation efficiency was defined as the mean of the gain change computed across the 20 last trials of the adaptation phase. Adaptation after-effect was defined as the mean of the gain change computed across all trials of the postadapt TMS phase (Fig. 2B).

Statistical analyses were performed with the Statistica 9 software package. In preadapt, repeated-measures ANOVA were run with the “TMS” factor (preadapt noTMS versus preadapt TMS) and the “session” factor (Crus I 0 ms vs. Crus I 30 ms vs. Crus I 60 ms vs. Vertex 30 ms) on saccadic gain, duration, velocity peak, acceleration duration, and deceleration duration. For the adaptation parameters (initial speed, efficiency, and after-effect of adaptation), the mean across the three timings (0 ms vs. 30 ms vs. 60 ms) was calculated because a first ANOVA testing this “timing over Crus I” factor revealed no effect (see “Results” section). Then, these adaptation parameters were submitted to repeated-measures ANOVAs with the “stimulation site” factor (Crus I vs. Vertex) and “saccade direction” factor (rightward versus leftward). Significant ANOVAs were followed by post-hoc tests. Statistical significance was set at $P < 0.05$.

RESULTS

TMS Over Crus I and Saccade Metrics

The 60 trials recorded before the adaptation phase (30 preadapt noTMS trials and 30 preadapt TMS trials) allowed us to test whether TMS over Crus I had a direct influence on saccade metrics, independently from its potential effects on saccadic adaptation. Because the preadaptation phases (noTMS and TMS) were identical in all three experiments, the data from all preadaptation phases were pooled together. They were then submitted to repeated-measures ANOVAs to seek an effect of the “TMS” factor (noTMS versus TMS) and the “session” factor (Crus I 0 ms vs. Crus I 30 ms vs. Crus I 60 ms vs. Vertex 30 ms) on saccadic gain, duration, velocity peak, acceleration duration, and deceleration duration.

A significant effect of the “TMS” factor and an interaction between “TMS” and “session” factors were found for the *gain* of rightward saccades ($F[1,24] = 4.73$; $P < 0.05$ and $F[3,72] = 4.83$; $P < 0.01$, respectively). Only an effect of the “TMS” factor was detected for the *gain* of leftward saccades ($F[1,24] = 7.71$; $P < 0.05$). Post-hoc Tukey’s HSD tests showed that, when TMS was applied over Crus I at saccade detection (0 ms), the *gain* of saccades in both directions was significantly smaller than when no TMS was applied ($P < 0.05$; see Fig. 2C,D for individual saccade recordings in preadaptation, and Fig. 3A). Looking at individual data, only four subjects out of 25 did not show this

induced hypometria for rightward saccades and five subjects out of 25 did not present this hypometria for leftward saccades. Because the target was switched off at saccade detection in preadapt phases, no compensatory corrective saccades were observed after the TMS-induced hypometric saccades (see Fig. 2C,D, for examples of saccades recorded

in preadaptation without TMS and with TMS over Crus I at 0 ms). In the preadapt phase with TMS applied over Crus I at 0 ms, the *duration* of ipsiversive and contraversive saccades was significantly smaller than in preadapt noTMS (ANOVA $F[3,72] > 14.1$; $P < 0.001$ and post-hoc Tukey's HSD tests, $P < 0.001$, Fig. 3B). In addition, the *duration* of rightward saccades in the Vertex session was larger in the TMS condition than in the noTMS condition (post-hoc Tukey's HSD test, $P < 0.01$). Finally, repeated-measures ANOVAs on the *peak velocity* showed a significant effect of the "TMS" factor ($F[1,24] > 6.42$, $P < 0.01$) due to a tendency of slower saccades with TMS than without TMS. This trend was only significant for leftward saccades with TMS over Crus I at 0 ms ($380.1 \pm 47.3^\circ/\text{s}$) relative to the no TMS condition ($391.6 \pm 39.9^\circ/\text{s}$; post-hoc Tukey's HSD test, $P < 0.05$).

The *acceleration duration* was not modified by TMS over Crus I (repeated-measures ANOVAs: $F[3,72] < 2.09$; $P > 0.11$). However, the *deceleration duration* significantly decreased with TMS over Crus I at 0 ms for rightward and leftward saccades (ANOVAs: $F[3,72] > 3.96$, $P < 0.05$ and post-hoc Tukey's HSD tests, $P < 0.05$, Fig. 3C).

Modifications of gain, duration, and deceleration duration were exclusively found when TMS was applied over Crus I at 0 ms. However, for the control session, TMS was applied over the Vertex at 30 ms and could thus not perfectly control for the metrics changes found with TMS applied over Crus I at 0 ms. To this aim, a subset of 10 subjects performed an additional preadaptation phase without TMS (30 trials) and with TMS (30 trials) over the Vertex at 0 ms. The mean values of gain of leftward and rightward saccades across these 10 subjects are presented in Table I (left). For comparison, the mean preadaptation values with and without TMS over Crus I (0 ms) re-calculated in the same subjects are also shown in Table I (right). We submitted these gain values to a three-way ANOVA with the site (Vertex 0 ms vs. Crus I 0 ms), the phase (pre-noTMS vs. pre-TMS), and the direction (rightward vs. leftward) factors. A significant interaction between the site and the phase factors was detected ($F[1,9] = 5.35$, $P < 0.05$). This interaction is due to the fact that when stimulating the Vertex at 0 ms, no modification of gain is induced (post-hoc Fisher's LSD test, $P > 0.62$) whereas TMS over

Figure 3.

Saccadic parameters in preadaptation phases. Mean values of saccade gain (A), duration (B), and deceleration duration (C) in preadaptation phases across the 25 subjects that performed the different experiments (10 subjects for the backward experiment, 9 subjects for the forward experiment, and 6 participants for the control experiment). Values without TMS (◆) and with TMS (●) are represented. Error bars are standard errors of the mean. Statistically significant differences between preadapt noTMS (pre-noTMS) and preadapt TMS (pre-TMS) are indicated by (* $P < 0.05$), (** $P < 0.01$), and (***) $P < 0.001$).

TABLE I. Results of the subgroup of 10 subjects that performed preadaptation tests with TMS applied at 0 ms over both the Vertex and Crus I

	Vertex 0 ms		CrusI 0 ms	
	Pre-noTMS	Pre-TMS	Pre-noTMS	Pre-TMS
LeftW sacc	0.90 ± 0.03	0.91 ± 0.02	0.95 ± 0.02	0.92 ± 0.03
RightW sacc	0.96 ± 0.03	0.96 ± 0.02	0.98 ± 0.03	0.94 ± 0.02

Mean values of gain of leftward and rightward saccades across the 10 subjects are shown in upper and lower lines, respectively, for TMS over the Vertex at 0 ms (left) and for TMS over CrusI at 0 ms (right). Standard errors are SEMs.

Crus I produced hypometria for saccades in both directions (post-hoc Fisher's LSD test, rightward saccades $P = 0.02$ and leftward saccades $P = 0.07$). Thus, the hypometria induced in preadaptation with TMS over Crus I at 0 ms (see Fig. 3) appears to be specific of the stimulation site.

In conclusion, TMS applied at saccade detection over Crus I (but not over the Vertex) induced hypometria of both leftward and rightward saccades. This hypometria was associated with a decrease of saccade duration, which is due to a shorter deceleration duration without change of acceleration duration. The velocity peak was decreased by TMS but this effect was significant only for leftward saccades (contraversive to the stimulation side). Finally, no significant changes were found for other TMS timings.

TMS Over Crus I and Saccadic Adaptation

The initial speed, efficiency, and after-effect of adaptation will be presented sequentially. For each of these three parameters, one-way repeated-measures ANOVAs testing the "timing over Crus I" factor (0 ms vs. 30 ms vs. 60 ms) were performed for rightward and leftward saccades of the backward, forward, and control experiments. No significant effect of this factor was found for any of these parameters (maximum F -value associated with minimum P -value, for the backward experiment initial adaptation speed: $F[2,18] < 1.60$; $P > 0.22$). Therefore, data were pooled across the three timings by calculating for each subject the mean of all Crus I stimulation sessions. These mean data were then submitted to two-way repeated-measures ANOVAs testing the stimulation site factor (Crus I vs. Vertex) and the saccade direction factor (leftward saccades vs. rightward saccades).

TMS Over Crus I Does Not Modify Initial Adaptation Speed

The initial adaptation speed was calculated separately for each saccade direction, as the slope of the linear relationship between saccade gain and trial number during the first 50 trials of the adaptation phase. These relationships were

fitted separately for the different sessions of the backward (Fig. 4A), forward (Fig. 4B), and control experiments (Table II). For the backward experiment, there was an effect of the saccade direction factor (Fig. 4C; $F[1,9] = 6.20$; $P < 0.05$) but no effect of the stimulation site nor any interaction ($F[1,9] < 3.02$; $P > 0.12$). This pattern of results is due to a slightly larger initial adaptation speed for the rightward saccades relative to the leftward saccades, independently of the stimulation site (post-hoc Fisher's LSD test, $P > 0.07$). For the forward experiment (Fig. 4D) and control experiment (Table II), no effects of the stimulation site or saccade direction factors, nor any interaction were found (forward experiment: $F[1,8] < 2.03$; $P > 0.19$; control experiment: $F[1,5] < 0.81$; $P > 0.41$). In conclusion, in both backward and forward experiments, TMS over Crus I did not significantly modify the initial speed of adaptation.

TMS Over Crus I Does Not Significantly Modify Adaptation Efficiency

Adaptation efficiency (i.e., amount of adaptation accumulated at the end of the adaptation phase) was calculated separately for each saccade direction as the mean of the gain change across the 20 last trials of the adaptation phase (see "Materials and Methods" section). For the backward experiment (Fig. 5A), there was no effect of the stimulation site or of the saccade direction factors, nor any interaction (repeated-measures ANOVAs, $F[1,9] < 2.79$; $P = 0.13$). In this experiment, the gain was decreased at the end of the adaptation phase by $10.6 \pm 1.3\%$ with Crus I stimulation and by $13.1 \pm 1\%$ with Vertex stimulation. For the forward experiment, the stimulation site and the saccade direction factors again had no effect on the adaptation efficiency and no interaction of these factors was found (Fig. 5B; repeated-measures ANOVAs, $F[1,8] < 1.42$; $P > 0.27$). Here, the gain was increased at the end of the adaptation by $6.9 \pm 1\%$ with Crus I stimulation and by $5.2 \pm 1\%$ with Vertex stimulation. And similarly to the two adaptation experiments, repeated-measure ANOVA in the control experiment showed no effect of the stimulation site or the saccade direction factors, nor any interaction on the gain changes of leftward and rightward saccades ($F[1,5] < 1.99$; $P > 0.22$; Table II). In this experiment, the gain change at the end of the so-called "adaptation" phase (no intrasaccadic target jump) was rather small ($0.7 \pm 1.6\%$ for Crus I stimulation and $2.5 \pm 1.5\%$ for Vertex stimulation) as compared to the two adaptation experiments. Thus, TMS over Crus I did not induce saccadic gain changes (control experiment) and did not significantly modify the efficiency of adaptation (backward and forward experiments).

TMS Over Crus I Modifies the After-Effect of Adaptation

The adaptation after-effect (i.e., amount of adaptation retained after the end of the adaptation phase) was

Figure 4.

Initial adaptation speed in backward (A, C) and forward (B, D) experiments. (A) and (B): Time-course of saccade gain for the 50 first trials of the adaptation phase, for two representative subjects with TMS applied over the Vertex. Different symbols indicate the leftward (□) and rightward (■) saccades. The linear relationship between the saccade gain and the trial number is represented separately for leftward and rightward saccades. The slope of this lin-

ear relationship defines the initial adaptation speed. (C) and (D): Mean values of the initial adaptation speed [slope of linear relationship illustrated in panels (A–B)] across the 10 subjects of the backward experiment (C) and the 9 subjects of the forward experiment (D). The values of initial adaptation speed are represented separately for leftward (□) and rightward (■) saccades as a function of the stimulation site, Vertex and Crus I.

calculated as the mean gain change in postadapt TMS (see Materials and Methods section).

For the backward adaptation, there was an interaction between the stimulation site and saccade direction factors on the after-effect (two-way repeated-measures ANOVA, $F[1,9] = 5.01$; $P = 0.05$). Indeed for leftward saccades, the adaptation after-effect was similar for Crus I and for Vertex stimulation (respectively: $9.9 \pm 1.8\%$ and $10.7 \pm 2.3\%$; Fig. 5C), whereas for rightward saccades it was weaker when TMS was applied over Crus I ($8.0 \pm 1.1\%$) than over the Vertex ($13.3 \pm 1.1\%$; post-hoc Fisher's LSD test, $P < 0.01$).

For forward adaptation, the stimulation site factor had a significant effect on the after-effect (two-way repeated-measures ANOVA, $F[1,8] = 6.58$; $P < 0.05$), but there was no effect of the saccade direction factor ($F[1,8] = 1.86$; $P = 0.21$) nor any interaction between the two factors ($F[1,8] = 0.14$; $P = 0.72$). Indeed for leftward saccades, the adaptation after-effect was $8.4 \pm 1.5\%$ with TMS over Crus I whereas it was $3.6 \pm 1.4\%$ for Vertex stimulation (Fig. 5D). For rightward saccades, the after-effect was also stronger for Crus I than for Vertex stimulation (respectively: $6.3 \pm 1.5\%$ and $2.4 \pm 1.8\%$).

TABLE II. Results of control experiment

	"Adaptation speed" (slope of gain vs. trial relationship)		"Adaptation efficiency" (gain change end "adapt" re- preTMS)		"Adaptation after-effect" (gain change post TMS re- preTMS)	
	Vertex	Crus I	Vertex	Crus I	Vertex	Crus I
LeftW sacc	3.9×10^{-4}	1.7×10^{-4}	$1.7 \pm 1.1\%$	$0.6 \pm 1.3\%$	$2.3 \pm 1.2\%$	$-0.8 \pm 1.5\%$
RightW sacc	9.1×10^{-4}	2.6×10^{-4}	$3.2 \pm 1.9\%$	$0.8 \pm 1.9\%$	$2.4 \pm 2.2\%$	$0.5 \pm 2.0\%$

Mean values of the "adaptation speed", "efficiency" and "after-effect" across the 6 subjects of the control experiment ($\pm$ SEM). These parameters are the same as those calculated in the adaptation experiments, but because no adaptation was elicited in this experiment, words related to adaptation are written in quotes.

Finally for the control experiment, the gain changes in postadapt TMS were rather small for both saccade directions and stimulation sites (Table II). A repeated-measures ANOVA did not identify any effect of the stimulation site or saccade direction factors, nor any interaction on the "after-effect" ($F[1,5] < 0.90$; $P > 0.39$). Thus in this experiment, gain in postadapt TMS was very similar to the gain in preadapt TMS for the two stimulation sites. The results of this control experiment show firstly that TMS itself was not able to induce saccadic adaptation, and second that the changes of after-effect reported for the two adaptation experiments were specifically related to TMS over Crus I interfering with saccadic adaptation.

DISCUSSION

The goal of this study was to investigate whether the lateral cerebellum is involved in saccade performance and/or in saccadic plasticity. Results showed that TMS over Crus I applied at saccade detection (0 ms) induced hypometria of saccades in both directions. This hypometria was related to a specific reduction of the deceleration duration of saccades. Furthermore, TMS over Crus I had different effects on saccadic adaptation, depending on the direction of saccades and on the type of adaptation: TMS over the lateral cerebellum depressed the after-effect of backward adaptation for ipsiversive saccades whereas it potentiated the after-effect of forward adaptation for saccades in both directions.

Effect of TMS Over Crus I on Saccade Performance

The finding that TMS over Crus I induces hypometria of saccades in both directions indicates that Crus I is involved in saccade performance. Although quite small (difference of gain of 0.03), this induced hypometria is consistently observed in 20 of 25 subjects. An implication of the lateral cerebellum in saccadic control was so far unclear mainly because of lack of direct evidence (see "Introduction"). The only study that revealed a causal relation between cerebellar perturbation and changes of reactive saccades metrics

used TMS over the oculomotor vermis [Hashimoto and Ohtsuka, 1995]. Using a figure-of-eight coil, these authors applied single-pulse TMS at different timings relative to saccade onset. They found that TMS pulses applied at saccade onset reduced the amplitude of contraversive saccades whereas pulses applied either at saccade onset or 20 or 40 ms later rendered the ipsiversive saccades hypermetric. We note however that the hypermetria of ipsiversive saccades could correspond to the dynamic overshoot additionally reported by these authors (see their Fig. 5B). In addition, because the vermis is deeper relative to the coil than paravermal and hemispheric regions, it is doubtful whether the vermis could have been reached without interfering with these more superficial areas. Finally, because no neuronavigation system was used to place the TMS coil in Hashimoto and Ohtsuka [1995], the exact stimulated neural structures remain uncertain. In comparison, our study is the first which, thanks to a neuronavigation system and individual T1-scans, perturbed activity in a specific area of the lateral cerebellum (Crus I) and disclosed saccade metrics changes.

A recent study [Xu-Wilson et al., 2010] reported that TMS over different brain areas, including the medial part of the cerebellum and the vertex, can stop 15° saccades in flight after a delay of at least 45 ms. As a consequence, primary saccades became hypometric. We would like to argue that the hypometria revealed here is not due to this pause effect. In the present study, TMS applied over Crus I at saccade detection (timing called "Crus I at 0 ms") actually occurred around 18 ms after saccade onset (see Materials and Methods section), which would thus produce a possible pause effect 63 ms (i.e., $18 + 45$) after saccade onset. Because we studied saccades of 10° , saccades were already completed at that time (mean saccade duration in pre no TMS: 47 ± 0.5 ms) and the pause would thus have occurred too late to contribute to the hypometria reported here. Thus, this study reveals a reduction of saccade amplitude occurring less than 29 ms (i.e., $47-18$) after TMS over Crus I, which cannot be accounted for by the nonspecific pause reported by Xu-Wilson et al. [2010]. Moreover, we tested the effect of TMS applied over the Vertex at saccade detection in 10 subjects and found no modification of gain (see Table I). For these same subjects, the gain was decreased when stimulating Crus I at 0 ms.

Figure 5.

Amount of adaptation in backward (**A, C**) and forward (**B, D**) experiments. Mean saccadic gain changes for the last 20 trials of the adaptation phase [efficiency of adaptation, (**A**) and (**B**)] and for the postadaptation phase [after-effect of adaptation, (**C**) and (**D**)] relative to preadapt TMS. Results for leftward saccades are shown with gray bars and data for rightward saccades are shown

with black bars. For the backward experiment, statistically significant differences of the adaptation after-effect between Vertex and Crus I stimulation for rightward saccades are indicated by (* $P < 0.05$, post-hoc Fisher's LSD test). For the forward experiment, repeated-measures ANOVA showed a significant effect of the stimulation site factor on the adaptation after-effect (* $P < 0.05$).

This reinforces the idea that the lateral cerebellum is specifically responsible for the induced hypometria and thus plays a role in saccadic performance.

Our finding of a bilateral hypometria induced by TMS over Crus I apparently differs from the conclusions of a recent lesion study in the monkey [Ohki et al., 2009]. In this study, unilateral lesions of the cerebellar hemisphere VI–VII (including Crus I) did not induce hypo- or hypermetria but increased the trial-to-trial variability in the amplitude of visually guided saccades. However, beside species differences, this apparent difference could be

explained by the smaller saccades investigated in Ohki et al.'s study (5° as compared to 10° in ours) or by the fact that monkeys could have recovered from a potential dysmetria during the 2 weeks period between the surgery and the first postlesion recording. Note that the hypometria observed in our study is bilateral, like the transitory bilateral hypometria induced by a midline vermal lesion in the monkey in the early postlesion phase [as soon as 2 days; Barash et al., 1999]. This raises the question whether TMS pulses over Crus I could additionally modulate neural activity in the vermis. In the mouse, Coutinho et al.

[2004] electrically stimulated slices of cerebellar cortex and found that Purkinje cells located 1–3 mm from the stimulation locus were activated through the parallel fibers. Although TMS is not as focal and does not have the same properties as electrical stimulation, it is uncertain whether TMS activation of parallel fibers could reach the vermis by propagating over 3.5 cm in our human subjects (see Materials and Methods section). Thus, our TMS effects can be assumed to be largely related to modification of neural activity within the Crus I lobule and strongly suggest that the lateral cerebellum is involved in saccade performance.

Effect of TMS Over Crus I on Saccadic Adaptation

TMS over Crus I did not significantly modify the initial speed or the efficiency of adaptation for either the backward or forward experiments. However, it significantly influenced the adaptation after-effect in different ways: for the backward adaptation, the after-effect for rightward saccades (ipsiversive to the stimulated cerebellar hemisphere) was reduced whereas for forward adaptation, the after-effect for saccades in both directions was increased. These modifications were, most likely, not related to the changes of saccade metrics obtained in preadaptation phase (see previous paragraph: “Effect of TMS over Crus I on saccade performance”). Indeed, whereas the induced hypometria in the preadaptation phase was only observed when stimulating Crus I at 0 ms, the modifications of adaptation were observed for the three TMS timings. Moreover, this hypometria was quite small (difference of gain of 0.03) and seems insufficient to explain the qualitatively different effects on saccadic adaptation of Vertex and Crus I stimulations. In addition, no effect of TMS was observed in the control experiment, indicating that the effects of TMS disclosed in the forward and backward experiments are specifically associated with adaptation mechanisms.

The present single-pulse TMS approach allows us to evaluate the time relative to saccade production at which the lateral cerebellum is involved in saccadic adaptation. Because modifications of adaptation were observed when stimulating Crus I at 0, 30, and 60 ms after saccade detection, Crus I seems to be implicated in saccadic adaptation around saccade execution time, corresponding to the occurrence of the target jump or the immediately following period. Thus, the stimulation could have interfered with intra- and postsaccadic mechanisms, like the cerebellar processing of error signals or the synaptic modifications resulting from the re-iteration of error signals. The lack of an effect of pulse timing could be explained by the fact that the 60 ms range of TMS timings was too narrow relative to the duration of the cerebellar involvement in saccadic adaptation. Another non exclusive possibility is that the TMS-induced modifications of adaptation after-effect are the consequences of an “rTMS-like” effect slowly building up over a session, rather than of a purely single-

pulse TMS effect. rTMS effects are commonly created by administering high frequency (>0.5 Hz) pulse trains for several minutes, after which an enhancement or inhibition of brain function is observed for several minutes [Aydin-Abidin et al., 2006]. Although we cannot rule out such an explanation, the low repetition rate of TMS pulses in our paradigm (0.2–0.3 Hz range) seems unlikely to create an “rTMS-like” effect. In addition, the timing-dependent modifications of saccade performance disclosed in the preadaptation phase clearly reveal the predominant contribution of a non rTMS-like effect in our study. Note further that the interpretation proposed in the following is valid irrespective of whether a pure single-pulse effect or a rTMS-like effect took place in our study.

Backward and forward adaptations are known to follow different time-courses: gain decrease is usually faster/easier to achieve than gain increase [Miller et al., 1981; Noto et al., 1999; Panouilleres et al., 2009; Straube and Deubel, 1995; Straube et al., 1997]. Similar differences of gain changes between the two adaptation types were observed in the present study. Indeed in the Vertex session, the after-effect represented a gain change of around 3% for forward adaptation and of 10% for backward adaptation. Note that the small after-effect of forward adaptation does not affect our general conclusion, since TMS over Crus I turned out to have a significant facilitatory effect (whereas if no adaptation difference had been reported, a floor effect due to the low adaptation in the Vertex session could have been invoked). Therefore, our results strongly suggest that the stimulated cerebellar lobule is effectively involved in forward adaptation.

Another issue worth discussing is that TMS over Crus I seemed to specifically interfere with the after-effect of adaptation (Fig. 5, lower panels). One explanation would be that Crus I is involved in keeping in memory the adapted saccade gain reached after the adaptation phase, but not in the development of adaptive gain change *per se*. However, note that the significant effects of TMS on adaptation after-effects are paralleled by similar trends on adaptation efficiency (Fig. 5, upper panels). This observation suggests that TMS over Crus I started depressing backward adaptation and potentiating forward adaptation during the adaptation phase itself, and these effects become significant only when measuring the after-effect.

In the Introduction, three hypotheses about the potential role of Crus I in saccadic adaptation were proposed, assuming a single action of TMS. However, none of these hypotheses appears to adequately explain the present results. Indeed, Crus I is not specifically involved in the adaptation of saccades in the ipsiversive direction because the effect of TMS on forward adaptation was observed for both saccade directions. Moreover, for the same reason, Crus I is not specifically involved in processing one direction of error signals. Finally, Crus I is not specifically involved in one of the two adaptation types (backward or forward) because TMS over Crus I induced changes in both adaptation types. The demonstrated effectiveness of

cerebellar TMS on both types of adaptation additionally suggests that they are neurally controlled mechanisms, contrary to what has been proposed by Golla et al. [2008] for backward adaptation. These authors suggested that backward adaptation had a substantial passive component which is based on uncompensated fatigue. However, in addition to ours, the study of Jenkinson and Miall [2010] disputes this proposal by showing a partial reduction of backward adaptation with rTMS over the oculomotor vermis. Thus, these two studies strongly suggest that backward adaptation is an active mechanism, which relies on intact cerebellar function.

Because we found a differential TMS effect on the two adaptation types, we propose an alternative hypothesis assuming a dual effect of Crus I TMS on saccadic adaptation mechanisms. According to this hypothesis, TMS pulses could deactivate a network of neurons that is specifically involved in backward adaptation, leading to a reduction of adaptation after-effects. TMS pulses could also activate another network that is implied in forward adaptation, increasing the size of after-effects. These two networks of neurons could either occupy slightly different locations in the cerebellar hemisphere (e.g.: Purkinje cells of Crus I directly affected by TMS and Purkinje cells in neighbouring areas indirectly recruited via the parallel fiber system) or be functionally different within the same cerebellar area (Crus I). However, TMS does not provide further anatomical information on these cerebellar networks because several cell populations can be directly or indirectly affected by the TMS pulses (inhibitory interneurons, parallel fibers, and Purkinje cells). This dual-action hypothesis is consistent with the fact that TMS can generate both an excitatory effect and an inhibitory one. Indeed, TMS over the motor cortex excites pyramidal neurons and also inhibits them through inhibitory neurons activation [see for review: Terao and Ugawa, 2002]. To conclude, the present data provide a functional dissociation between backward and forward adaptation mechanisms and suggest separate neural substrates in the lateral cerebellum for these two plasticity mechanisms.

CONCLUSION

Our study provides the first clear evidence that the lateral cerebellum (Crus I) is involved in saccade metrics control and in saccadic adaptation in humans. Because TMS over Crus I had a dual effect on backward and forward adaptation and, respectively, impaired and enhanced the after-effects of these processes, our study confirms that these two types of adaptations are both active but separate mechanisms. Accordingly, a reappraisal of the current models of motor plasticity is required where not only the medial part of the cerebellum but also the lateral cerebellum contribute to saccade adaptation mechanisms, with possible separate neuronal populations in the lateral cerebellum involved in adaptive lengthening and shortening.

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