Behavioral/Cognitive

The Role of the Posterior Cerebellum in Saccadic Adaptation: A Transcranial Direct Current Stimulation Study

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The posterior vermis of the cerebellum is considered to be critically involved in saccadic adaptation. However, recent evidence suggests that the adaptive decrease (backward adaptation) and the adaptive increase (forward adaptation) of saccade amplitude rely on partially separate neural substrates. We investigated whether the posterior cerebellum could be differentially involved in backward and forward adaptation by using transcranial direct current stimulation (TDCS). To do so, participants' saccades were adapted backward or forward while they received anodal, cathodal, or sham TDCS. In two extra groups, subjects underwent a nonadaptation session while receiving anodal or cathodal TDCS to control for the direct effects of TDCS on saccadic execution. Surprisingly, cathodal stimulation tended to increase the extent of both forward and backward adaptations, while anodal TDCS strongly impaired forward adaptation and, to a smaller extent, backward adaptation. Forward adaptation was accompanied by a greater increase in velocity with cathodal stimulation, and reduced duration of change for anodal stimulation. In contrast, the expected velocity decrease in backward adaptation was noticeably weaker with anodal stimulation. Stimulation applied during nonadaptation sessions did not affect saccadic gain, velocity, or duration, demonstrating that the reported effects are not due to direct effects of the stimulation on the generation of eye movements. Our results demonstrate that cerebellar excitability is critical for saccadic adaptation. Based on our results and the growing evidence from studies of vestibulo-ocular reflex and saccadic adaptation, we conclude that the plasticity at the level of the oculomotor vermis is more fundamentally important for forward adaptation than for backward adaptation.

Key words: **adaptation; cerebellum; saccades; TDCS**

Introduction

Motor adaptation is needed to maintain the accuracy of movements despite physical, physiological, or pathological perturbations to the motor system. The cerebellum is a key structure for sensorimotor adaptation, and damage to the cerebellum has been shown to impair locomotor adaptation (Morton and Bastian, 2006) and visuomanual adaptation to force-field perturbations (Maschke et al., 2004; Smith and Shadmehr, 2005) or to distorted visual feedback (Martin et al., 1996; Tseng et al., 2007; Werner et al., 2009, 2010). Cerebellar integrity has also been demonstrated to be necessary for saccadic adaptation in humans (Straube et al., 2001; Alahyane et al., 2008; Choi et al., 2008; Golla et al., 2008; Panouillères et al., 2013). Electrophysiological and lesion studies in nonhuman primates have shown that a portion of the posterior vermis of the cerebellum composed of the vermal lobules VI–VII [also called oculomotor vermis (OMV)] and the associated caudal fastigial nucleus are crucial for saccadic adaptation (Takagi et al., 1998; Barash et al., 1999; Robinson et al., 2002). The involvement of these specific areas of the cerebellum in saccadic adaptation in humans has been indirectly investigated using neuroimaging (Desmurget et al., 1998) and, more directly, using repetitive transcranial magnetic stimulation over the posterior vermis (Jenkinson and Miall, 2010).

Saccades can be adapted in both a gain-increasing (forward adaptation) and a gain-decreasing (backward adaptation) manner. Behavioral studies of saccadic adaptation suggest that these two processes are underpinned, at least in part, by different mechanisms that probably rely on separate neural substrates (Straube et al., 1997; Noto et al., 1999; Kojima et al., 2004; Ethier et al., 2008; Hernandez et al., 2008; Panouillères et al., 2009; Zimmermann and Lappe, 2010; Schnier and Lappe, 2011, 2012). Although it is not clear as to what these substrates might be, there is evidence that the mechanisms underpinning the two types of adaptation (backward and forward) may both be associated with the cerebellum. For example, recordings of Purkinje cells in the

Received Oct. 1, 2014; revised Jan. 27, 2015; accepted Feb. 10, 2015.

Author contributions: M.T.N.P., R.C.M., and N.J. designed research; M.T.N.P. performed research; M.T.N.P. analyzed data; M.T.N.P., R.C.M., and N.J. wrote the paper.

This study was funded by Research Grant MR/J004588/1 from the Medical Research Council UK, and was supported by the Parkinson's UK/Oddfelows Trust (Grant G-1108), the Wellcome Trust (Grant WT087554), the Oxford Biomedical Research Centre, and the National Institute for Health Research Oxford Cognitive Health Clinical Research Facility. We thank the participants for contributing their time and effort to this study. We also thank Professor Kate Watkins and Dr. Janet Bultitude for their help with the statistics, and Dr. Alexandre Mathy for discussion of cerebellar plasticity. In addition, we thank the two anonymous reviewers for their insightful comments, which have helped us considerably.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.4064-14.2015

 0270-6474/15/355471-09$15.00/0

OMV of nonhuman primates demonstrated differences in firing patterns during backward and forward adaptation (Catz et al., 2008). Moreover, single-pulse TMS of the lateral cerebellar lobule Crus I has differential effects on the retention of backward and forward adaptation (Panouillères et al., 2012). Finally, Golla et al. (2008) demonstrated that patients with lesions involving the cerebellar OMV had a greater deficit in forward adaptation relative to backward adaptation. However, despite these studies, the exact role of the posterior vermis in backward and forward saccadic adaptation in healthy humans remains to be investigated.

Transcranial direct current stimulation (TDCS) can be used to modulate the excitability of the cerebellum in a polarity-dependent manner (Galea et al., 2009). In this study, we investigated the behavioral consequences of modulating the excitability of the midline cerebellum on backward and forward saccadic adaptation. We used the classic double-step target paradigm (McLaughlin, 1967) to adapt saccades either forward or backward, while participants received anodal, cathodal, or sham TDCS to the scalp over the midline of the cerebellum. For simplicity, we refer to this site as the oculomotor vermis, although we cannot be certain that the stimulation did not affect other functional regions.

Materials and Methods

Participants. Seventy-nine participants were included in this study (mean age, 25.1 ± 4.5 years old; 44 females; 9 left-handed subjects). All subjects had normal or corrected-to-normal vision. This study included eight experimental groups with 10 subjects in each group (with the exception of one group, where only 9 subjects were included). There was no difference in subjects' age, sex, or handedness among the eight groups (one-way ANOVA with group factor: age: $F_{(7,94)} < 1, p > 0.95$). Experimental procedures conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki), and were approved by the appropriate national, regional and institutional research ethics committees. Written informed consent was obtained from all participants.

Setup and eye movement recordings. Subjects sat with their heads stabilized by chin and forehead rests 57 cm away from a 150 Hz computer screen (30° × 40°), and additional stabilization was provided using a band behind the head. Saccadic targets (6-mm-diameter black circles on a gray background) were presented on the computer screen and were controlled using Experiment Builder (SR Research).

Movements of the right eye were recorded using an infrared tracker (Eyelink 2000; SR Research) with a frequency of 1000 Hz and a spatial resolution of 0.01°. At the beginning of each recording session, the eye tracker was calibrated by having subjects fixate on a sequence of 5 points forming a cross on the computer screen. Eye movement data were recorded and stored on computer disk for off-line analysis.

TDCS. TDCS was applied via two saline-soaked sponge electrodes (5 × 7 cm) using a DC-STIMULATOR Plus (NeuroConn). In separate groups, anodal or cathodal stimulation was applied in the midline over the posterior cerebellum by placing the active electrode centered over the inion, and the reference electrode over the superior aspect of the right trapezius muscle. The stimulation was delivered at 2 mA for 25 min. Stimulation current was gradually ramped on and off over 10 s. TDCS started after the first preadaptation (Pre0) block and ended around the end of the postadaptation (Post) block (Fig. 1*A*). In two control groups, sham TDCS was applied using the same procedure as above except that the stimulation only lasted 30 s.

Experimental design and procedures of the TDCS sessions. Participants in the four experimental groups received either anodal or cathodal stimulation during a session of either forward or backward adaptation. To control for a placebo effect of stimulation, two control groups were given sham stimulation during either forward or backward adaptation. To test whether stimulation alone had an effect on saccadic amplitude, two additional control groups received anodal or cathodal stimulation during a session of nonadaptive eye movements (nonadaptation).

Each experimental session was composed of the following five phases (Fig. 1*A*): Pre without TDCS (Pre0; $n = 24$ trials); Pre after 5 min of TDCS (Pre5; $n = 24$ trials); Pre after 10 min of TDCS (Pre10; $n = 24$ trials); adaptation or nonadaptation ($n = 240$ trials); and Post ($n = 24$ trials). Adaptation was elicited using the classic double-step target paradigm (McLaughlin, 1967).

Every adaptation trial started with the subject fixating a central point for a random duration between 700 and 1300 ms. When the fixation point disappeared, a target appeared 10° horizontally to the left or to the right of the fixation point, in a random order. Once the saccade toward this target was detected (velocity threshold, 50°/s), the target was displaced. The intrasaccadic step corresponded to 30% of the initial target eccentricity for the first 120 adaptation trials (60 in each direction) and then to 45% for the remaining 120 trials. For backward adaptation sessions, the intrasaccadic target displacement was directed toward the center of the screen (final target location was at ±7° and ±6.5° from the center, respectively, for the first and second half of the adaptation session; Fig. 1*B*); for forward adaptation sessions, the target was directed away from the center (final target location was at ±13° and ±14.5°, respectively, for the first and second half of the adaptation session; Fig. 1*C*). The final target position remained illuminated for 700 ms, and its disappearance signaled to the subject that they could redirect their gaze toward the center of the screen where the fixation point for the next trial would reappear after a random duration between 600 and 1200 ms. In the nonadaptation sessions (Fig. 1*D*), the target did not jump when the saccade was detected, but remained at its initial position before disappearing 700 ms later.

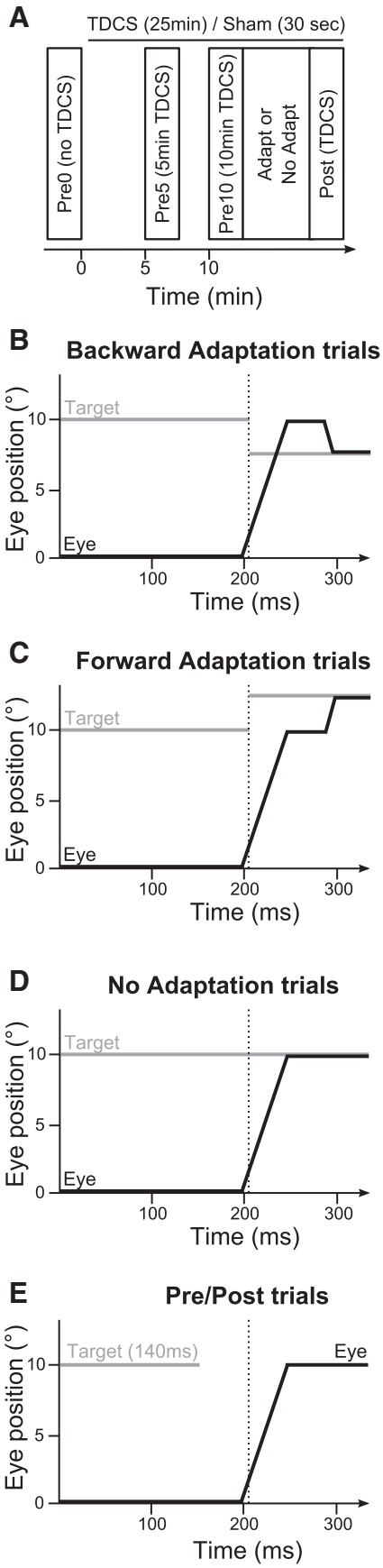
Preadaptation and postadaptation phases (Fig. 1*E*) consisted of short blocks of 24 trials (12 in each direction). Trials started with the presentation of a fixation point for a random duration lasting between 700 and 1300 ms. Immediately following the disappearance of the fixation point, the target was presented at ±10° for only 140 ms. Once a saccade was completed to fixate the no-longer-visible target, subjects were required to direct their gaze back to the center of the screen where the fixation point reappeared between 1300 and 1900 ms later.

Data analysis. Horizontal movements of the right eye were analyzed off-line with a custom program developed in Matlab (MathWorks). The position and time of the initiation and termination of each primary saccade (first saccade after target presentation) were automatically detected by the Eyelink eye movement parser (velocity threshold, 30°/s) and manually checked by the operator. Anticipated saccades, saccades contaminated by a blink or performed in the wrong direction, were excluded from further analysis (on average, 3.5 ± 2.5% of trials per session). For each trial, saccadic gain was calculated as the ratio of saccadic amplitude to initial target eccentricity. In preadaptation, the latency, peak velocity, and duration of each primary saccade were computed. Gain changes were calculated for each saccade (separately for the two saccade directions) for the adaptation, nonadaptation, and postadaptation phases relative to the mean gain in the Pre10 phase as follows:

$$\text{Gain change saccade n} = \frac{\text{Gain saccade n} - \text{Mean gain Pre10}}{\text{Mean gain Pre10}}.$$

Changes in duration and peak velocity were calculated the same way. The adaptation and nonadaptation phases were then divided into 10 blocks of 12 saccades for each direction. For each subject, saccadic gain, duration, and velocity changes were averaged within bins of 12 trials separately for each saccade direction. Saccades with a gain outside the mean ±2 SDs were excluded from further analysis.

Statistical analyses. Statistical analyses were performed with the SPSS statistical software package (IBM). In preadaptation, the latency, gain, duration, and peak velocity were submitted to three-way ANOVAs with saccade direction (leftward and rightward) and blocks (Pre0, Pre5, and Pre10) as within-subject factors and stimulation (anodal, cathodal, and sham) as between-subjects factor. Initial analyses on the adaptation phases and postadaptation did not reveal any effect of left or right initial target direction on gain changes (backward experiment: $F_{(5,143)} < 1.93$, $p > 0.09$; forward experiment: $F_{(1,27)} < 2.52$, $p > 0.12$; no adaptation experiment: $F_{(1,153)} < 2.51$, $p > 0.13$). Thus, the two saccadic directions were pooled for further statistical analyses. To compare for differential effects of TDCS on backward and forward adaptations, we computed the



absolute values of gain change, duration change, and velocity change, resulting in positive values directly comparable between the two adaptation types. Then, separate three-way ANOVAs were performed on the saccadic gain change, duration change, and velocity change, with adaptation blocks (1–10) as a within-subject factor, and with the two between-subjects factors of adaptation type (backward and forward) and stimulation condition (anodal, cathodal, and sham). To estimate the specific effects of TDCS on each adaptation type, separate two-way ANOVAs were performed for backward and forward adaptations on saccadic gain change, duration change, and velocity change with blocks (1–10) as a within-subject factor and stimulation (anodal, cathodal, and sham) as a between-subjects factor. The saccadic gain change, duration change, and velocity change of the nonadaptation phases (control groups) were also submitted to two-way ANOVA with blocks as the within-subject factor and stimulation (anodal and cathodal only) as the between-subjects factor. Finally, saccadic gain change in postadaptation (also called aftereffect), duration change, and velocity change in postadaptation were submitted to ANOVAs similar to the ones described above, but without the within-subject factor of block. Greenhouse–Geisser corrections to the degrees of freedom were applied if Mauchly's sphericity test revealed a violation of the assumption of sphericity for any of the factors in the ANOVAs. Significant main effects or interactions in the ANOVAs were followed by pairwise comparisons where appropriate.

Results

Baseline performance

Each session started with subjects performing the following three preadaptation blocks: the first without TDCS (Pre0) followed by two (Pre5 and Pre10) after the onset of anodal, cathodal, or sham TDCS. We compared saccade parameters (latency, gain, duration, and peak velocity) during these three preadaptation blocks to evaluate whether the stimulation influenced saccadic performance, independently of any adaptation. We found that latencies of leftward saccades were longer in the sham group compared with the cathodal and anodal groups (Fig. 2*A*; significant direction × stimulation interaction: $F_{(2,134)} = 5.67$, $p < 0.01$). However, this difference was present even when no TDCS was applied (Pre0), suggesting that this effect was a pre-existing difference among the groups rather than a result of the stimulation condition. In the three preadaptation blocks, rightward saccades had higher gains ($F_{(1,152)} = 6.59$, $p < 0.05$; Fig. 2*B*) and higher velocities ($F_{(1,152)} = 59.81$, $p < 0.001$; Fig. 2*C*) than leftward saccades. Saccadic gain remained constant during the three preadaptation blocks (no significant block effect or interaction with direction and stimulation factors: $F_{(2,152)} < 1.85$, $p > 0.16$). Saccadic gain, velocity, and duration were not affected by the stimulation conditions (no stimulation effect or interaction: $F_{(2,76)} < 1.20$, $p > 0.31$). Saccadic velocity decreased in Pre10 relative to Pre0 and Pre5 (block effect: $F_{(2,152)} = 6.52$, $p < 0.01$; pairwise comparisons: $p < 0.01$; Fig. 2*C*). This velocity decrease was compensated for by an increase in the duration of movements in the Pre10 block relative to Pre0 and Pre5 (Fig. 2*D*; block effect: $F_{(2,152)} = 4.06$, $p < 0.05$; pairwise comparisons: $p < 0.05$).

In summary, anodal and cathodal TDCS did not modify saccade metrics at baseline. Small differences in performance were

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Figure 1. ***A–E***, Time course of an experimental session (***A***) and of the different categories of trials (***B–E***). ***A***, Each session started with a first pre-adaptation block without TDCS (Pre0). Five and 10 minutes into stimulation, another two blocks of preadaptation (Pre5 and Pre10) were achieved, immediately followed by the adaptation (Adapt) or non-adaptation (No Adapt) phase and the post-adaptation block (Post). ***B–E***, Schematics of trials in the backward adaptation (***B***), forward adaptation (***C***), nonadaptation (***D***), and postadaptation (***E***) phases are represented with eye (black line) and target (gray lines) positions as a function of time. Saccade onset is symbolized with the vertical dashed line.

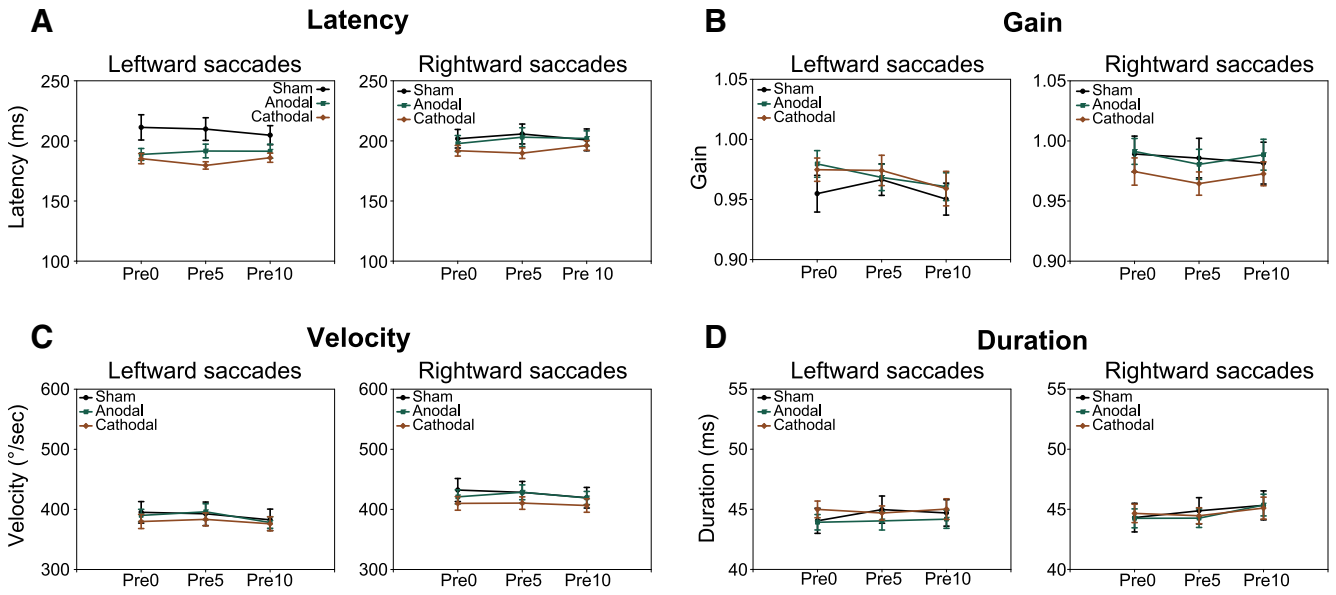

Figure 2. Saccade parameters in the preadaptation blocks. ***A–D***, Mean values of latency (***A***), gain (***B***), peak velocity (***C***), and duration (***D***) for the 12 rightward saccades and the 12 leftward saccades of Pre0, Pre5, and Pre10 were averaged across the subjects who received sham TDCS (black line), anodal TDCS (green line), and cathodal TDCS (brown line) over the oculomotor vermis. Errors bars indicate SEM.

detected between rightward and leftward saccades, and, in the last preadaptation block, a slight decrease in saccadic velocity was compensated by an increase in duration.

Effect of TDCS on the gain change during the adaptation phase

A three-way ANOVA was performed on the gain change, with the two types of adaptation (backward and forward) and the stimulation conditions (anodal, cathodal, and sham) as between-subjects factors and adaptation blocks as the within-subject factor. For both backward and forward adaptation protocols (Fig. 3*A*, left and middle), a progressive and significant change in gain occurred during the adaptation phase, in accordance with the direction of the intrasaccadic step (block effect: $F_{(7,756)} = 195.69$, $p < 0.001$). The adaptive changes tended to start similarly for the two adaptation processes, but backward adaptation led to statistically larger gain modifications than forward adaptation (adaptation effect: $F_{(1,114)} = 37.48$, $p < 0.001$; adaptation × blocks interaction: $F_{(7,756)} = 21.54$, $p < 0.001$). The ANOVA revealed a main effect of stimulation ($F_{(2,114)} = 3.36$, $p < 0.05$) as well as an interaction between blocks and stimulation ($F_{(13,755)} = 1.94$, $p < 0.05$). This effect is mainly due to the significant difference in gain changes between anodal and cathodal stimulation conditions, especially toward the end of the adaptation phase (anodal and cathodal pairwise comparisons for blocks 4, 6, 7, 8, and 10: $p < 0.05$). No interaction between stimulation condition and adaptation type was detected (stimulation × adaptation: $F_{(2,114)} < 1$, $p = 0.79$; blocks × stimulation × adaptation: $F_{(13,756)} = 1.44$, $p = 0.13$), suggesting that TDCS over the cerebellum had a similar effect on forward and backward adaptations.

To test for a selective effect of TDCS polarity on either the forward or backward adaptive process, separate ANOVAs were performed on the gain change, with the blocks as within-subject factor and stimulation conditions as between-subject factor. For backward adaptation (Fig. 3*A*, left), the different stimulation conditions had no significant effect on the gain changes across the 10 blocks of the adaptation phase (stimulation effect: $F_{(2,57)} = 1.20$, $p = 0.31$; stimulation × block interaction: $F_{(12,345)} = 1.07$, $p = 0.39$). However, for forward adaptation (Fig. 3*A*, middle), a significant interaction between adaptation blocks and stimulation is detected ($F_{(13,363)} = 2.32$, $p < 0.01$). This effect is mainly due to the adaptation starting similarly for the three stimulation conditions, but progressing more slowly for subjects receiving anodal TDCS, while it was faster for subjects receiving cathodal TDCS (anodal and cathodal pairwise comparisons for blocks 6, 7, 8, and 10: $p < 0.05$).

To sum up, anodal TDCS led to significantly smaller changes than cathodal TDCS. We found that TDCS over the oculomotor vermis affected the two adaptive processes in the same way, but this effect was significant only for forward adaptation.

Effect of TDCS on adaptation gain aftereffects, measured in the postadaptation phase

Immediately after the adaptation phase, subjects performed a further 24 trials without postsaccadic feedback. The gain change measured during this postadaptation block relative to the mean Pre10 gain reveals the aftereffect of the adaptation, which is a reliable measure of plastic changes underlying sensorimotor adaptation (Bastian, 2008). To compare the effect of TDCS on the aftereffects of the two adaptive processes, we performed an ANOVA on the Post phase gain changes with the two types of adaptation and the stimulation conditions as between-subjects factors. Significantly larger aftereffects were detected for backward compared with forward adaptation (adaptation effect: $F_{(1,114)} = 65.20$, $p < 0.001$), mirroring the greater adaptive change seen during backward adaptation. Moreover, the type of stimulation statistically affected the aftereffects ($F_{(2,114)} = 6.54$, $p < 0.01$), with aftereffects significantly smaller for the anodal stimulation relative to the sham or cathodal stimulation (pairwise comparisons: $p < 0.01$ and $p < 0.001$, respectively). There was no significant interaction between stimulation condition and adaptation type ($F_{(2,114)} = 1.22$, $p = 0.30$), which suggests that stimulation affected the aftereffects of backward and forward adaptations in a similar manner.

More specifically, for backward adaptation, there was a trend only toward smaller aftereffects with anodal TDCS relative to sham (stimulation effect: $F_{(2,57)} = 1.89$, $p = 0.16$; pairwise comparisons:

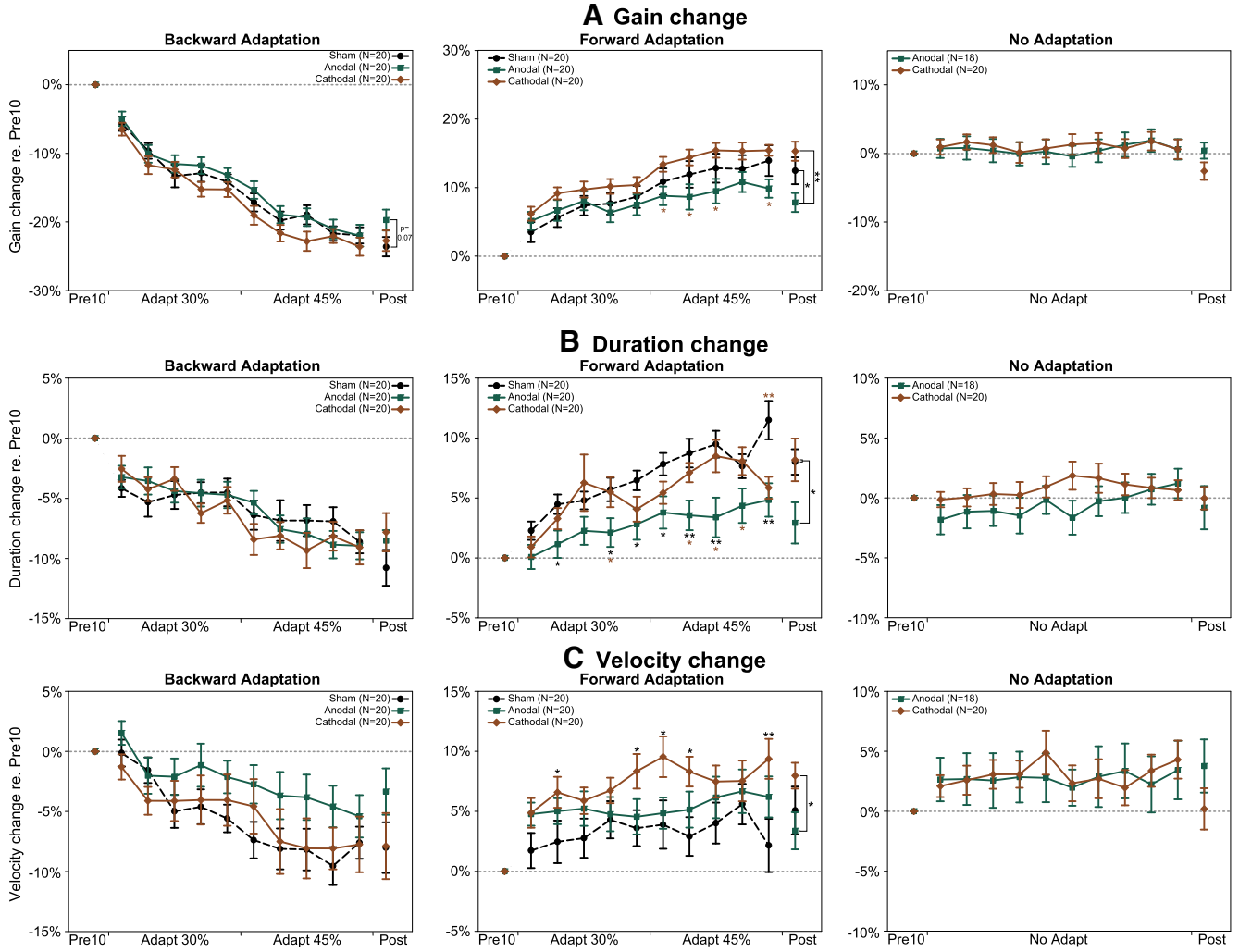

Figure 3. ***A–C***, Development of the gain (***A***), duration (***B***) and velocity (***C***) changes in the different sessions. Gain, duration, and velocity changes relative to the mean gain in Pre10 were averaged across blocks of 12 saccades, with the first five blocks (Adapt 30%) corresponding to trials with an intrasaccadic target jump of 30% of target eccentricity and the last five blocks (Adapt 45%) corresponding to trials with an intrasaccadic target step of 45% of target eccentricity. The plots are built for backward adaptation (left), forward adaptation (middle), and nonadaptation (right) sessions. The black, green, and brown lines represent changes, respectively, for sham, anodal, and cathodal TDCS. Errors bars indicate SEM. Statistically significant differences are indicated as follows: $*p < 0.05$ and $**p < 0.01$, pairwise comparisons following ANOVAs. The black or brown asterisks adjacent to the curves in the central column indicate data points that are significantly different from the sham and cathodal data, respectively.

$p = 0.07$). For forward adaptation, there was a significant effect of stimulation ($F_{(2,57)} = 5.58$, $p < 0.01$), which was explained by a significantly smaller aftereffect when subjects received anodal TDCS compared with either sham or cathodal TDCS (pairwise comparisons: $p < 0.05$ and $p < 0.01$, respectively).

In summary, the aftereffects of both forward and backward adaptations were smaller with anodal TDCS than with the sham and cathodal stimulation, and this effect is again stronger for forward adaptation than backward adaptation.

Effects of TDCS on the saccadic duration changes during the adaptation sessions

Because TDCS over the cerebellum altered saccadic gain during the adaptation sessions, we examined whether the TDCS also affected saccadic duration or velocity during adaptation. Changes in saccadic duration and peak velocity were measured during the adaptation and postadaptation relative to the mean duration and velocity in Pre10.

Changes in saccadic duration during backward and forward adaptation sessions are plotted in Figure 3*B* (left and middle). A three-way ANOVA was performed on the absolute values of duration change, with the two types of adaptation and the stimulation conditions as between-subjects factors, and the 10 adaptation blocks as the within-subject factor. A progressive and significant change in duration occurred during the adaptation phase, which is in agreement with the change of saccadic gain (block effect: $F_{(6,739)} = 44.60$, $p < 0.001$). A significant interaction between blocks and stimulation factors was detected ($F_{(13,739)} = 1.75$, $p < 0.05$), as well as among adaptation, blocks, and stimulation factors ($F_{(13,739)} = 2.45$, $p < 0.01$). These two interactions demonstrate that the effect of the stimulation on the saccadic duration varied with the adaptation blocks and differed depending on the adaptation type. In Post, significantly larger duration changes occurred during backward adaptation compared with forward adaptation (adaptation effect: $F_{(1,114)} = 5.02$, $p < 0.05$; no adaptation × stimulation interaction: $F_{(2,114)} = 2.09$, $p = 0.13$). Moreover, smaller modifications of duration occurred with anodal TDCS compared with the sham condition (stimulation effect: $F_{(2,114)} = 3.23$, $p < 0.05$; pairwise comparisons: $p < 0.05$). To follow these analyses, separate ANOVAs were

performed to understand the specific effect of the stimulation on the duration change for each adaptation type.

During backward adaptation, cathodal TDCS produced the strongest changes of saccadic duration for blocks 4, 6, and 8 of adaptation, while for the first adaptation block the changes for this group were the smallest (Fig. 3*B*, left; blocks × stimulation interaction: $F_{(13,384)} = 2.07$, $p < 0.05$; planned contrasts comparing block × stimulation interaction using first block as reference: $p < 0.05$). In Post, there were no significant differences of duration changes among the three stimulation conditions (stimulation effect: $F_{(2,57)} = 1.29$, $p = 0.28$). For forward adaptation, a progressively smaller increase in duration occurred when subjects received anodal TDCS compared with sham and cathodal TDCS (Fig. 3*B*, middle; stimulation effect: $F_{(2,57)} = 5.01$, $p < 0.01$; block × stimulation interaction: $F_{(10,291)} = 2.12$, $p < 0.05$; pairwise comparisons: $p < 0.05$). This smaller increase of duration with anodal TDCS compared with sham and cathodal TDCS was still present in the Post phase (stimulation effect: $F_{(2,57)} = 3.70$, $p < 0.05$; pairwise comparisons: $p < 0.05$).

To sum up, cathodal TDCS marginally enhanced the reduction in duration for some blocks of the backward adaptation, while anodal TDCS consistently reduced the increase in duration during forward adaptation relative to cathodal and sham conditions.

Effects of TDCS on the velocity changes during the adaptation sessions

Changes in velocity during the adaptation sessions are plotted in Figure 3*C* (left and middle). A three-way ANOVA was performed on the absolute values of velocity change with the two types of adaptation and the stimulation conditions as between-subjects factors, and the 10 adaptation blocks as the within-subject factor. Saccadic velocity significantly changed during the adaptation sessions (block effect: $F_{(6,685)} = 17.32$, $p < 0.001$). A significant interaction between the blocks and the type of adaptation ($F_{(6,716)} = 3.86$, $p < 0.001$) indicates differences in the rate of velocity changes for backward and forward adaptations. Indeed, stronger changes in velocity were detected during backward adaptation compared with the forward adaptation. No main effects or interactions involving the type of stimulation factor were detected ($F_{(12,716)} > 1.51$, $p > 0.11$). In Post, anodal TDCS tended to lead to smaller changes relative to the cathodal condition (stimulation effect: $F_{(2,114)} = 2.83$, $p = 0.06$; pairwise comparisons: $p < 0.05$).

Two separate ANOVAs were then performed for backward and forward adaptation. In the case of backward adaptation, there was no significant effect of stimulation condition or interaction with the block factor ($F_{(2,57)} < 1.44$, $p > 0.21$). However, note that the reduction of velocity while subjects received anodal TDCS appeared to be less than that for the other two groups (Fig. 3*C*, left). We then conducted one-sample *t* tests comparing the values of velocity changes for the different adaptation blocks and the different stimulation conditions with 0. For the sham and cathodal conditions, the reduction in velocity significantly differed from 0 for 8 and 6 of the 10 adaptation blocks, respectively ($t_{(19)} < -2.5$, $p < 0.05$). In contrast, for the anodal group, the velocity change only differed from 0 for the last two blocks of the adaptation phase ($t_{(19)} < -2.6$, $p < 0.05$), suggesting that the change in velocity for this stimulation condition was slower than for the other stimulations. These differences between conditions are reflected in the Post phase, where the change in velocity significantly differed from 0 for both the sham and cathodal groups ($t_{(19)} < -2.86$, $p < 0.01$), but not for the anodal group ($t_{(19)} = -1.73$, $p = 0.10$).

During the forward adaptation, there was a trend for stronger velocity changes observed for blocks 2, 5, 6, 7, and 10 in the cathodal group relative to the sham group (Fig. 3*C*, middle; $F_{(2,57)} = 2.5$, $p = 0.09$; pairwise comparisons, $p < 0.05$). No main effect of the factor stimulation was found in the Post phase, although a significantly higher velocity change was achieved with cathodal relative to anodal stimulation ($F_{(2,57)} = 2.15$, $p = 0.13$; pairwise comparisons between anodal and cathodal, $p < 0.05$).

To conclude, anodal TDCS over the posterior cerebellum slowed down the reduction of velocity during backward adaptation, while cathodal TDCS led to stronger velocity changes compared with sham during forward adaptation.

Absence of TDCS effects on the nonadaptation sessions

To assess whether the effects reported in the above sections are due to TDCS effects on the execution of the saccades themselves, two groups of participants received anodal or cathodal TDCS while performing a nonadaptation session (Fig. 3, right). For these two groups, saccadic gain did not change as a function of the nonadaptation blocks (Fig. 3*A*, right; $F_{(6,201)} = 1.23$, $p = 0.30$), and the anodal or cathodal stimulation did not affect the saccadic gain (stimulation effect: $F_{(1,36)} < 1$, $p = 0.81$; stimulation × block interaction: $F_{(6,201)} < 1$, $p = 0.74$). In the Post phase, saccadic gain change was again not affected by the stimulation ($t_{(36)} = 1.71$, $p = 0.10$).

Similar analyses were performed on the change in saccade duration and velocity in the nonadaptation sessions and during the corresponding Post phases (Fig. 3 *B*,*C*, right panels). For the nonadaptation sessions, there was no significant effect of the stimulation factor or a significant interaction involving this factor on either duration or velocity ($F_{(6,227)} < 1.86$, $p > 0.09$). Moreover, in the Post phase, there were no differences in velocity and duration between the two stimulation conditions ($t_{(36)} > -1.29$, $p > 0.21$).

To conclude, TDCS over the cerebellum did not directly affect saccadic gain, duration, and velocity in the nonadaptation sessions, and thus the TDCS effects reported above are specific to the saccadic adaptation processes.

Discussion

Many neurophysiological studies have implicated the cerebellar cortex as the potential site of saccadic adaptation (Waespe and Baumgartner, 1992; Desmurget et al., 1998; Takagi et al., 1998; Barash et al., 1999; Straube et al., 2001; Scudder, 2002; Inaba et al., 2003; Scudder and McGee, 2003; Golla et al., 2008; Xu-Wilson et al., 2009; Jenkinson and Miall, 2010; Panouillères et al., 2013). This study is the first to investigate the role of the oculomotor vermis of the cerebellum for saccadic adaptation using TDCS in healthy humans. We found that TDCS targeting the oculomotor vermis modifies saccadic adaptation. Indeed, bidirectional modifications of gain were seen in both forward and backward adaptation with anodal and cathodal TDCS. TDCS had a larger influence on gain modification during forward adaptation than backward adaptation. Interestingly, even though the stimulation apparently affected the forward and backward adaptations of gain similarly (i.e., cathodal facilitating and anodal inhibiting), its effect on saccade duration and velocity was dependent on adaptation type. Here, cathodal TDCS promoted larger changes in velocity (with associated increased gain) during forward adaptation but with a tendency for larger duration changes for backward adaptation. In contrast, anodal TDCS led to small adaptive gain changes, and these were associated with smaller changes in dura-

tion for forward adaptation and smaller changes in velocity for backward adaptation.

In preadaptation, rightward saccades had higher gains and higher velocities than leftward saccades, independent of any stimulation effects. Previous studies (Vergilino-Perez et al., 2012; Jóhannesson and Kristjánsson, 2013) have demonstrated that saccades directed to the side of the dominant eye were larger and faster than the saccades directed to the side of the nondominant eye. The majority of our subjects were right handed; and thus, most of them are likely to have dominant right eyes, so it is possible that the left–right asymmetry in preadaptation is due to eye dominance. Notwithstanding this small pre-existing asymmetry at baseline, similar gain changes were produced for the two target directions (see Materials and Methods), demonstrating that it did not influence the adaptation. We also report that saccade velocity decreased in the last preadaptation block (Pre10) relative to the two previous blocks (Pre0 and Pre5), but saccadic amplitude remained constant due to an increase in saccade duration. The decrease in peak velocity is probably due to the repetition of saccades to the same target locations, and the compensation of this reduction, made visible by an increase in saccadic duration, has been shown to be under the control of the cerebellum (Xu-Wilson et al., 2009). That there was no change in saccadic velocity or duration with cerebellar stimulation for normal, unadapted saccades suggests that the mechanisms that compensate for saccadic variability were not affected by the stimulation. Moreover, neither anodal nor cathodal stimulation of the oculomotor vermis modified saccadic gain, duration, or velocity at baseline or during the nonadaptation session. It would therefore appear that the TDCS did not interfere with the cerebellar processes contributing to the execution of the saccades themselves, but specifically interacted with the mechanisms contributing to the adaptation process.

Our finding that anodal TDCS impairs saccadic adaptation, while cathodal TDCS tended to improve it, was quite unexpected. Anodal TDCS is usually described as increasing brain excitability and enhancing behavioral responses, while cathodal TDCS normally has the opposite effect. These responses are thought to be due to the depolarizing and hyperpolarizing effects of anodal and cathodal TDCS, respectively, with consequent excitatory and inhibitory neurotransmitter-mediated plastic consequences (Stagg and Nitsche, 2011). More specifically, when applied over the lateral cerebellum, anodal TDCS has been shown to facilitate adaptation of the upper limb to force-field (Herzfeld et al., 2014) and rotated feedback (Galea et al., 2011; Block and Celnik, 2013), as well as locomotor adaptation (Jayaram et al., 2012) and eye-blink conditioning (Zuchowski et al., 2014). In contrast, cathodal TDCS over the lateral cerebellum impairs force-field adaptation and eye-blink conditioning (Herzfeld et al., 2014; Zuchowski et al., 2014). The behavioral response to TDCS is sensitive to variations in electrode montage (Nitsche et al., 2007, 2008; Moliadze et al., 2010), and changes in stimulation parameters (intensity, duration and time of stimulation) can invert the polarity effects of TDCS (Batsikadze et al., 2013; Monte-Silva et al., 2013). Thus, anodal TDCS in the present study could have decreased the excitability of the posterior vermis, impairing adaptation; while cathodal TDCS could have had the opposite effect. However, another potential explanation for the results in the present study could be that the cerebellar mechanisms or the sites involved in saccadic adaptation differ from upper limb adaptation and eye-blink conditioning; for example, the lateral and medial parts of the cerebellum may well be differently involved in motor adaptation.

In this study, we found the differential effect of the stimulation polarity on the movement kinematics of forward and backward saccadic adaptations. Indeed, cathodal TDCS slightly increased the reduction of saccadic duration during backward adaptation, while it boosted the velocity increase of forward adaptation. On the other hand, the impaired saccadic adaptation with anodal TDCS was associated with a reduction in the normal increase of saccadic duration for forward adaptation and a reduction in the decrease of velocity for backward adaptation. In monkeys, Catz et al. (2008) have shown that simple-spike firing of vermal Purkinje cells changed differently for backward and forward adaptations. Forward adaptation was associated with an increase of saccade duration, and, as the duration increased, the population firing of simple-spike was delayed in time. Because simple-spike population bursts are thought to encode the termination time of unadapted saccades (Thier et al., 2002), delaying the simple-spike firing during forward adaptation results in adapted saccades with increased duration. For backward adaptation, the cell population fired fewer spikes than for unadapted saccades, and the population burst stopped before saccade completion. The authors then proposed that the changes in the population burst could underlie the reduction of velocity that characterizes this adaptation. Based on this study, we can propose that anodal TDCS over the posterior cerebellum interfered with the simple-spike firing of Purkinje cells and then limited the adaptive changes of gain for both adaptations by acting respectively on saccade duration and velocity.

One of the most studied forms of adaptation is another type of eye movement—the vestibulo-ocular reflex (VOR). Saccades and VOR share many similar properties, not least that both operate in "open loop" without the advantage of on-line feedback to update their accuracy and both possess the basic cerebellar control circuitry. It has been hypothesized (Ito, 1982; Boyden and Raymond, 2003) and demonstrated many times (De Zeeuw et al., 1998; van Alphen and De Zeeuw, 2002; Boyden et al., 2006; Hansel et al., 2006) that one of the main cerebellar mechanisms underpinning the adaptation of VOR is long-term depression (LTD), specifically at the parallel fiber/Purkinje cell synapse (PF/PC). The aforementioned studies have shown that strains of mice with impaired LTD in their Purkinje cells present a more pronounced deficit in gain-increasing adaptation of the VOR than gain-decreasing adaptation. More recently, it has been demonstrated that climbing fiber input to the Purkinje cell, which is thought to be the key driver of LTD at the PF/PC synapse (Lisberger, 1998), selectively contributes to gain-increasing VOR adaptation but not to the gain-decreasing adaptation (Kimpo et al., 2014). For saccadic adaptation, electrophysiological studies (Kojima et al., 2007; Kaku et al., 2009; Soetedjo et al., 2009) proposed that the error signal necessary to drive saccadic adaptation is similarly conveyed from the inferior olivary nucleus to the oculomotor vermis via the climbing fibers. A specific involvement of the human cerebellar cortex in gain-increasing saccadic adaptation is supported by evidence that individuals with cerebellar lesions involving the vermis exhibit barely any forward adaptation, but show relatively preserved backward adaptation (Golla et al., 2008). Similar to VOR adaptation, normal LTD is required for saccadic adaptation in humans (Coesmans et al., 2003). These strands of evidence complement our results and lead us to suggest that gain-increasing adaptation is dependent on mechanisms—we propose LTD—and occurs at a site—the oculomotor vermis—that are more easily influenced by TDCS than gain-decreasing adaptation. We speculate that if forward adaptation is dependent on climbing fiber-induced LTD in the

cerebellar cortex then—as we were applying the TDCS during adaptation—the additional hyperpolarizing effect of cathodal TDCS over the cerebellum would have a facilitatory effect on LTD, improving the adaptation. In contrast, anodal stimulation, by acting against the LTD, would have the opposite effect, as we see in this study. The relatively small effect of TDCS on backward adaptation suggests that, as with the growing body of evidence for gain-decreasing VOR adaptation (Nguyen-Vu et al., 2013; Kimpo et al., 2014), climbing fiber-induced plasticity at the level of the cerebellar cortex may not be as fundamentally important for backward saccadic adaptation as it is for forward adaptation.

We therefore conclude that the human posterior vermal cerebellum plays a crucial role in saccadic adaptation and appears to be more heavily involved in the adaptive increase and, to a lesser extent, in the decrease of saccade gain.

References

Alahyane N, Fonteille V, Urquizar C, Salemme R, Nighoghossian N, Pelisson D, Tilikete C (2008) Separate neural substrates in the human cerebellum for sensory-motor adaptation of reactive and of scanning voluntary saccades. Cerebellum 7:595–601. CrossRef Medline

Barash S, Melikyan A, Sivakov A, Zhang M, Glickstein M, Thier P (1999) Saccadic dysmetria and adaptation after lesions of the cerebellar cortex. J Neurosci 19:10931–10939. Medline

Bastian AJ (2008) Understanding sensorimotor adaptation and learning for rehabilitation. Curr Opin Neurol 21:628–633. CrossRef Medline

Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA (2013) Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 591:1987–2000. CrossRef Medline

Block H, Celnik P (2013) Stimulating the cerebellum affects visuomotor adaptation but not intermanual transfer of learning. Cerebellum 12:781–793. CrossRef Medline

Boyden ES, Raymond JL (2003) Active reversal of motor memories reveals rules governing memory encoding. Neuron 39:1031–1042. CrossRef Medline

Boyden ES, Katoh A, Pyle JL, Chatila TA, Tsien RW, Raymond JL (2006) Selective engagement of plasticity mechanisms for motor memory storage. Neuron 51:823–834. CrossRef Medline

Catz N, Dicke PW, Thier P (2008) Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. Proc Natl Acad Sci U S A 105:7309–7314. CrossRef Medline

Choi KD, Kim HJ, Cho BM, Kim JS (2008) Saccadic adaptation in lateral medullary and cerebellar infarction. Exp Brain Res 188:475–482. CrossRef Medline

Coesmans M, Sillevis Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, van Alphen AM, Luo C, van der Geest JN, Kros JM, Gaillard CA, Frens MA, de Zeeuw CI (2003) Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. Ann Neurol 53:325–336. CrossRef Medline

Desmurget M, Pélisson D, Urquizar C, Prablanc C, Alexander GE, Grafton ST (1998) Functional anatomy of saccadic adaptation in humans. Nat Neurosci 1:524–528. CrossRef Medline

De Zeeuw CI, Hansel C, Bian F, Koekkoek SK, van Alphen AM, Linden DJ, Oberdick J (1998) Expression of a protein kinase C inhibitor in Purkinje cells blocks cerebellar LTD and adaptation of the vestibulo-ocular reflex. Neuron 20:495–508. CrossRef Medline

Ethier V, Zee DS, Shadmehr R (2008) Changes in control of saccades during gain adaptation. J Neurosci 28:13929–13937. CrossRef Medline

Galea JM, Jayaram G, Ajagbe L, Celnik P (2009) Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. J Neurosci 29:9115–9122. CrossRef Medline

Galea JM, Vazquez A, Pasricha N, de Xivry JJ, Celnik P (2011) Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. Cereb Cortex 21:1761–1770. CrossRef Medline

Golla H, Tziridis K, Haarmeier T, Catz N, Barash S, Thier P (2008) Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. Eur J Neurosci 27:132–144. CrossRef Medline

Hansel C, de Jeu M, Belmeguenai A, Houtman SH, Buitendijk GH, Andreev D, De Zeeuw CI, Elgersma Y (2006) αCaMKII is essential for cerebellar LTD and motor learning. Neuron 51:835–843. CrossRef Medline

Hernandez TD, Levitan CA, Banks MS, Schor CM (2008) How does saccade adaptation affect visual perception? J Vis 8(8):3 1–16. CrossRef Medline

Herzfeld DJ, Pastor D, Haith AM, Rossetti Y, Shadmehr R, O'Shea J (2014) Contributions of the cerebellum and the motor cortex to acquisition and retention of motor memories. Neuroimage 98:147–158. CrossRef Medline

Inaba N, Iwamoto Y, Yoshida K (2003) Changes in cerebellar fastigial burst activity related to saccadic gain adaptation in the monkey. Neurosci Res 46:359–368. CrossRef Medline

Ito M (1982) Questions in modeling the cerebellum. J Theor Biol 99:81–86. CrossRef Medline

Jayaram G, Tang B, Pallegadda R, Vasudevan EV, Celnik P, Bastian A (2012) Modulating locomotor adaptation with cerebellar stimulation. J Neurophysiol 107:2950–2957. CrossRef Medline

Jenkinson N, Miall RC (2010) Disruption of saccadic adaptation with repetitive transcranial magnetic stimulation of the posterior cerebellum in humans. Cerebellum Lond Engl 9:548–555. CrossRef

Jóhannesson OI, Kristjánsson A (2013) Violating the main sequence: asymmetries in saccadic peak velocities for saccades into the temporal versus nasal hemifields. Exp Brain Res 227:101–110. CrossRef Medline

Kaku Y, Yoshida K, Iwamoto Y (2009) Learning signals from the superior colliculus for adaptation of saccadic eye movements in the monkey. J Neurosci 29:5266–5275. CrossRef Medline

Kimpo RR, Rinaldi JM, Kim CK, Payne HL, Raymond JL (2014) Gating of neural error signals during motor learning. eLife 3:e02076. CrossRef Medline

Kojima Y, Iwamoto Y, Yoshida K (2004) Memory of learning facilitates saccadic adaptation in the monkey. J Neurosci 24:7531–7539. CrossRef Medline

Kojima Y, Yoshida K, Iwamoto Y (2007) Microstimulation of the midbrain tegmentum creates learning signals for saccade adaptation. J Neurosci 27:3759–3767. CrossRef Medline

Lisberger SG (1998) Cerebellar LTD: a molecular mechanism of behavioral learning? Cell 92:701–704. CrossRef Medline

Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT (1996) Throwing while looking through prisms I. Focal olivocerebellar lesions impair adaptation. Brain 119:1183–1198. CrossRef Medline

Maschke M, Gomez CM, Ebner TJ, Konczak J (2004) Hereditary cerebellar ataxia progressively impairs force adaptation during goal-directed arm movements. J Neurophysiol 91:230–238. CrossRef Medline

McLaughlin SC (1967) Parametric adjustment in saccadic eye movements. Percept Psychophys 2:359–362. CrossRef

Moliadze V, Antal A, Paulus W (2010) Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. Clin Neurophysiol 121:2165–2171. CrossRef Medline

Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, Nitsche MA (2013) Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 6:424–432. CrossRef Medline

Morton SM, Bastian AJ (2006) Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci 26:9107–9116. CrossRef Medline

Nguyen-Vu TD, Kimpo RR, Rinaldi JM, Kohli A, Zeng H, Deisseroth K, Raymond JL (2013) Cerebellar Purkinje cell activity drives motor learning. Nat Neurosci 16:1734–1736. CrossRef Medline

Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W (2007) Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 97:3109–3117. CrossRef Medline

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A (2008) Transcranial direct current stimulation: state of the art 2008. Brain Stimul 1:206–223. CrossRef Medline

Noto CT, Watanabe S, Fuchs AF (1999) Characteristics of simian adaptation fields produced by behavioral changes in saccade size and direction. J Neurophysiol 81:2798–2813. Medline

Panouillères M, Weiss T, Urquizar C, Salemme R, Munoz DP, Pélisson D (2009) Behavioral evidence of separate adaptation mechanisms control-

ling saccade amplitude lengthening and shortening. J Neurophysiol 101: 1550–1559. CrossRef Medline

Panouillères M, Neggers SF, Gutteling TP, Salemme R, van der Stigchel S, van der Geest JN, Frens MA, Pélisson D (2012) Transcranial magnetic stimulation and motor plasticity in human lateral cerebellum: dual effect on saccadic adaptation. Hum Brain Mapp 33:1512–1525. CrossRef Medline

Panouillères M, Alahyane N, Urquizar C, Salemme R, Nighoghossian N, Gaymard B, Tilikete C, Pélisson D (2013) Effects of structural and functional cerebellar lesions on sensorimotor adaptation of saccades. Exp Brain Res 231:1–11. CrossRef Medline

Robinson FR, Fuchs AF, Noto CT (2002) Cerebellar influences on saccade plasticity. Ann N Y Acad Sci 956:155–163. CrossRef Medline

Schnier F, Lappe M (2011) Differences in intersaccadic adaptation transfer between inward and outward adaptation. J Neurophysiol 106:1399–1410. CrossRef Medline

Schnier F, Lappe M (2012) Mislocalization of stationary and flashed bars after saccadic inward and outward adaptation of reactive saccades. J Neurophysiol 107:3062–3070. CrossRef Medline

Scudder CA (2002) Role of the fastigial nucleus in controlling horizontal saccades during adaptation. Ann N Y Acad Sci 978:63–78. CrossRef Medline

Scudder CA, McGee DM (2003) Adaptive modification of saccade size produces correlated changes in the discharges of fastigial nucleus neurons. J Neurophysiol 90:1011–1026. CrossRef Medline

Smith MA, Shadmehr R (2005) Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration. J Neurophysiol 93:2809–2821. CrossRef Medline

Soetedjo R, Fuchs AF, Kojima Y (2009) Subthreshold activation of the superior colliculus drives saccade motor learning. J Neurosci 29:15213–15222. CrossRef Medline

Stagg CJ, Nitsche MA (2011) Physiological basis of transcranial direct current stimulation. Neuroscientist 17:37–53. CrossRef Medline

Straube A, Fuchs AF, Usher S, Robinson FR (1997) Characteristics of saccadic gain adaptation in rhesus macaques. J Neurophysiol 77:874–895. Medline

Straube A, Deubel H, Ditterich J, Eggert T (2001) Cerebellar lesions impair rapid saccade amplitude adaptation. Neurology 57:2105–2108. CrossRef Medline

Takagi M, Zee DS, Tamargo RJ (1998) Effects of lesions of the oculomotor vermis on eye movements in primate: saccades. J Neurophysiol 80:1911–1931. Medline

Thier P, Dicke PW, Haas R, Thielert CD, Catz N (2002) The role of the oculomotor vermis in the control of saccadic eye movements. Ann N Y Acad Sci 978:50–62. CrossRef Medline

Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ (2007) Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol 98:54–62. CrossRef Medline

van Alphen AM, De Zeeuw CI (2002) Cerebellar LTD facilitates but is not essential for long-term adaptation of the vestibulo-ocular reflex. Eur J Neurosci 16:486–490. CrossRef Medline

Vergilino-Perez D, Fayel A, Lemoine C, Senot P, Vergne J, Doré-Mazars K (2012) Are there any left-right asymmetries in saccade parameters? Examination of latency, gain, and peak velocity. Invest Ophthalmol Vis Sci 53:3340–3348. CrossRef Medline

Waespe W, Baumgartner R (1992) Enduring dysmetria and impaired gain adaptivity of saccadic eye movements in Wallenberg's lateral medullary syndrome. Brain 115:1123–1146. Medline

Werner S, Bock O, Timmann D (2009) The effect of cerebellar cortical degeneration on adaptive plasticity and movement control. Exp Brain Res 193:189–196. CrossRef Medline

Werner S, Bock O, Gizewski ER, Schoch B, Timmann D (2010) Visuomotor adaptive improvement and aftereffects are impaired differentially following cerebellar lesions in SCA and PICA territory. Exp Brain Res 201:429–439. CrossRef Medline

Xu-Wilson M, Chen-Harris H, Zee DS, Shadmehr R (2009) Cerebellar contributions to adaptive control of saccades in humans. J Neurosci 29: 12930–12939. CrossRef Medline

Zimmermann E, Lappe M (2010) Motor signals in visual localization. J Vis 10(6):2 . CrossRef Medline

Zuchowski ML, Timmann D, Gerwig M (2014) Acquisition of conditioned eyeblink responses is modulated by cerebellar tDCS. Brain Stimul 7:525–531. CrossRef Medline