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After Effects of Cerebellar Continuous Theta Burst Stimulation on Reflexive Saccades and Smooth Pursuit in Humans

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Abstract The use of cerebellar repetitive transcranial magnetic stimulation has been attempted for perturbing reflexive and voluntary eye movements, but discrepancies are seen between the results of distinct studies possibly due to the different stimulation sites, intensities, and paradigms. We describe the after effects of 20 and 40 s continuous Theta Burst Stimulation (cTBS) as compared to sham stimulation, applied over the lateral cerebellar vermis and paravermis on Reflexive Saccades (RS) and Smooth Pursuit (SP) eye movements, recorded in the 30 min following stimulation. The experiments were carried out in eight healthy volunteers, and eye movements were recorded monocularly with video-oculography. The 40 s cTBS significantly increased the amplitude of ipsilateral RS and the acceleration of the ipsilateral SP, and this effect was detectable all over the 30-min recording period; 40 s cTBS did not modify the other parameters, namely the peak velocity, the duration and the latency of RS, and the latency and the velocity of SP. The 20 s cTBS was ineffective on all RS and SP parameters. Finally, we detected a significant quite-linear reduction of RS peak velocity over time, but this was independent from cTBS and was probably caused by fatigue. The effects of 40 s cTBS in our experiments mimic the disorder of ocular motility in Wallenberg's syndrome and could result from functional impairment of cerebellopontine pathways. This effect lasts 30 min at least, and can provide a useful framework for adaptive ocular motor studies.

Keywords Cerebellum · cTBS · Saccades · Smooth pursuit

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Introduction

Transcranial magnetic stimulation (TMS) techniques are used increasingly in neuroscience research to enhance or reduce cortical excitability and to modify related physiological activities. Specifically, repetitive TMS (rTMS) can induce lasting changes in corticospinal excitability which is thought to involve long-term potentiation/depression (LTP/LTD)-like effects on cortical synapses, resulting in quantifiable changes in behavior that outlast the period of stimulation and can be measured without interfering with the experimental procedures. Huang et al. [1] developed original protocols to deliver rTMS, aimed at producing clear after effects in the human motor cortex through repeated application of modified "theta burst" paradigms (theta burst stimulation, TBS), in which three pulses of stimulation are given at 50 Hz, repeated every 200 ms. They found TBS to be safe in normal subjects, and able to produce consistent, rapid, and controllable electrophysiological and behavioral changes in the function of the human motor system. These outlast the period of stimulation by more than 60 min [1, 2].

Most physiological studies that have been carried out to detect changes in function that outlast the application of particular patterns of rTMS have chosen the motor cortex, as it is possible to treat the size of the electromyographic (EMG) response to a single TMS pulse as an objective measure of cortical excitability, but the method proved useful also in other regions of the brain, both in the study of normal human physiology and for therapeutic manipulation of brain plasticity.

In particular, rTMS can be used for investigating the cerebellar function in humans [see 3 for a review], and recent investigations showed that when TBS protocols are applied over the lateral cerebellum, long lasting changes occur in the excitability of the contralateral M1 [4]. Popa el al. [5] found a significant cerebello-cortical inhibition (CBI) suppression to the left motor cortex up to 30 min after a train of 600 uninterrupted TBS stimuli where given over the right cerebellum (continuous theta burst stimulation pattern, cTBS), but not after 600 TBS stimuli where given in 2 s trains repeated every 10 s (intermittent theta burst stimulation pattern iTBS). Recently, cTBS was used to modulate cerebellar function [6–8], and as a probe for cerebellar plasticity [9].

The use of cerebellar TMS has also been attempted for perturbing reflexive and voluntary eye movements in adaptive [10–12] and in non-adaptive paradigms (see [13] for a review), but discrepancies are seen between the results of distinct studies, possibly due to the different stimulation sites, intensities, and paradigms. More specifically, Hashimoto and Ohtsuka [14] observed that contralateral saccades became hypometric when single TMS pulses were delivered over the posterior cerebellum (7 mm caudal and lateral to the inion) at the onset of saccades, but not when TMS was triggered 20, 40, or 60 ms after the onset of saccades, while ipsilateral saccades became hypermetric when single TMS pulses were delivered on the same site at 0, 20, or 40 ms after the onset of saccades. Panouilleres et al. [12] observed bilateral hypometria of saccades when TMS pulses were delivered over the right hemisphere of the cerebellum (stimulation sites were located in Crus I, slightly above the horizontal fissure and 3.5-cm lateral to the interhemispheric line) at saccade detection. Jenkinson and Miall [11] observed no effects on reflexive saccades metrics when subjects made repeated eye movements to a fixed 16 target for 100 trials with rTMS at a frequency of 1 Hz directed at the posterior cerebellum before the start (120 pulses) and throughout the trials.

In summary, the characteristics and time course of the effects on eye movements of cerebellar cTBS with different duration and the time window over which these effects can be detected has never been described.

The aim of the current study was to describe the after effects of 20 and 40 s cTBS applied over the cerebellum on RS and SP eye movements, recorded in the 30 min following stimulation. This time window was chosen on the basis of previous works in humans, showing that cerebellar cTBS after

effects may last up to 30 min [5]. The cerebellar vermis seemed the more suitable target since single-pulse TMS over the medial cerebellum resulted in impaired accuracy of reflexive [14] and memory guided saccades [10], acceleration of smooth pursuit [15], coordination of saccades and head movements [16], and saccade adaptation in a double-step paradigm [11]. Thereby, we hypothesized that cTBS protocols with different duration applied over the medial cerebellum may induce long lasting modification of RS and SP specific to the stimulation duration.

Methods

Subjects

Eight healthy right handed subjects (4 males; mean age 23.2 ± 2.9 years) underwent bilateral horizontal reflexive saccades (RS) and smooth pursuit (SP) in three separate recording session. None of the subjects had a personal history of ocular motor, brainstem, or cerebellar disorders, and their neurological, including saccades and smooth pursuit eye movements, examination at baseline was normal. With each subject, three experiments were performed in randomized order, with a time-interval between experimental sessions of at least 1 week. In the 20 s cTBS experiment, the cerebellum was stimulated using a cTBS protocol of 300 bursts. In the 40 s cTBS experiment, the cerebellum was stimulated using a cTBS protocol of 600 bursts. In the sham cTBS experiment, which served as control condition, sham cTBS was applied over the same cerebellar site. The subjects were asked to keep their eyes closed throughout the stimulation procedure.

In each experiment, the recording device was calibrated immediately after cTBS application, and the oculomotor paradigm was performed in six RS and SP blocks, each lasting on average 40 s. In each RS block, 15 saccades to the left and 15 saccades to the right side were performed in total; the direction of the saccades was pseudo-randomized. In each SP block, ten SP to the left and ten SP to the right side were performed in total; the direction of SP was pseudo-randomized. The blocks started immediately after cTBS application, i.e., after 0, 5, 10, 15, 20, and 25 min. Finally, mean pulse amplitude, latencies, duration, and velocity for leftward and rightward RS, and mean acceleration, velocity and latency of leftward, and rightward SP of each experimental condition were calculated for each subject.

The research protocol received approval from the local Ethics Committee, and all the procedures were conducted in accordance with the Declaration of Helsinki. All the subjects gave written informed consent before participating in the study.

Repetitive Transcranial Magnetic Stimulation

A MagStim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK), connected with a figure-of-eight coil with a diameter of 70 mm was used to deliver cTBS. Three-pulse bursts at 50 Hz repeated every 200 ms (equivalent to "continuous theta burst stimulation, cTBS" in Huang et al. [1] were delivered for 20 s (300 pulses) or 40 s (600 pulses) at 100% of resting motor threshold (RMT), defined as the lowest intensity that evoked five small responses (about 50 mV) in the contralateral FDI muscle in a series of ten stimuli when the subject kept the FDI muscles relaxed in both hands [17]. RMT was tested over the motor cortex of the left hemisphere. Electromyographic (EMG) traces were recorded from the FDI muscles of the right hand using 9-mm-diameter Ag-AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified with a Digitimer D360 amplifier (Digitimer Ltd., Welwyn Garden City, Herts, UK), processed through a band-pass filter with corner frequencies of 20 Hz and 2 kHz, then recorded by a computer using SIGNAL software with a sampling rate of 5 kHz per channel (Cambridge Electronic Design, Cambridge, UK). In our subjects, stimulation intensity for cTBS was 42.9 ± 3,8% (mean ± SD) of the maximum stimulator output.

Sham stimulation was delivered through a 70-mm figure-of-eight focal coil angled at 90 with only the edge of the coil resting on the scalp. Stimulus intensity, expressed as a percentage of the maximum stimulator output, was set at only 40% RMT for the first dorsal interosseous (FDI). The order of presentation (20 s cTBS, 40 s cTBS or sham cTBS) was counterbalanced across subjects. This stimulation intensity along with the tilted arrangement of the figure-of-eight focal coil, while ineffective in inducing any cortical activation or unpleasant sensations [3, 18, 19], ensures an adequate noise and scalp sensation.

Stimulation Site Identification

At the beginning of each TMS session, the stimulation site was identified for each subject based on an estimated MRI calculated using a 3D warping procedure, which is based on a set of points digitized from the subject's scalp by means of a computer-assisted procedure (SofTaxicOptic, EMS s.r.l., Bologna, Italy). The stimulation site was localized onto the 3D realistic MR-based brain model. Furthermore, spatial coordinates of the stimulated site was referred to the stereotaxic Talairach coordinate system, corresponding to the right side of the posterior vermal lobules VI–VII (Fig. 1). The coil position and orientation was calibrated and then placed over the occiput on the right side of the area caudal to the inion and adjusted with the aid of the neuronavigation system. During cTBS,

the coil position and orientation was continuously monitored in order to keep it fixed onto the subject's scalp over the desired stimulation site.

Eye Movement Recording

Eye movements were calibrated and recorded monocularly from the right/left eye using an infrared video system (EyeSeeCam, sampling rate 220 Hz, spatial resolution 0.1). The subjects were seated in a dark room with their head in the upright position and holding a bite-bar support.

Reflexive Saccades

Each trial started from the central fixation point. The target had unpredictable direction and amplitude (10, 15, and 20 to the right and left of the subject's sagittal plane). The target remained in position until the individual saccade ended and when necessary the subjects made corrective saccades.

Smooth Pursuit

Each trial started from the central fixation point. The fixation point disappeared after a random time between 1 and 1.5 s, and a tracking target appeared at 3 on the left or on the right of the subject's sagittal plane moving at a constant velocity of 15 /s in the opposite direction. Target movement randomly stopped between 17 and 22 from the middle of the screen.

Data Analysis

Data were analyzed offline using Matlab (Math-Works) custom developed software. Raw eye position was calibrated using a second order polynomial fit and filtered using a second order 50 Hz Butterworth low pass filter (50 Hz cutoff frequency). Eye velocity data were calculated using the Savitzky-Golay four point derivative filter.

Reflexive Saccades

Saccades were identified finding peaks in eye velocity; the beginning and the end of each saccade was found by using a velocity threshold of 10 /s. We considered the following parameters:

– amplitude and accuracy: namely the ratio of actual to expected saccade amplitude, this latter is corresponding to target amplitude;
– peak velocity: Because of the amplitude/peak-velocity relationship that is quite linear for the saccades amplitude range of this study, the actual peak velocity values were normalized, i.e., they were divided by the actual saccade amplitude.
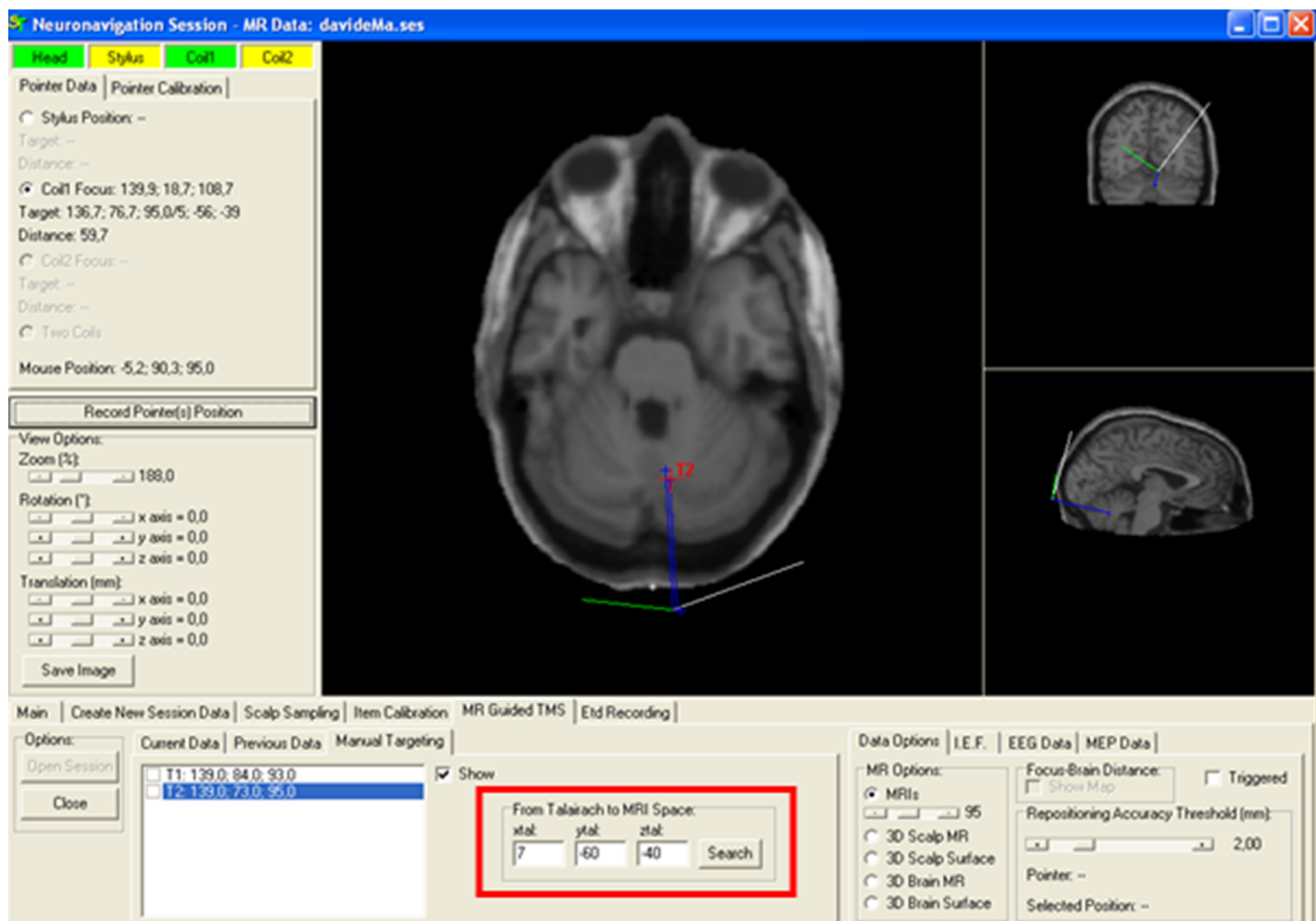
Fig. 1 Localization of the stimulated site referred to the stereotaxic Talairach coordinate system as 7, −60, −40, corresponding to the right side of the posterior vermis lobules VI–VII. The coil position and orientation was be calibrated and then placed over the occiput on the right side of the area caudal to the inion and adjusted with the aid of the neuronavigation system

- duration: Because of the amplitude/duration relationship, the duration values also were normalized by actual saccade amplitude.
- latency: the time interval from target presentation to saccade onset

- Acceleration computed as the slope of the linear regression of the first 70 ms of eye velocity after smooth pursuit onset;
- Latency of the smooth pursuit onset from target movement onset

Smooth Pursuit Eye Movements

Corrective saccades made during smooth pursuit were automatically detected and deleted with a straight line that connected the eye velocity before and after the saccade. Smooth pursuit beginning was found using a fitting curve composed by a constant value and a linear function. We considered the following parameters:

- Three mean velocity values computed respectively between 200 and 400 ms, 400–600 ms and 600–800 ms from pursuit onset;

Statistical Analyses

Data were analyzed separately for each parameter (RS pulse amplitude, peak velocity, duration, and latency; SP acceleration, velocity, and latency) and movement direction (leftward, rightward).

The effects of 20 or 40 s cTBS and their timeline were analyzed by repeated measures analyses of variance. We considered two within-subject factors (recording block at six levels; stimulation at two levels: sham stimulation versus either 20 or 40 s cerebellar stimulation) and their interaction. The significance level was set at $p = 0.05$.

Table 1 Reflexive saccade accuracy. Mean and standard deviation (SD) of leftward and rightward reflexive saccades accuracy, namely the ratio of saccade amplitude to target amplitude, for each experimental condition (20 s cTBS, 40 s cTBS, and sham cTBS)

| | Leftward reflexive saccades | | | | | | Rightward reflexive saccades | | | | | |
| | Sham | | 20 s | | 40 s | | Sham | | 20 s | | 40 s | |
Block no.	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	0.94	0.04	0.93	0.05	0.94	0.02	0.97	0.02	0.95	0.02	0.98	0.03
2	0.94	0.03	0.93	0.04	0.95	0.02	0.96	0.03	0.97	0.02	0.99	0.05
3	0.96	0.03	0.94	0.04	0.94	0.03	0.97	0.02	0.97	0.03	0.99	0.04
4	0.96	0.03	0.94	0.05	0.95	0.03	0.96	0.03	0.95	0.03	1.00	0.04
5	0.96	0.04	0.96	0.03	0.96	0.05	0.96	0.03	0.97	0.03	1.02	0.05
6	0.96	0.03	0.95	0.02	0.96	0.04	0.97	0.03	0.97	0.03	1.00	0.03

Results

No Adverse Effects of Cerebellar cTBS Were Reported

The mean and the standard deviation values of the parameters for which we detected a significant effect are reported in Tables 1–3.

The stimulation factor proved to be significant for two parameters:

– The amplitude (and therefore the accuracy) of rightward saccadic pulse was larger after 40 s cerebellar stimulation (0.99) than in basal recording (0.96): $F_{(1,7)} = 11.91$ $p = 0.011$. Figure 2 shows an example of this effect in a typical subject.

– The rightward smooth pursuit acceleration was larger after 40 s cerebellar stimulation (100.84 /s^2) than in basal recording; (87.32 /s^2): $F_{(1,7)} = 8.67, p = 0.022$. Figure 3 shows an example of this effect in a typical subject.

The recording block factor was significant only for saccade peak velocity that showed a reduction as the block number increased. When we compared basal recording to 20 s cerebellar stimulation the block number factor was significant in both directions (rightward $F_{(3,5)} = 13.14; p = 0.03$; leftward $F_{(3,5)} = 15.46\ p = 0.02$), with a linear trend detectable by contrast analysis ($F_{(1,7)} = 19.52, p = 0.003$ and $F_{(1,7)} = 54.1, p < 0.001$, respectively, for rightward and leftward saccades). In the comparison between basal recording and 40 s cerebellar stimulation, the block number factor was significant for leftward ($F_{(3,5)} = 10.9, p = 0.04$) and borderline for rightward ($F_{(3,5)} = 7.25, p = 0.06$) saccades; again a linear trend was detectable by contrast analysis ($F_{(1,7)} = 14.69, p = 0.006$ and $F_{(1,7)} = 23.71, p = 0.002$, respectively, for rightward and leftward saccades).

The interaction between the stimulation and the recording block factors was never significant.

Discussion

We tested the eye movement effects of cTBS applied over the lateral cerebellar vermis and paravermis by using two different stimulation duration, and we checked for how long these effects lasted.

Table 2 Reflexive saccade peak velocity. Mean and standard deviation (SD) of leftward and rightward reflexive saccades peak velocity, normalized by saccade amplitude, for each experimental condition (20 s cTBS, 40 s cTBS, and sham cTBS)

| | Leftward reflexive saccades | | | | | | Rightward reflexive saccades | | | | | |
| | Sham | | 20 s | | 40 s | | Sham | | 20 s | | 40 s | |
Block no.	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	30.46	2.67	28.53	2.41	28.87	2.91	29.17	2.53	27.44	3.02	27.97	3.13
2	29.22	2.58	27.25	2.07	28.51	2.61	29.66	2.28	26.84	2.32	28.16	3.52
3	29.44	2.06	28.58	2.49	28.36	3.07	28.24	2.63	26.86	2.05	28.52	3.58
4	29.46	2.99	27.74	1.91	28.11	2.64	28.25	2.33	27.33	2.89	28.15	2.81
5	28.32	2.06	28.09	2.47	28.41	3.12	27.92	2.26	26.15	2.76	27.85	3.32
6	28.56	2.10	27.73	2.59	27.86	2.82	27.70	2.66	26.95	2.91	27.71	2.98

Table 3 Smooth pursuit eye movement acceleration. Mean and standard deviation (SD) of leftward and rightward smooth pursuit acceleration for each experimental condition (20 s cTBS, 40 s cTBS, and sham cTBS)

| | Leftward smooth pursuit | | | | | | Rightward smooth pursuit | | | | | |
| | Sham | | 20 s | | 40 s | | Sham | | 20 s | | 40 s | |
Block no.	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	79.58	14.10	82.48	14.37	107.19	25.98	87.19	28.75	94.95	25.49	104.77	34.24
2	86.13	10.12	90.78	20.70	100.40	23.33	86.19	18.78	83.69	28.85	108.41	30.93
3	81.32	14.37	83.83	11.12	96.33	16.51	88.56	19.15	76.77	32.30	99.31	36.69
4	92.53	12.99	79.78	30.30	96.00	26.15	93.31	22.90	78.45	21.53	101.64	27.78
5	90.35	15.39	82.15	21.00	106.97	22.28	93.89	47.83	94.25	30.97	103.4	24.91
6	77.05	19.47	82.56	22.05	72.93	23.16	74.81	19.57	74.83	41.78	87.55	22.87

Our data showed that (i) cTBS increases the amplitude of ipsilateral saccades and the acceleration of ipsilateral smooth pursuit eye movements, (ii) the effects are detectable after 40 s but not after 20 s cTBS stimulation, and (iii) the effects persisted and did not change over all the time period that was tested by our protocols, namely 30 min in agreement with the paper by Popa et al. [5]. The only modification over time that we observed was a reduction of saccade peak velocity, that occurred in the same way both after sham and after cTBS stimulation, thus, suggesting that fatigue rather than cTBS could account for it.

We suggest that cTBS in our experiments induced different plastic changes in Purkinjie cells or in local interneurons, resulting in indirect changes in the excitability of the caudal fastigial nucleus on the stimulated side.

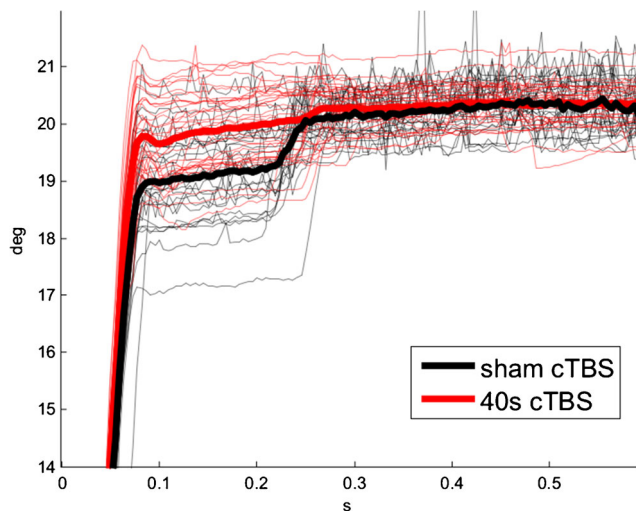The posterior vermis lobulus VIc and VII (ocular motor vermis, OVM) and the caudal fastigial nucleus (cFN) are responsible for the accuracy of reflexive saccades. OVM inhibits cFN neurons, which in turns project to the burst generator where a "pulse signal" is generated and fed to the ocular motor neurons to bring the eyes in the new desired position [20].

cFN neurons fire 8 ms before the starting of reflexive saccades directed contralaterally (to accelerate the eye at the beginning of the saccade) and at the end of reflexive saccades directed ipsilaterally (to stop the eye on target) [21].

In monkeys, the unilateral inhibition of cFN by muscimol injection [22] results in ipsilateral hypermetria and in contralateral hypometria. In humans, this pattern of saccadic
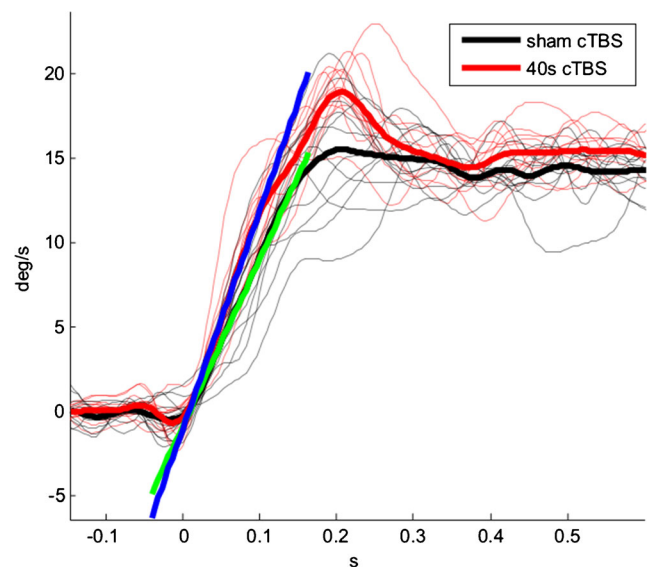

Fig. 2 Saccade amplitude. Amplitude of rightward saccadic pulse in a representative subject. *Thin lines* represent eye position in each saccade, *thick lines* represent the mean of 15 saccades executed by the same subject, respectively, after sham (*black lines*) and after 40 s cerebellar cTBS (*red lines*). Pulse amplitude was larger after 40 s than after sham cerebellar stimulation

Fig. 3 Smooth pursuit acceleration. Velocity of rightward smooth pursuit in a representative subject. *Thin lines* represent eye velocity in each smooth pursuit, *thick lines* represent the mean of 15 smooth pursuit executed by the same subject respectively after sham (*black lines*) and after 40 s cerebellar cTBS (*red lines*). *Blue* and *green lines* represent the linear fit of the 70 ms after pursuit onset, respectively, in the 40 s cTBs and in the sham cTBS condition. The slope of linear regression was larger after 40 s than after sham cerebellar stimulation (98.9 /s^2 in sham condition and 129.35 /s^2 in 40 s cTBS condition)

dysmetria is detectable after single pulse TMS stimulation [14], and in Wallenberg's syndrome [23] where the interruption of climbing fibers results in an increased firing of OMV Purkinje cells and hence in a larger inhibition of cFN.

Our results are in keeping with the hypothesis that 40 s cTBS on the right OVM results in an increased inhibition of ipsilateral cFN, although we were able to detect only an increased amplitude of ipsilateral saccades but not a significant reduction of the amplitude of contralateral saccades. This difference can be explained because the magnitude of cFN influences are different on ipsilateral and on contralateral saccades [24], Moreover, as compared to basal recordings, the amplitude modification observed in inactivation studies was larger than those detectable in our subjects. We found a 103% increase of ipsilateral saccade amplitude, whereas in inactivation studies, the increase could be as large as 180% [22, 25] and was associated with a smaller (about 70–75%) contralateral saccade amplitude reduction. Overall, we might have induced an inhibition of cFN that was weaker than the one reached by inactivation (or in Wallenberg's syndrome), so that only the effect on ipsilateral saccade proved to be significant.

SP eye movements aim at keeping on the fovea the image either of a moving object, or of stationary object while moving the head. The OVM and cFN are responsible for maintaining the velocity of the eyes matched to the velocity of the moving target during SP [20]. cFN dysfunction determined by muscimol injection [26], posterior vermis infarction [27], Wallenberg's syndrome [28], or single pulse TMS [15] result in deceleration of contralateral directed SP and acceleration of ipsilateral directed SP. As for saccades, these results are in keeping with ours, but we did not find a significant effect on contralateral directed SP.

A different after effect of 20 and 40 s cTBS was already described after stimulation of the motor cortex and might be attributed either to a different balance of long-term potentiation and depression of postsynaptic transmission or to a different extent of the stimulus consequences at different synapses.

Experiments carried out using rTMS over the motor cortex have suggested that the frequency of stimulation is the most important determining factor in the direction of the aftereffects. Thus, low frequency (1 Hz) stimulation tends to reduce cortico-spinal excitability (i.e., an LTD-like effect), whereas higher frequencies (5 Hz or more) tend to increase excitability (i.e., an LTP-like effect). However, with TBS, the direction of the after effects depends on whether the bursts are delivered continuously (cTBS, producing LTD-like effects) or intermittently (iTBS producing LTP-like effects). Furthermore, the duration of the after effects was less when fewer TMS pulses were applied in the cTBS pattern. Gamboa et al. [29] investigated the effects of inhibitory (intermittent) and excitatory (continuous) TBS protocols on motor cortex excitability with different stimulation duration and found that facilitatory iTBS

converted into inhibitory, and inhibitory cTBS became facilitatory when stimulation duration was doubled. Huang et al. [2] gave a simple model that explains why the pattern of delivery and stimulation duration is critical in determining the direction of change in synaptic efficiency.

In conclusion, our data show that 40 s cTBS can result in indirect inhibition of cFN, lasting at least 30 min; this condition can be a useful framework for experiments on saccadic or smooth pursuit adaptation.

References

1. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45(2):201–6.
2. Huang YZ, Rothwell JC, Chen RS, Lu CS, Chuang WL. The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. Clin Neurophysiol. 2011;122(5):1011–8.
3. Koch G. Repetitive transcranial magnetic stimulation: a tool for human cerebellar plasticity. Funct Neurol. 2010;25(3):159–63.
4. Koch G, Mori F, Marconi B, Codeca C, Pecchioli C, Salerno S, et al. Changes in intracortical circuits of the human motor cortex following theta burst stimulation of the lateral cerebellum. Clin Neurophysiol. 2008;119(11):2559–69.
5. Popa T, Russo M, Meunier S. Long-lasting inhibition of cerebellar output. Brain Stimul. 2010;3(3):161–9.
6. Brusa L, Ponzo V, Mastropasqua C, Picazio S, Bonni S, Di Lorenzo F, et al. Theta burst stimulation modulates cerebellar-cortical connectivity in patients with progressive supranuclear palsy. Brain Stimul. 2014;7(1):29–35.
7. Colnaghi S, Honeine JL, Sozzi S, Schieppati M. Body Sway Increases After Functional Inactivation of the Cerebellar Vermis by cTBS. Cerebellum. 2016.
8. Di Lorenzo F, Martorana A, Ponzo V, Bonni S, D'Angelo E, Caltagirone C, et al. Cerebellar theta burst stimulation modulates short latency afferent inhibition in Alzheimer's disease patients. Front Aging Neurosci. 2013;5:2.
9. Monaco J, Casellato C, Koch G, D'Angelo E. Cerebellar theta burst stimulation dissociates memory components in eyeblink classical conditioning. Eur J Neurosci. 2014;40(9):3363–70.
10. Colnaghi S, Ramat S, D'Angelo E, Cortese A, Beltrami G, Moglia A, et al. Theta-burst stimulation of the cerebellum interferes with internal representations of sensory-motor information related to eye movements in humans. Cerebellum. 2011;10(4):711–9.
11. Jenkinson N, Miall RC. Disruption of saccadic adaptation with repetitive transcranial magnetic stimulation of the posterior cerebellum in humans. Cerebellum. 2010;9(4):548–55.
12. Panouilleres M, Neggers SF, Gutteling TP, Salemme R, van der Stigchel S, van der Geest JN, et al. Transcranial magnetic stimulation and motor plasticity in human lateral cerebellum: dual effect on saccadic adaptation. Hum Brain Mapp. 2012;33(7):1512–25.
13. Colnaghi S, Ramat S, D'Angelo E, Versino M. Transcranial magnetic stimulation over the cerebellum and eye movements: state of the art. Funct Neurol. 2010;25(3):165–71.
14. Hashimoto M, Ohtsuka K. Transcranial magnetic stimulation over the posterior cerebellum during visually guided saccades in man. Brain. 1995;118(Pt 5):1185–93.
15. Ohtsuka K, Enoki T. Transcranial magnetic stimulation over the posterior cerebellum during smooth pursuit eye movements in man. Brain. 1998;121(Pt 3):429–35.

16. Nagel M, Behrmann H, Zangemeister WH. Disturbance of predictive response initiation of eye and head movements in cerebellar patients. Eur Neurol. 2008;60(4):179–85.

17. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994;91(2):79–92.

18. Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods. 1997;74(2):113–22.

19. Tofts PS. The distribution of induced currents in magnetic stimulation of the nervous system. Phys Med Biol. 1990;35(8):1119–28.

20. Leigh RJ, Zee DS. The neurology of eye movements. Fifth ed. New York: Oxford University Press; 2015.

21. Ohtsuka K, Noda H. Saccadic burst neurons in the oculomotor region of the fastigial nucleus of macaque monkeys. J Neurophysiol. 1991;65(6):1422–34.

22. Robinson FR, Straube A, Fuchs AF. Role of the caudal fastigial nucleus in saccade generation. II. Effects of muscimol inactivation. J Neurophysiol. 1993;70(5):1741–58.

23. Helmchen C, Straube A, Buttner U. Saccadic lateropulsion in Wallenberg's syndrome may be caused by a functional lesion of the fastigial nucleus. J Neurol. 1994;241(7):421–6.

24. Kojima Y, Robinson FR, Soetedjo R. Cerebellar fastigial nucleus influence on ipsilateral abducens activity during saccades. J Neurophysiol. 2014;111(8):1553–63.

25. Eggert T, Robinson FR, Straube A. Modeling inter-trial variability of saccade trajectories: effects of lesions of the oculomotor part of the fastigial nucleus. PLoS Comput Biol. 2016;12(6):e1004866.

26. Fuchs AF, Robinson FR, Straube A. Participation of the caudal fastigial nucleus in smooth-pursuit eye movements. I Neuronal activity J Neurophysiol. 1994;72(6):2714–28.

27. Vahedi K, Rivaud S, Amarenco P, Pierrot-Deseilligny C. Horizontal eye movement disorders after posterior vermis infarctions. J Neurol Neurosurg Psychiatry. 1995;58(1):91–4.

28. Waespe W, Wichmann W. Oculomotor disturbances during visual-vestibular interaction in Wallenberg's lateral medullary syndrome. Brain. 1990;113(Pt 3):821–46.

29. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst aftereffect with prolonged stimulation. Exp Brain Res. 2010;204(2):181–7.