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A cortical substrate for the long-term memory of saccadic eye movements calibration

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A B S T R A C T

How movements are continuously adapted to physiological and environmental changes is a fundamental question in systems neuroscience. While many studies have elucidated the mechanisms which underlie short-term sensorimotor adaptation (~10–30 min), how these motor memories are maintained over longer-term (>3–5 days) -and thanks to which neural systems-is virtually unknown. Here, we examine in healthy human participants whether the temporo-parietal junction (TPJ) is causally involved in the induction and/or the retention of saccadic eye movements' adaptation. Single-pulse transcranial magnetic stimulation (spTMS) was applied while subjects performed a ~15min size-decrease adaptation task of leftward reactive saccades. A TMS pulse was delivered over the TPJ in the right hemisphere (rTPJ) in each trial either 30, 60, 90 or 120 msec (in 4 separate adaptation sessions) after the saccade onset. In two control groups of subjects, the same adaptation procedure was achieved either alone (No-TMS) or combined with spTMS applied over the vertex (SHAM-TMS). While the timing of spTMS over the rTPJ did not significantly affect the speed and immediate after-effect of adaptation, we found that the amount of adaptation retention measured 10 days later was markedly larger (42%) than in both the No-TMS (21%) and the SHAM-TMS (11%) control groups. These results demonstrate for the first time that the cerebral cortex is causally involved in maintaining long-term oculomotor memories.

Introduction

Eye movements are a critical component of our visual perceptual capabilities in everyday life. Visual perception may thus be endangered by physiological alterations of our oculomotor system related to aging or growth, or by pathological disturbances like impairments of the extra-ocular muscles or nerves (Optican and Robinson, 1980; Hopp and Fuchs, 2004). Fortunately, sensorimotor adaptation mechanisms respond to these disturbances and contribute to maintaining the accuracy of saccadic eye movements over the long term, whether these saccades are of the reactive type ("RS", externally trigered) or of the voluntary type ("VS", internally trigered) (McLaughlin, 1967; Deubel et al., 1986; Straube et al., 1997; Hopp and Fuchs, 2004; Alahyane et al., 2007). Saccadic adaptation can be investigated non-invasively thanks to the double-step target paradigm (McLaughlin, 1967). This paradigm consists in stepping the target systematically and by a fixed amount during the saccade to artificially produce an error, the repetition of which elicits an adaptive increase or decrease of saccade gain for forward or backward target steps, respectively (McLaughlin, 1967; Hopp and Fuchs, 2004; Pélisson et al., 2010; Herman et al., 2013). Such modifications of saccade amplitude are gradual until the saccade eventually lands close to the stepped target position.

While many studies have elucidated the mechanisms which underlie short-term sensorimotor adaptation (~10–30 min), little is known about long-term maintenance of such learning processes (>3–5 days) and their specific neural underpinnings. To the best of our knowledge, only one study investigated the duration of oculomotor changes following a single adaptation session (Alahyane and Pélisson, 2005) and reported a significant retention lasting up to 5 days. Note that stronger and longer retention has been observed under the following very specific conditions of visual context: visual targets presented in an otherwise very dark environment and displaced to a stepped location at saccade onset for only 30 msec (Wang et al., 2012), complete visual deprivation of adapted monkeys in-between adaptation sessions performed over successive days (Robinson et al., 2006), short-lasting visual deprivation (ganzfeld or sleep) between adaptation sessions in human subjects (Voges et al., 2015). To date, this long-term retention of adaptation has not been studied at the physiological level. This is not surprising when considering that the prominent role of the cerebral cortex in short-term saccadic adaptation has started to be disclosed only recently (see Zimmermann and Lappe, 2016). Long considered to rely on exclusively cerebellar and subcortical structures (see for reviews Hopp and Fuchs, 2004, Iwamoto

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and Kaku, 2010, Pélisson et al., 2010), a functional magnetic resonance imaging study revealed the involvement of the temporo-parietal junction (TPJ) during short-term adaptation of RS but not of VS (Gerardin et al., 2012). This study also revealed a specific involvement of the posterior intraparietal sulcus (pIPS), but opposite to that of the TPJ, as the metabolic activation of pIPS was observed during adaptation of VS but not of RS. Note that adapted RS and VS were all directed leftward, and the associated cortical activations found in the right hemisphere. While the pIPS specialization for VS adaptation was confirmed by a study using transcranial magnetic stimulation (TMS) (Panouillères et al., 2014), the role played by TPJ in RS adaptation remains so far unaddressed.

Here we tested the hypothesis that rTPJ plays a critical role in the adaptation of leftward RS, using MRI-guided single-pulse transcranial magnetic stimulation (spTMS). Based on the evidence reviewed above, we predicted that an appropriately timed TMS-induced perturbation of rTPJ relative to saccade onset would interfere with the acquisition of RS adaptation. However, our results could not confirm this prediction but, unexpectedly, disclosed that spTMS of rTPJ led to a strong enhancement of the long-term retention of RS adaptation, as measured ~10 days after.

Materials and methods

Participants

Three groups of healthy subjects were enrolled in this study: twelve right-handed healthy subjects in the 'rTPJ' group (7 females and 5 males; mean age: 24.3, SEM ± 0.9; 10 were naive to the goal of the study and to TMS stimulation), twelve right-handed healthy subjects in the 'SHAM-TMS' control group (7 females and 5 males; mean age: 25.3, SEM ± 0.9, 9 were naïve to the goal of the study and to TMS stimulation) and thirteen right-handed healthy subjects in the 'No-TMS' control group (8 females and 5 males; mean age: 25.8, SEM ± 1.2, all were naïve to the goal of the study). The last two groups were recruited after the 'rTPJ' group analyses had unexpectedly revealed a marked strengthening of adaptation retention. All participants had normal or corrected-to-normal vision, and had no history of neurological or psychiatric disorder. Subjects gave their informed written consent to participate to the experiment. All safety procedures of TMS experimentation were followed. The experiment conformed to the code of ethics of the World Medical Association – Declaration of Helsinki of 2008 and was approved by the local ethics committee (CCPPRB Lyon-B).

Ten subjects of the 'rTPJ' group performed for this study an anatomical T1-weighted scan with a 1.5-T Siemens Sonata MRI scanner at CERMEP (Bron, France), the remaining two participants already had both anatomical and functional scans from a previous study (Gerardin et al., 2012).

Apparatus and stimulus

The experiment took place in a dimly lit room, subjects were sitting 57 cm away from a computer screen (vertical refresh rate of 140 Hz) covering 30° × 40° of visual angle. Head movements were limited by a chin rest, cheekbone rests and forehead support. The presentation of visual stimuli on the computer screen was controlled by a VSG system (Visual Stimuli Generation system - CRS Cambridge, United Kingdom). Visual stimuli were black dots of 0.6° in diameter or a black fixation cross on a grey background.

Eye movement recording

The horizontal and vertical positions of both eyes were recorded at a frequency of 500 Hz and a spatial resolution of 0.05° using an infrared tracker (EyeLink 1000, SR Research, Canada). At the beginning of each session, calibration of the eye tracking system was performed by asking the subject to look successively at nine fixation dots forming a rectangle of 28° × 38°. A custom-made software allowed on-line monitoring of eye movements, triggering of the visual stimulation, and triggering of the TMS pulse relative to the primary saccade detected on-line.

Transcranial magnetic stimulation

A figure of eight coil (90 mm) coupled to a Magstim Rapid system was used to deliver single-pulse transcranial magnetic stimulation. For each subject of the 'rTPJ' and 'SHAM-TMS' groups, the motor threshold was first identified by applying the TMS coil over the right motor cortex. The motor threshold was defined as the lowest stimulation intensity able to induce a visible movement of the contralateral, relaxed, hand at least 5 times out of 10 (Schutter and Honk, 2006).

For subjects of the 'rTPJ' group, the single pulse TMS was then applied over the right TPJ with an intensity corresponding to 120% of the motor threshold in 8 subjects or to 100% of the motor threshold in the remaining four subjects who found the stimulation at 120% uncomfortable. Across all 12 subjects, the average TMS intensity applied over the right TPJ corresponded to 58.8% (SEM: ± 3%) of the maximum output intensity (2T). At the beginning of each session, the positioning of the TMS coil on the right TPJ was performed with the help of a neuronavigation system (SofTaxicOptic, EMS srl, Bologna, Italy). In two subjects, the Talairach coordinates of the rTPJ site (x = 48, y = −45, z = 16: see Fig. 1A; and x = 52, y = −54, z = 8) were based on their functional scan from the 'saccade localizer task' of the study of Gerardin et al., 2012. The Talairach coordinates of the stimulated site in the 10 other subjects (x = 50, y = −42, z = 20; Fig. 1B) were based on two previous fMRI studies (Chica et al., 2013; Gerardin et al., 2012).

For subjects of the 'SHAM-TMS' group, the single pulse TMS was applied over the Vertex with an intensity corresponding to 120% of the motor threshold. The average TMS intensity applied over the Vertex corresponded to 71%. TMS stimulation of Vertex was used as a procedure of SHAM stimulation to control for non-specific factors, such as the associated auditory and tactile stimulations, which could potentially contribute to the effect of TMS in the rTPJ experiment. The Vertex was chosen as a control site, because Vertex is located far enough from saccadic areas of the cerebral cortex.

Experimental design and statistical analysis

rTPJ experiment

We used a within-subject design with TMS timings similar to that used previously to demonstrate a causal involvement of IPS in voluntary saccades adaptation (Panouillères et al., 2014): each subject of the 'rTPJ' group participated in four sessions separated by at least one week (an inter-session duration longer than the maximum duration −5 days-for which a significant retention was observed in a previous study: Alahyane and Pélisson, 2005). All sessions were identical in terms of task, visual stimulation and TMS application except for the timing of single pulse TMS: the stimulation of the right TPJ was delivered at 30, 60, 90 (as in Panouillères et al., 2014) and 120 ms after the onset of the horizontal reactive saccade. Here the 120 ms timing was added as a potentially ineffective timing to provide an internal control. The order of these four TMS-timing sessions was counterbalanced across participants, according to the assignment illustrated in Table 1.

Each session consisted of three phases: a pre-adaptation phase without TMS application, an adaptation phase with TMS and a post-adaptation phase without TMS.

Pre- and post-adaptation phases. These two phases were identical, and comprised each 24 trials (12 rightward and 12 leftward in random order). At the beginning of each trial subjects fixated a central fixation cross during 1600–2000 ms. The fixation turned off and simultaneously a peripheral target appeared in the left or right hemi-field at an eccentricity of ±11°. Subjects had to look at the target as quickly and accurately as possible. Once the horizontal reactive saccade was detected (velocity

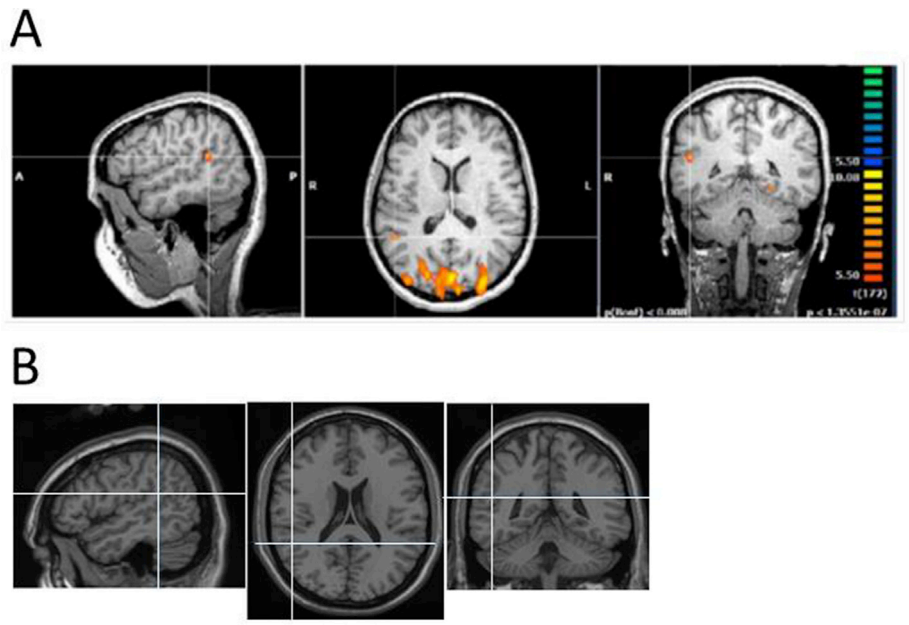

Fig. 1. **(A)** Representative results of fMRI localizer scan in a single subject. Cross-hairs represent the center of oculomotor area of the right TPJ (Talairach coordinates: x = 48; y = −45; z = 16). **(B)** Projection on a reference brain of the TPJ Talairach coordinates of right TPJ (x = 50, y = −42, z = 20) used in 10 subjects.

Table 1
Order of testing of the 4 spTMS delays relative to saccade onset (30, 60, 90 and 120 msec).

Subjects	Session 1	Session 2	Session 3	Session 4
1–3	30 msec	60 msec	90 msec	120 msec
4–6	60 msec	90 msec	120 msec	30 msec
7–9	90 msec	120 msec	30 msec	60 msec
10–12	120 msec	30 msec	60 msec	90 msec

threshold: 80–90°/s), the target turned off. After 1700 ms the trial ended, a beep informed the subject to look back at the center of the screen and to prepare for the next trial starting 1200 ms after the beep. While the pre-adaptation phase allowed measuring baseline saccadic gain, the post-adaptation phase aimed at measuring adaptation after-effect (see Data analysis).

Adaptation phase. This phase comprised 3 blocks of 48 leftward saccades trials (Block1, Block2, Block3). Backward adaptation was induced using a classical double-step target paradigm (McLaughlin, 1967): the time sequence in adaptation trials was the same as for pre- and post-adaptation trials, except that upon detection of the horizontal reactive saccade, the target jumped toward the fixation, reducing its eccentricity from −11° to −7° (i.e. a 36% backward jump). The backward stepped target remained visible at its new location for 50 msec, a duration chosen based on the following two considerations (see Panouillères et al., 2014). First, as spTMS effects are usually short-lived, restricting the temporal window over which the stepped target is visible increases the likelihood of interfering with adaptation. Secondly, a target duration as short as 50 ms is nonetheless sufficient to induce an optimal saccadic adaptation (Panouillères et al., 2011). Single pulse TMS was applied over the right TPJ for all adaptation trials, with a delay after detection of horizontal saccade depending on each of the four sessions (respectively 30, 60, 90 or 120 ms). After 1700 ms, at the end of each trial a beep informed the subject to look back at the center of the screen.

SHAM-TMS control experiment

Each subject of the 'SHAM-TMS' group participated in two separate sessions (mean delay between sessions = 10.75 ± 0.22 days) with TMS used only in the first session. Session 1 was identical to sessions performed in the 'rTPJ' experiment except that TMS was applied over the Vertex and that each spTMS timing used in the 'rTPJ' experiment (30, 60, 90 and 120 ms after the onset of the horizontal reactive saccade) was randomly distributed across the 12 subjects (3 subjects per timing). Session 2 consisted only of the pre-adaptation phase.

No-TMS control experiment

Each subject of the 'No-TMS' group participated in two sessions separated by 10.69 ± 1.60 days. These sessions were identical to the ones in the 'SHAM-TMS' experiment except that TMS was never used in session 1.

Data processing and statistical analysis

Eye movement data were analyzed off-line using custom software developed in the Matlab v.7.1 environment (Math Works Inc., Natick, MA, USA). Data from the left and right eyes were averaged. The beginning and end of each primary horizontal saccade were identified based on a velocity threshold of 50°/s and the starting and landing positions were extracted 50msec before and after these time points, respectively. For each primary horizontal saccade, saccadic gain was obtained as the ratio between horizontal saccade amplitude (distance between the starting and landing positions) and retinal error (distance between target initial position and saccade starting position). As in previous studies (e.g. Habchi et al., 2015; Panouillères et al., 2011, 2014), mean saccadic gain was obtained separately in each session, for the leftward saccades of the adaptation phase and for both leftward and rightward saccades of the pre- and post-adaptation phases. The gain change of each leftward saccade of the adaptation and post-adaptation phases was calculated with respect to the mean leftward saccade gain of the pre-adaptation phase; similarly, the gain change of each rightward saccade of the post-adaptation phase was calculated with respect to the mean rightward saccade gain of the pre-saccadic phase. Positive values indicate a decrease of saccadic gain relative to the pre-adaptation phase (thus corresponding to the expected gain decrease given the saccade shortening adaptation procedure); the gain change of saccades in the post-adaptation phase corresponds to the immediate after-effect of adaptation, hereafter "adaptation after-effect". How much adaptation after-effect was retained from the 1st session to the 2nd session, hereafter

"adaptation retention", was calculated as the change of baseline (pre--adaptation) gain between sessions 1 and 2 relative to the adaptation after-effect in session 1 (post-versus pre-adaptation gain change): retention rate (%) = 100 × ($Gain_{pre1}$-$Gain_{pre2}$)/($Gain_{pre1}$-$Gain_{post1}$). Saccades were excluded from analysis if primary saccade was not correctly detected online, was contaminated by eye blinks or showed a gain outside the range of mean ± 3 SD (using these data quality checks, the shortest latency of all saccades used for analyses in this paper was 96 msec). Eliminated trials represented 5.7% (SEM ± 0.19) for the rTPJ group, 9.3% (SEM ± 2.02) for the SHAM-TMS group and 5.7% (SEM ± 1.72) for the No-TMS group.

Statistical analyses were performed with Statistica 9 (Statsoft Inc., Tulsa, OK, USA). First, to quantify saccadic adaptation and test for any effect related to TMS application in the 'rTPJ' experiment, repeated-measures ANOVAs were performed with saccadic data of different sessions pooled together according to spTMS timing (see Table 1, e.g. for the 30 msec TMS delay: Session 1 of subjects 1–3 + Session 4 of subjects 4–6 + Session 3 of subjects 7–9 + Session 2 of subjects 10–12): a first ANOVA was performed on mean saccadic gain change during the adaptation phase (relative to pre-) with the within-subject factors TMS-timing (30, 60, 90, 120 ms) and Phase (Block1, Block2, Block3), and a second ANOVA was performed on the adaptation after-effect (mean saccadic gain change in post-adaptation relative to pre-adaptation) with within-subject factors TMS timing (30, 60, 90, 120) and Saccade Direction (leftward, rightward). Second, we determined in the 'rTPJ' experiment whether the repetition of the stimulation sessions led to any carry-over effect on the baseline (pre-adaptation) saccadic gain. For this analysis, data of different spTMS timing were pooled together according to Session order (see Table 1, e.g. for Session 1: subjects 1–3 at 30 ms delay + subjects 4–6 at 60 ms delay + subjects 7–9 at 90 ms delay and subjects 10–12 at 120 ms delay). Baseline gain was submitted to a two-way repeated measure ANOVA, with the factors Testing Session (1, 2, 3 and 4) and Saccade Direction (leftward vs. rightward). One subject of the 'rTPJ' group (Subject 3, female, age 22) was excluded from this analysis and from any further analysis on the retention of adaptation because she showed a baseline gain measured in session 1 of 0.8, outside the mean ± 2SD range in this group. Third, for the 'SHAM-TMS' experiment, submitting the saccadic gain change measured in session 1 to a repeated measure ANOVA (within-subject factor Phase: Block1, Block2, Block3; and between-subject factor TMS timing: 30 ms, 60 ms, 90 ms and 120 ms) failed to reveal any effect of TMS timing ($F_{3,8} = 0.51$; $P > 0.67$) and thus, these data were pooled across the 4 TMS timings conditions. Finally, to test whether adaptation retention was similar between the 3 experiments, two further ANOVAs were performed: 1) baseline saccade gain (in pre-adaptation) was submitted to a two-way ANOVA with Sessions (1/2) and Saccade Direction (Left/Right) as within-subject factors and Experiments (rTPJ/Vertex/Control) as between-subject factor; 2) the adaptation after-effect in session 1 and rate of adaptation retention in session 2 were compared between 'rTPJ', 'SHAM-TMS' and 'No-TMS' experiments by means of a one-way ANOVA with the between-subject factor 'Experiment'. Bonferroni tests were used to explore significant interactions. Significance was set at $p < 0.05$. Values are reported as mean ± 1 SEM.

Results

No timing-dependent effect of spTMS over rTPJ on adaptation acquisition and after-effect

The initial objective of this study was to assess whether the application of TMS over rTPJ modifies adaptation of leftward reactive saccade (RS). We computed the mean latency separately for each subject, TMS timing, and block of adaptation trial. The latency grand average was 206 ± 27 msec (n = 144: 12 subjects x 4 timings x 3 blocks; with the shortest mean individual latency = 159 msec). These results are consistent with classical values of reactive saccades latency and not of anticipatory saccades. We then applied a repeated measure ANOVA with the TMS Timing (30, 60, 90, 120 msec), Block (1, 2, 3) as within-subject factors. This ANOVA disclosed no significant effect and no significant interaction [largest p value = 0.36, $F(3, 33) = 1.1$].

As a first qualitative evaluation of the adaptation data, we plot in Figs. 2 and 3 the time-course of leftward saccade gain during the adaptation phase of the rTPJ experiment. The mean gain over the 12 subjects was computed separately for each of the four timings of TMS over rTPJ: Fig. 2 represents the mean ± 1 SEM range of saccade gain during the adaptation phase for each timing, whereas Fig. 3 plots the mean gain superimposed for the four TMS timings (as well as the grand means in the pre- and post-adaptation phases). These figures depict the progressive decrease of saccade gain during the adaptation phase and the persisting gain reduction during the post-adaptation phase, which are two features commonly reported by saccadic adaptation studies.

Fig. 4 depicts the mean change of saccadic gain relative to the pre-adaptation phase calculated separately during the 3 different adaptation blocks and the 4 TMS timings. Mean gain change was then submitted to a two-way repeated measure ANOVA with the within-subjects factors TMS timing (30, 60, 90, 120) and Phase (Block1, Block2, Block3). The results revealed a significant effect of Phase ($F(2,22) = 55$, $p < 0.001$), consistent with the expected decrease of the gain during the adaptation phase. This adaptation-related decrease was marked for all 4 TMS timings, but tended to be slightly higher for the 60 ms TMS timing (2nd blue bar in Fig. 4) compared to the other 3 TMS timings, particularly during blocks 1 and 2. However, this trend did not reach significance (TMS timing factor: $F(3,33) = 1.88$, $p = 0.15$; interaction between TMS timing and Phase: $F(6,66) = 0.30$, $p = 0.93$). Thus, the timing of TMS applied over rTPJ did not significantly influence the time-course of leftward RS adaptation. Note further that this time-course is very similar to that measured in the 'SHAM-TMS' experiment (grey bar in Fig. 4).

This conclusion was supported by another analysis based on an exponential fit of saccade gain over time during the adaptation phase. This fitting procedure allowed us to compute, separately for each TMS timing and for each subject, the saccade gain at the onset and termination of the adaptation phase. We then submitted these saccade gain values to a repeated measure ANOVA with the Phase (pre, post) and the TMS Timing (30, 60, 90 and 120 msec) as within-subject factors. This ANOVA disclosed only a significant effect of the Phase ($F(1, 10) = 299$, $p = 0.000001$) but no effect of the Timing factor ($F(3, 30) = 0.7$, $p = 0.57$) and no significant Timing × Phase interaction ($F(3, 30) = 0.98$, $p = 0.42$). Therefore, this analysis confirms the lack of significant effect of TMS applied over rTPJ onto the time-course of leftward RS adaptation. Furthermore, we re-assessed the speed of initial adaptation by computing the slope of the linear fit of the gain change during the first block of adaptation. This slope parameter was then submitted to a repeated measure ANOVA with the TMS Timing (30, 60, 90 and 120 msec) as within-subject factor. This ANOVA disclosed no significant effect of the Timing factor ($F(3,12) = 0.3$, $p = 0.85$)), and therefore did not confirm the trend of a faster initial gain decrease observed in Fig. 4 for the 60 ms timing.

Then, we tested whether the application of TMS over rTPJ modified the after-effect of RS adaptation measured during the post-adaptation phase. As detailed in Methods, after-effect was computed as the gain change in post-adaptation relative to pre-adaptation, separately for leftward and rightward saccades and for the 4 TMS timings (Fig. 5). Submitting this gain change to a two-way repeated measure ANOVA with the factors TMS timing (30, 60, 90 and 120 ms) and Saccade Direction (leftward vs. rightward), we found a significant effect of Saccade Direction ($F(1,11) = 68.11$, $p < 0.001$) due to a much higher gain change of leftward saccades (adapted) (12.2 ± 1.5% on average) than of rightward saccades (non-adapted) (2.1 ± 0.9% on average). This direction specificity was expected from the known lack of transfer of adaptation from saccades in one horizontal direction to saccades in the opposite direction (see for references Pélisson et al., 2010). The ANOVA also disclosed a lack of significant effect of the TMS timing factor ($F(3,33) = 0.78$, $p = 0.51$)

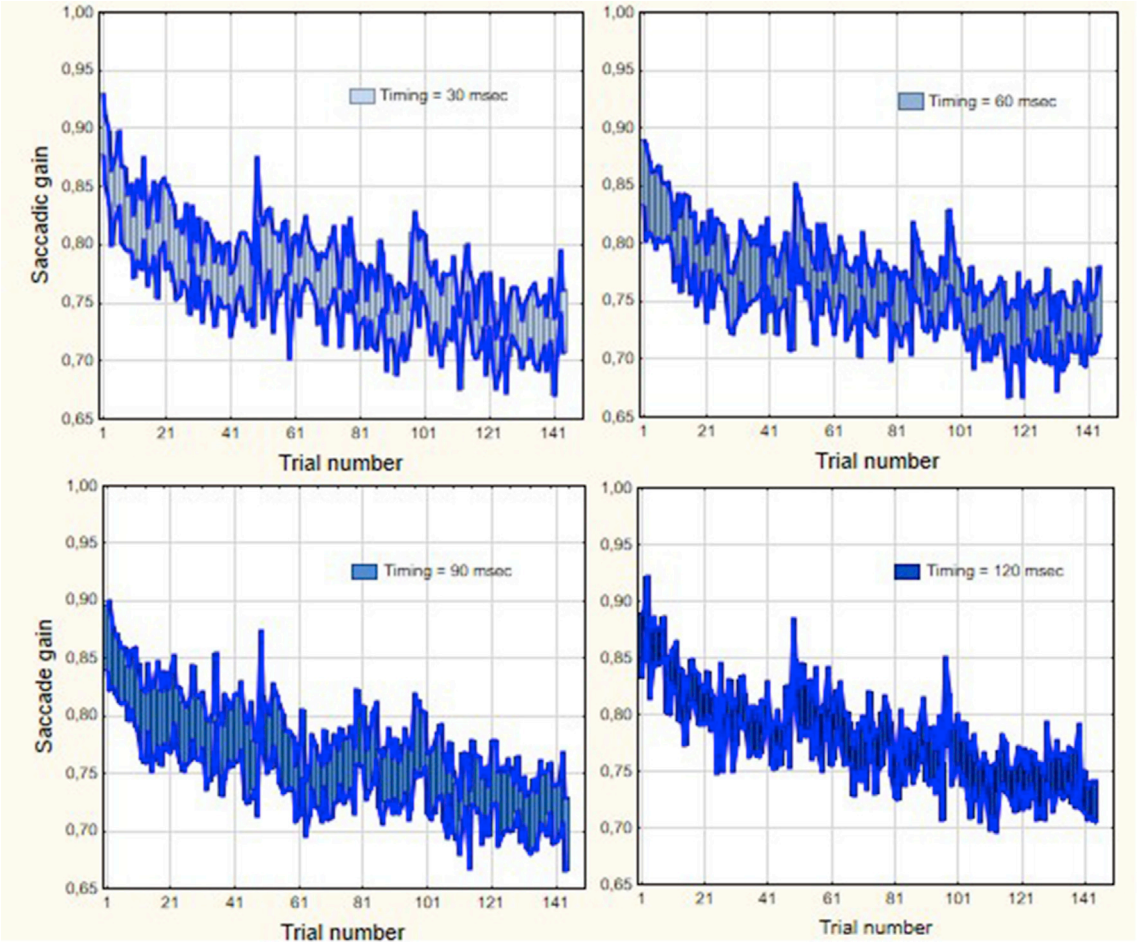

Fig. 2. Mean ± 1 SEM range (n = 12 subjects) of saccade gain during the adaptation phase. The different TMS timings are plotted in panels A (30 msec), B (60 msec), C (90 msec) and D (120 msec).

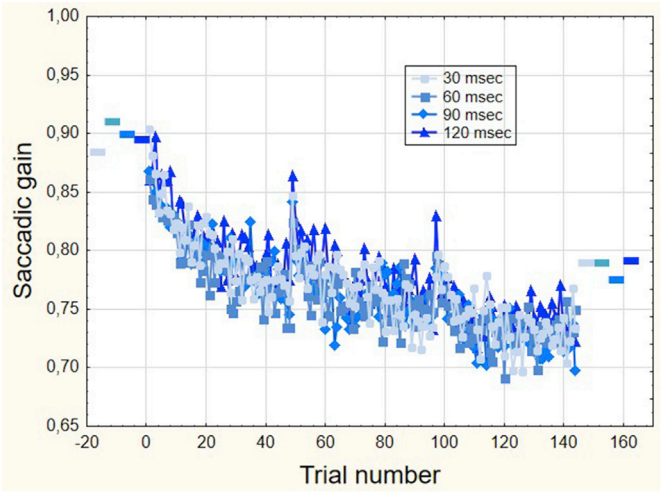

Fig. 3. Mean saccade gain (n = 12 subjects) during the adaptation phase superimposed for the four TMS timings. The figure also depicts for the pre- and post-adaptation phases the grand means (n = 12 subjects x 12 trials).

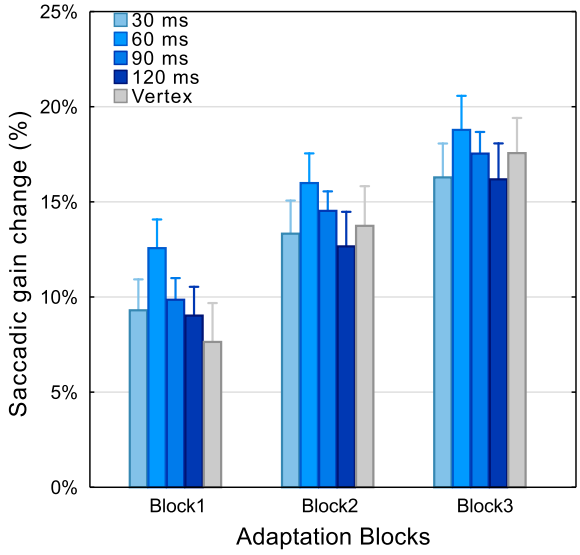

Fig. 4. Saccadic gain change during the adaptation phase (Block1, Block2 and Block3) for the leftward adapted saccades. In the 'rTPJ' experiment, each of the 4 TMS timings was tested in separate sessions represented by differently colored blue bars. In the 'SHAM-TMS' experiment, the 4 TMS timings were tested in 3 subjects each and the results collapsed together (grey bar). Error bars show SEMs.

and of significant interaction with the Saccade Direction factor ($F(3, 33) = 0.97$, $p = 0.42$). This indicates that TMS application over the rTPJ had no timing-dependent influence on saccadic adaptation after-effect, for both (adapted and non-adapted) saccade directions.

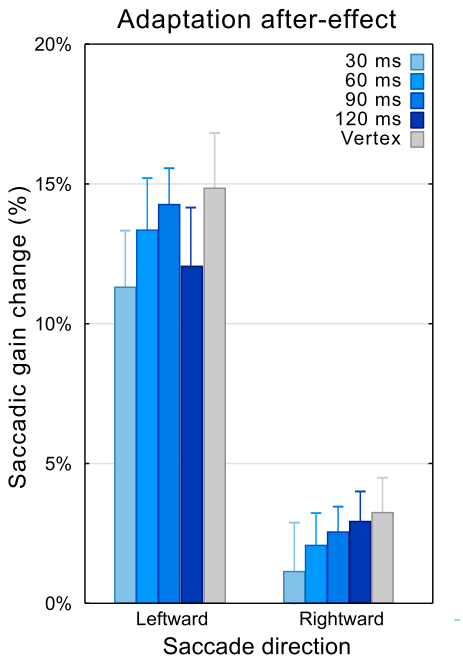

Fig. 5. Adaptation after-effect: saccadic gain change between the pre- and post-adaptation phases separately for leftward (adapted) saccades and for rightward (unadapted) saccades. Same color code as in Fig. 4. Error bars show SEMs.

In conclusion, no significant timing-dependent effect of TMS over rTPJ could be revealed, either on the time-course of gain change during adaptation acquisition, or on the gain change reached immediately after acquisition (after-effect).

Effect of spTMS over rTPJ on adaptation retention

We then looked for a possible effect on saccadic adaptation of repeating the TMS intervention over rTPJ 4 times. Since the 4 TMS timings were counterbalanced across subjects and evenly distributed in each of the 4 experimental sessions (see Methods), we could evaluate this TMS repetition effect independently of any TMS timing effect evaluated in the previous paragraphs. We thus pooled data within each testing session (labelled 1st to 4th) irrespective of TMS timing. All results presented in the following are based on 11 subjects (see Methods).

The baseline gain measured in the pre-adaptation phase is plotted in Fig. 6. As shown in this figure, the baseline gain of leftward saccades (performed in the adapted direction) progressively decreases from the 1st to the 4th testing sessions, which contrasts with the fairly constant gain of rightward saccades (un-adapted direction) across testing sessions. A two-way repeated measure ANOVA with the factors Testing Session (1st, 2nd, 3rd 4th) and Saccade Direction (leftward vs. rightward) on the saccadic gain revealed a significant effect of Saccade Direction ($F(1,10) = 14.06$, $p = 0.004$) due to the higher baseline gain of rightward (non-adapted) saccades than of leftward (adapted) saccades. Noticeably, there was also a significant effect of Testing Session ($F(3,30) = 11.55$, $p = 3.4 \times 10^{-5}$) and a significant interaction ($F(3,30) = 17.51$, $p = 10^{-6}$), which could be explained by a significant decrease of mean gain across successive sessions for the leftward (adapted) saccades, but not for the rightward saccades. Indeed, for leftward saccades, the gain in the 2nd session (0.90 ± 0.02), 3rd session (0.88 ± 0.02) and 4th session (0.86 ± 0.02) was significantly lower than in the 1st session (0.97 ± 0.01) (Bonferroni tests, all $p < 0.00002$), and the gain in 4th session was lower than in the 2nd session ($p < 0.007$). The gain in the 4th session was lower than in the 3rd but this difference did not reach significance ($p > 0.05$). Conversely, for rightward saccades (non-adapted direction), saccadic gain was fairly constant between different sessions and very close to that of leftward saccades in the 1st session.

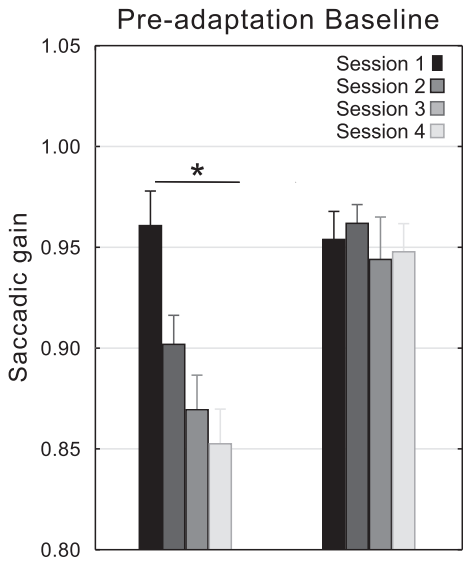

Fig. 6. Baseline saccadic gain: gain in the pre-adaptation phase of Testing Sessions 1, 2, 3 and 4 (decreasing grey shades), for the leftward (adapted) saccades and rightward (unadapted) saccades. The asterisk for the leftward saccades indicates significant interaction between Testing Session and Saccade Direction (see text for details). Error bars show SEMs.

In conclusion, the baseline saccadic gain measured during pre-adaptation progressively decreased from one testing session to the next, despite several days had elapsed (average delay across the 11 subjects: 10.5 ± 7.3 days).

Adaptation retention after spTMS over rTPJ is enhanced relative to control groups

The data presented in the preceding paragraph indicate that baseline saccadic gain progressively decreased over successive testing sessions, revealing an incomplete recovery of gain during the ~10 day-long inter-session periods. Since the gain recovery measured by Alahyane and Pélisson (2005) 11 days after the adaptation session was strong (i.e. saccadic gain was no longer significantly different from that measured just before adaptation at day 0), the present data suggest that TMS over the rTPJ strengthened the long term retention of adaptation. To directly assess this hypothesis, we performed the 'No-TMS' and 'SHAM-TMS' control experiments to yield adaptation after-effect and retention measures between Sessions 1 and 2 in the absence of TMS application over the rTPJ.

First, we investigated whether, for leftward saccades measured during the 1st session, the baseline gain before adaptation and the gain changes during and immediately after adaptation training differed between the 3 experiments. A one-way ANOVA disclosed no significant effect of the 'Experiment' factor on baseline saccadic gain ($F(2, 33) = 0.4$, $p = 0.6$). Regarding the time-course of saccadic gain change during adaptation, a two-way ANOVA (factors 'Experiment' and 'Adaptation Block') again failed to reveal any difference between 'rTPJ', 'No-TMS' and 'SHAM-TMS' experiments ($F(2,99) = 0.11$, $p = 0.89$ and $F(4,99) = 0.13$, $p = 0.96$ for the 'Experiment' factor and 'Experiment' x 'Block' interaction, respectively), and only the 'Adaptation Block' effect was significant: $F(2,99) = 22.2$ $p < 0.001$). Finally, regarding the immediate adaptation after-effect, and as shown in Fig. 8A, again no significant difference between the 3 experiments was found (one-way ANOVA with the between-subject factor 'Experiment' $F(2, 33) = 0.2$, $p = 0.8$). The results of these analyses confirm the lack of effect of TMS over the rTPJ both on the acquisition and after-effect of adaptation and in so doing, also validate the 'SHAM-TMS' and 'No-TMS' control data for providing adequate reference in the retention analysis performed in the following.

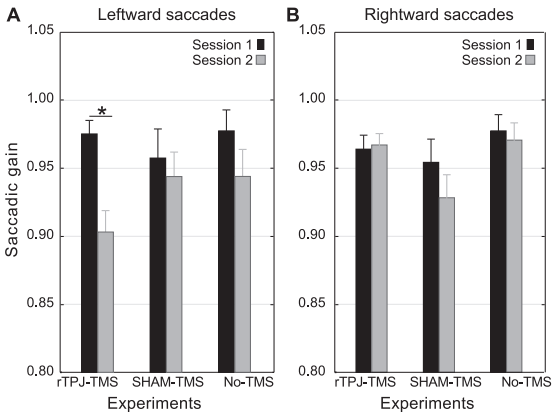

Fig. 7. Baseline saccadic gain: gain in the pre-adaptation phase of Testing Sessions 1 and 2 for the 3 experiments: 'rTPJ' (left), 'SHAM-TMS' (middle) and 'No-TMS' (right). (A) Leftward (adapted) saccades. The asterisk indicates a significantly reduced gain in Session 2 relative to Session 1 in the rTPJ experiment (see text for details). (B) Rightward (unadapted) saccades. Error bars show SEMs.

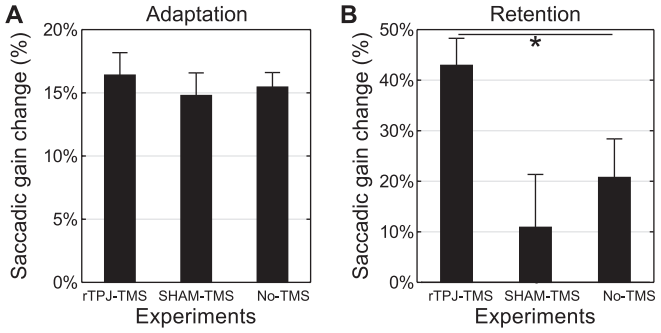

Fig. 8. Adaptation after-effect and retention of leftward saccades in the 3 experiments. (A) The mean saccadic gain change between the post- and pre-adaptation phases of Session 1 (after-effect) is plotted separately for the 3 experiments: 'rTPJ' (left), 'SHAM-TMS' (middle) and 'No-TMS' (right). There was no statistical difference between the 3 experiments (see text for details). (B) Amount of retention from Session 1 to Session 2: mean ratio of saccadic gain change between the post-adaptation phase of Session 1 and the pre-adaptation phase of Session 2 over the adaptation after-effect in Session 1. The asterisk indicates a significant difference between the 3 experiments (see text for details). Error bars show SEMs.

Second, we tested whether the change of baseline gain across sessions reported above for the rTPJ experiment was also found in the Vertex and Control experiments or whether it was specific of the application of TMS over rTPJ. To do so, baseline gain (in pre-adaptation) was submitted to a two-way ANOVA with Sessions (1/2) and Saccade Direction (Left/Right) as within-subject factors and Experiments (rTPJ/Vertex/Control) as between-subject factor. Significant results were found for the Session factor ($F1,33 = 19.2$, $p = 0.0001$) and its interactions with Direction ($F1,33 = 11.4$, $p = 0.0018$) and with Direction and Experiment (3-way interaction: $F2,33 = 7.9$, $p = 0.0016$). As shown in Fig. 7A, baseline gain of leftward saccades was significantly reduced between Sessions 1 and 2 in the rTPJ experiment (post-hoc Bonferroni test: $p = 0.00002$), but not for the other two experiments, nor for rightward saccades in any experiment (Fig. 7B, all $p > 0.05$). Thus, the decrease of baseline gain between sessions 1 and 2 was specific of the application of TMS over rTPJ.

Next, to check that these between-session changes of gain were not related to any change, albeit not significant, of size of adaptation between experiments, we computed for each experiment the retention rate from the 1st session to the 2nd session, as defined as the ratio of the change of baseline gain between sessions 1 and 2 over the adaptation after-effect achieved in session 1 (see Methods). As shown in Fig. 8B, this retention rate was low and very similar in the 'No-TMS' and 'SHAM-TMS' experiments ($21\% \pm 8$ and $11\% \pm 8$, respectively) but remarkably, reached $43\% \pm 9$ in the 'rTPJ' experiment, corresponding to a 2–3.8-fold increase. A one-way ANOVA with the between-subject factor 'Experiment' confirmed a significant effect ($F(2, 33) = 3.8$, $p = 0.033$). Given that the mean delay between sessions 1 and 2 was comparable across the 3 experiments (10.5, 10.7 and 10.7 days in 'rTPJ, 'SHAM-TMS' and 'No-TMS' experiments, respectively), the larger adaptation retention in the 'rTPJ' experiment reflects a higher resistance to recovery. These observations confirm that TMS delivered over the rTPJ led to a marked strengthening of oculomotor memory modifications.

Discussion

Consistent with its localization between the inferior parietal lobule, the lateral occipital cortex and the posterior part of the superior temporal sulcus (Mars et al., 2012), TPJ is thought to be a major multimodal and integrating cortical region. Numerous imaging and lesion studies have indeed suggested a role for TPJ in various functions, including attention, visual processing, auditory processing, theory of mind (Donaldson et al., 2015). In the present study, we aimed at deciphering the potential role of the right TPJ in the adaptation of reactive saccades (RS). This role was predicted based on the metabolic activation of rTPJ observed during the adaptation of leftward RS in a previous neuroimaging study (Gerardin et al., 2012). This role would also be consistent with the recently reported boosting effect of leftward RS adaptation onto covert exogenous attention processes (Habchi et al., 2015) which are known to recruit the rTPJ (Corbetta and Shulman, 2002; Corbetta et al., 2008; Chica et al., 2013; Donaldson et al., 2015; Painter et al., 2015). We addressed this question by means of a single-pulse TMS approach during a saccadic adaptation task in healthy subjects. The rationale was that TMS-induced perturbation of rTPJ activity elicited repeatedly during each saccade of the adaptation phase would, at least for one of the four TMS timings tested, interfere with saccade adaptation mechanisms (as in most previous spTMS studies, we used the neuronal excitatory effect of spTMS as a means to interfere with the normal cortical activity). However, as discussed in the following, the results did not support this hypothesis, but led to the serendipitous observation that spTMS over rTPJ largely enhance the long-term retention of saccadic adaptation. The discovery of the potential role played by rTPJ in the long-term memory of saccadic eye movements calibration was then specifically addressed by two additional control experiments.

TMS over rTPJ and acquisition of saccadic adaptation

TMS applied 60 ms after saccade detection tended to facilitate the saccadic gain change during the earliest phase of adaptation acquisition (blocks 1 and 2), but this facilitation did not reach statistical significance. The possibility of an insufficiently powered design is unlikely because, first, the number of subjects and procedures (TMS and saccadic adaptation) were similar to those in our two previous studies which successfully revealed a role in saccadic adaptation of cerebellum (Panouillères et al., 2012) and parietal cortex (Panouillères et al., 2014) and, second, the same design allowed us to clearly disclose a TMS effect on adaptation retention, as discussed below. Alternatively, none of our 4 different TMS timings was appropriate to capture the putative rTPJ involvement in saccadic adaptation, which we consider unlikely as an even narrower TMS timing range (60 versus 90 ms) was successfully used in these two previous studies. At any rate, a potential causal role of rTPJ in the adaptation acquisition of leftward RS remains unsupported at this stage. The metabolic activation which was previously demonstrated in the same cortical area during adaptation of leftward RS (Gerardin et al., 2012) might then reflect sensorimotor signals which do not causally contribute to the short-term saccadic adaptive changes. We speculate that such signals could result from a drive exerted on rTPJ by other neural centers

causally involved in saccadic adaptation, such as the cerebellum (Jenkinson and Miall, 2010; Panouillères et al., 2012, 2015; Avila et al., 2015), subtending the transfer of saccadic adaptation to visuo-attentional processes (Zimmermann and Lappe, 2010; Habchi et al., 2015). Another possibility is that, although not specifically tested by Gerardin et al. (2012), these signals revealed by fMRI actually identified ongoing memorization processes that are now revealed by the present TMS approach, as discussed in the following.

TMS over rTPJ and retention of saccadic adaptation

We incidentally discovered a strong cumulative effect of sessions repetition on saccadic adaptation parameters. Indeed, the baseline gain of saccades performed in the leftward -adapted- direction (but not those in the un-adapted rightward direction) decreased from the 1st session to subsequent sessions performed several days later (average delay between sessions 1 and 2 = 10.5 days). This decrease of baseline gain indicates an incomplete recovery from the preceding adaptation session (or, stated differently, a significant retention of adaptation across sessions). Since in each session, the 4 TMS timings were evenly distributed over subjects, this increase in adaptation retention cannot be related to specific timings of TMS over rTPJ. Nonetheless, comparing these data with those of the 'SHAM-TMS' and 'No-TMS' control experiments clearly indicates that rTPJ stimulation markedly and selectively enhanced long-term retention. Indeed, the baseline saccade gain (pre-adaptation) in the 1st session was similar in all 3 experiments. Moreover, the time-course of leftward gain change during adaptation in the 1st session did not differ between 'rTPJ', 'No-TMS' and 'SHAM-TMS' experiments and the adaptation after-effect (post-adaptation) in the 1st session was similar across the 3 experiments (~15%), a value close to that we found in a previous behavioral study (13.2%: Habchi et al., 2015) using the same double step target procedure and the same number of trials. Finally, the rate of adaptation retention (how much adaptation elicited in session 1 was retained in session 2 performed ~10 days later) was much higher in the 'rTPJ' experiment than in the 'SHAM-TMS' and 'No-TMS' control experiments (42%, 11% and 20.7%, respectively). This was still higher than the retention measured in Alahyane and Pélisson's study (2005) (a non significant retention rate of 15% at 11 days) despite a higher number of trials was used to elicit adaptation than here (220 versus 144). The fluctuation of the mean retention level of different groups of subjects in the absence of TMS applied over the rTPJ, ranging here from 11% to 21%, actually matches the natural inter-individual variability of retention level, which most likely relates to differences in eye-scanning behavior during the ~10 days post adaptation delay. For example, previous work (Alahyane and Pélisson, 2005) reported an intermediate and non-significant value of 15% of retention. However, as the 42% retention level found in the rTPJ group was clearly outside this natural range, we conclude that the rTPJ stimulation favored, rather than induced, saccadic retention. Altogether, these observations converge in demonstrating that TMS over the rTPJ has led to a 2–3.8-fold increase of the rate of adaptation retention over ~10 days.

Role of rTPJ in saccadic adaptation

How can we explain this unexpected facilitation of TMS over the rTPJ on the retention, but not on the acquisition, of adaptation of leftward reactive saccades?

One possibility is that TMS had actually interfered with plastic processes allowing saccadic responses to recover back to their baseline gain level. Since backward adaptation was studied here, recovery would involve gain-increasing adaptive processes, which cortical substrates are still completely unknown. Note that this hypothesis implies TMS perturbation effects to extend beyond the recording session, while subjects perform saccades to stationary visual targets during their daily activities, like inhibitory effects induced by low frequency repetitive TMS procedures. However, comparing our spTMS procedure to classical inhibitory rTMS protocols (Walsh and Pascual-Leone, 2005, Siebner et al., 2009) lead us to consider this "rTMS-like" effect quite unlikely. First, the repetition rate of spTMS during the adaptation exposure was irregular and averaged a lower frequency rate (~0.2 Hz) than in rTMS protocols ($\geq$1 Hz). Second, the inter-session delay of the present study (~10 days) was several orders of magnitude longer than the duration of rTMS effects classically described (5–20 min after cessation of the stimulation). Note that, in relation to this second point, although de-adaptation would start soon after the cessation of the TMS session (i.e. immediately after completion of the post-adaptation phase), it would unfold over a much longer period of time than putative rTMS effects. Indeed, when TMS was not applied over the rTPJ, the gain of leftward saccades measured 10 days post-adaptation was still 2.25% lower than before adaptation (mean value across the SHAM-TMS and No-TMS conditions), revealing that normal de-adaptation was not fully completed at that time. We thus believe that the hypothesis of TMS effectively interfering with a de-adaptation process can hardly explain our results.

Another possible explanation of the facilitation of the retention of adaptation is that TMS stimulation of the rTPJ around the time of saccade execution (30–120 msec following onset) has boosted consolidation processes involved in long-term saccadic retention. Although still debated (Caithness et al., 2004), consolidation mechanisms have been proposed to contribute to various types of long-term memory, including motor memories (Galea et al., 2011; de Beukelaar et al., 2014; Della-Maggiore et al., 2015; Moisello et al., 2015; Wessel et al., 2016). However, contrary to plasticity of skeletal-motor responses, long-term retention and consolidation mechanisms of oculomotor saccadic plasticity have been rarely investigated. A retention of saccade gain change has been observed 5 days after a single session of adaptation (Alahyane and Pélisson, 2005) or 5–20 days after several daily adaptation sessions (monkey: Robinson et al., 2006, Mueller et al., 2012; humans: Wang et al., 2012, M.T.N. Panouillères, personal communication). Robinson et al. (2006) additionally stressed that long-term adaptation induced by repeating daily adaptation sessions relies on mechanisms distinct from those underlying short-term adaptation induced in a single session. Contrary to evidence in the skeletal-motor system that cerebral or cerebellar neurostimulation can facilitate the consolidation of adaptation independently of its acquisition (Galea et al., 2011; Moisello et al., 2015; Wessel et al., 2016; O'Shea et al., 2017), the present findings are the first to support the existence of consolidation mechanisms for saccadic adaptation and of their possible neural substrate. The hypothesis that TMS stimulation of the rTPJ has boosted consolidation processes supposes an activating effect of TMS. Although it is generally acknowledged that spTMS has a perturbation effect on cognitive function, an excitatory effect would agree with the small trend of facilitation of saccadic adaptation acquisition mentioned above for the 60 msec delay spTMS. Excitatory effects of spTMS are also classically revealed by skeletal-motor contractions evoked by TMS over the primary motor cortex. They have also been suggested when other cortical areas are targeted by spTMS, but in these cases have been most often interpreted as remote effects on structures that are linked to the stimulated cortical zone through direct or indirect anatomical pathways (e.g., FEF: Nyffeler et al., 2004; IPS: Panouillères et al., 2014). Such TMS remote effects are supported by data from positron emission topography (Paus et al., 1997), fMRI (Ruff et al., 2006), electroencephalography (Fuggetta et al., 2005; Taylor et al., 2007), or by data using a second "test" TMS pulse (Ugawa et al., 1995; Pascual-Leone and Walsh, 2001; Silvanto et al., 2006; Ruff et al., 2008). We thus propose that the strengthening effect of the rTPJ stimulation on adaptation retention could be due to a direct involvement of the rTPJ in adaptation consolidation and/or an activation of remote structures such as the cerebellum. Further studies will be required to disentangle these possibilities.

In conclusion

By showing that stimulation over rTPJ strongly facilitates the long-

term retention of saccadic adaptation, independently from its acquisition, here we provide the first evidence for a cortical involvement in the long-term consolidation of saccadic oculomotor memories.

Conflicts of interest

The authors declare no competing financial interests.

Author contributions

D.P., O.H. and A.F. designed research; O.H. and C.H. performed research; O.H. and D.P. analyzed data; D.P., M.T.N.P. and A.F. wrote the paper.

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