A Role for the Parietal Cortex in Sensorimotor Adaptation of Saccades

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Abstract

Sensorimotor adaptation ensures movement accuracy despite continuously-changing environment and body. Adaptation of saccadic eye movements is a classical model of sensorimotor adaptation. Beside the well-established role of the brainstem-cerebellum in adaptation of reactive saccades, the cerebral cortex has been suggested to be involved in adaptation of voluntary saccades. Here, we provide direct evidence for a causal involvement of the parietal cortex in saccadic adaptation. First, the posterior intra-parietal sulcus (pIPS) was identified in each subject using functional magnetic resonance imaging (fMRI). Then, a saccadic adaptation paradigm was used to progressively reduce the amplitude of reactive and voluntary saccades, while single-pulse transcranial magnetic stimulation (spTMS) was applied over the right pIPS. The perturbations of pIPS resulted in impairment for the adaptation of voluntary saccades, selectively when spTMS was applied 60 ms after saccade onset. In contrast, adaptation of reactive saccades was facilitated by spTMS applied 90 ms after saccade initiation. The differential effect of spTMS relative to saccade types suggests a direct interference with pIPS activity for the voluntary-saccade adaptation and a remote interference with brainstem-cerebellum activity for the reactive-saccade adaptation. These results support the hypothesis that adaptation of voluntary and reactive saccades involves different neuronal substrates.

Keywords: Adaptation; Reactive saccades; Voluntary saccades; Posterior intra-parietal sulcus; transcranial magnetic stimulation

Introduction

Learning new motor skills, or optimizing existing ones, requires the ability to detect and correct movement errors. Enduring errors can be progressively corrected thanks to adaptation mechanisms. In laboratory conditions, motor errors eliciting sensorimotor adaptation are induced by perturbations of the movement, or its goal. For visuo-manual adaptation, the perceived trajectory or the actual trajectory of the limb is perturbed respectively through optical distortion, or force fields. Previous studies indicate that visuo-manual adaptation involves neural plasticity mechanisms in the cerebellum (Weiner et al. 1983; Martin et al. 1996; Pisella et al. 2005; Luaute et al. 2009; Werner et al. 2010; Taylor et al. 2010; Donchin et al. 2012) and in parieto-frontal areas of the cerebral cortex (Clower et al. 1996; Della-Maggiore et al. 2004; Pisella et al. 2004; Hadipour-Niktarash et al. 2007; Luaute et al. 2009). In contrast, only the brainstem-cerebellar centers have so far been shown to contribute to the adaptation of eye movements (smooth pursuit: Chou and Lisberger 2004, vestibulo-ocular-reflex: Anzai et al. 2010, vergence: Takagi et al. 2001, saccades: see reviews in Hopp and Fuchs 2004; Tian et al. 2009; Pelisson et al. 2010; Iwamoto and Kaku 2010).

The saccadic system provides one of the most well-established models of sensorimotor adaptation, because saccades are too fast to permit on-line corrections of the on-going eye trajectory and because the saccadic system has a major contribution to normal visual function (for reviews see Hopp and Fuchs 2004; Tian et al. 2009; Pelisson et al. 2010; Iwamoto and Kaku 2010). Reactive saccades elicited by sudden presentation of a visual target can be adapted by the classical saccadic adaptation paradigm (the “double-step target” paradigm: McLaughlin 1967). In this paradigm, a displacement of the saccadic target during the eye movements elicits an error signal. Because of saccadic suppression (Bridgeman et al. 1994), this intra-saccadic displacement is usually not consciously perceived by the subjects. Repeating this error signal over tens of trials leads to a progressive restoration of saccade

accuracy, through recalibration of oculomotor commands. In daily conditions, most saccades are generated during the self-paced viewing of a visual scene and are based on target selection and motor decision processes driven by endogenous cues. Such scanning saccades belong to the category of voluntary saccades (for a discussion about the convenient and common use of the terms 'reactive (or reflexive)' and 'voluntary' see Walker and McSorley 2006). The mechanisms of saccadic adaptation, mostly studied with reactive saccades, have long been thought to involve exclusively the cerebellum and associated brainstem structures (for reviews see (Hopp and Fuchs 2004; Tian et al. 2009; Pelisson et al. 2010; Iwamoto and Kaku 2010; Prsa and Thier 2011). However, mounting evidence suggest that adaptation of reactive and voluntary saccades involves different mechanisms, and partially separate neural substrates (Erkelens and Hulleman 1993; Deubel 1995; Fujita et al. 2002; Hopp and Fuchs 2002; Gaveau et al. 2005; Collins and Dore-Mazars 2006; Cotti et al. 2007; Alahyane et al. 2007; Alahyane et al. 2008a; Alahyane et al. 2008b; Cotti et al. 2009; Zimmermann and Lappe 2009; Hopp and Fuchs 2010; Panouilleres et al. 2011; Zimmermann and Lappe 2011). By assessing the transfer of adaptation to saccadic, visuo-manual or perceptual responses, these behavioural studies support the hypothesis that voluntary-saccade adaptation is acting both on sensory and motor processes and that reactive-saccade adaptation is acting preferentially on motor processes. Two relatively recent lines of evidence even suggest that the parietal cortex may play a key role in the adaptation of voluntary saccades. First, two of the behavioural studies quoted above (Cotti et al. 2007; Cotti et al. 2009) proposed that the early stages of the sensorimotor transformation affected by voluntary-saccade adaptation should rely on the frontal and/or the parietal cortex. Second, a recent functional magnetic-resonance imaging (fMRI) study of saccadic adaptation highlighted the involvement of the posterior intra-parietal sulcus (pIPS) in the adaptation of voluntary saccades, but not in the adaptation of reactive

saccades (Gerardin et al. 2012). To date, however, there is no direct evidence showing that the parietal cortex is actually necessary for saccadic adaptation.

The first aim of the present study was to assess the role of the posterior intra-parietal sulcus (pIPS) in saccadic adaptation. We decided to target this area, which is thought to be the Parietal Eye Fields (for review see: Muri 2006), because of the fMRI results reported by Gerardin and colleagues (Gerardin et al. 2012). Further, we focussed on the pIPS of the right hemisphere because in the latter study, adaptation of leftward saccades was associated with activation in the contralateral (right), but not in the ipsilateral (left) hemisphere. The second aim of the study was to test whether the pIPS is similarly involved in adaptation of voluntary saccades (VS) and reactive saccades (RS). To these aims, we used fMRI-guided single-pulse transcranial magnetic stimulation (spTMS) to interfere with the normal processing of the right pIPS during adaptation of reactive and voluntary saccades.

Materials and Methods

Subjects

Eighteen healthy subjects participated in the study. Of these, six participated only in the first experiment (VS experiment); six participated only in the second experiment (RS experiment); and six participated in both experiments. Thus, each experiment involved twelve subjects. The two groups of twelve subjects were matched in age (VS experiment: 29 ±9.5; RS experiment: 29 ±9.6 years) and gender (six females and six males in each group). Thirteen participants were naïve to the goals of the study. All subjects had normal or corrected-to-normal vision, and no history of neurological or psychological disorder. Subjects gave their informed written consent and were financially compensated for their participation. All procedures complied with the Ethical Principles of the World Medical Association (Declaration of Helsinki) and were approved by the local ethics committee (CCPPRB-Lyon B).

Experimental design

Each experiment involved two steps. In the first step, fMRI was used to localise the oculomotor region of the posterior part of the right intra-parietal sulcus (pIPS) in each subject (see for detailed procedures: Gerardin et al. 2012). In the second step, single-pulse transcranial magnetic stimulation (spTMS) was used to assess the role of the pIPS in saccadic adaptation.

fMRI

fMRI was performed with a 1.5 Tesla Siemens Sonata MRI scanner at CERMEP (Bron, France). Following a T1-weighted anatomical scan (1×1×1 mm), T2*-weighted functional scans (EPI) were acquired from 29 axial slices covering the entire head (TR: 3000 ms, TE 50 ms, rotation angle: 80 °, resolution: 3×3×3 mm). These anatomical and functional scans were performed using an 8-channel SENSE^{TM} head coil.

The stimuli used during the functional scans were produced using light-emitting diodes (LEDs, 3 mm diameter) located at the rear of the magnet and visible through a mirror attached to the head coil. An infrared eye tracker (ISCAN, Woburn, MA, USA) located below the LEDs recorded, at a frequency of 240 Hz, the vertical and horizontal positions of the left eye via the same mirror. The eye tracker was calibrated by asking subjects to fixate a series of 9 LEDs covering the field used during scanning. The triggering of the scans, the monitoring of eye movements and the control of the visual stimuli were controlled in real time by customary software.

Functional saccade localizer scans were obtained by alternating pro- and anti-saccade blocks with central-fixation blocks. During pro-saccade blocks, a green fixation point indicated to subjects that they had to make a saccade toward the target. During anti-saccade

blocks, a red fixation point indicated to subjects that they had to make a saccade in the opposite direction, toward the mirror position of the target. Targets were presented for 1500 ms at a random location of 4°, 10°, 16° or 20° in the left or right visual hemifield.

The fMRI data were analyzed with the Brain Voyager QX software (Brain Innovations, Maastricht, The Netherlands). Pre-processing of functional images involved correcting for slice-scan time and head movements, temporal high-pass filtering (3 cycles), and linear-trend removal. No spatial smoothing was used. The functional images were aligned with the anatomical data (transformed into Talairach space). For each subject, the oculomotor part of the right pIPS was identified by contrasting all blocks of saccades (pro- and anti-) with fixation blocks and the locus of highest activity in the pIPS was used for the spTMS sessions.

fMRI-guided spTMS

spTMS sessions were run in a dark room. Subjects were sitting 57 cm away from a 140 Hz computer screen (30° × 40°), with their head stabilized by a chin rest, cheekbone rests, frontal support, and a band behind the head. The presentation of visual stimuli (6 mm diameter black circles on a grey background) on the screen was controlled by a Visual Stimuli Generation system (CRS, Cambridge, UK).

Binocular eye movements were recorded using an infrared tracker (Eyelink 1000; SR research, Canada) with a frequency of 500 Hz and a spatial resolution of 0.05°. At the beginning of each session, the eye tracker was calibrated by presenting a sequence of nine fixation points forming an array on the computer screen, and asking subjects to fixate each point in turn. Laboratory-made software allowed on-line monitoring of eye movements, triggering of the visual stimulation, and triggering of the spTMS pulses relative to the timing of primary-saccade detections. Eye-movement data were stored for off-line analysis.

spTMS was delivered via a figure-of-eight coil (90 mm) coupled to a Magstim Rapid. Prior to each session, TMS was applied to the right motor cortex to determine the motor threshold, which was defined as the lowest stimulation intensity inducing a visible twitch in the resting contralateral hand in 5 out of 10 trials (Schutter and van Honk 2006). The intensity of spTMS applied over the right pIPS and the vertex during the sessions was set to 120% of the motor threshold, corresponding to an average intensity of 67% (range: 52-84%) of the maximum output intensity (2T). The coil was precisely placed over the right pIPS by using a neuronavigation system (SofTaxicOptic, EMS s.r.l., Bologna, Italy), which was fed with the individual Talairach coordinates of fMRI-identified pIPS. The coil was maintained in place with a hydrostatic arm (Manfrotto, Feltre, Italy) for the entire duration of the session.

Experimental procedures of spTMS sessions

The involvement of the pIPS in saccadic adaptation was assessed separately for voluntary saccades (VS experiment) and for reactive saccades (RS experiment). Each experiment involved four spTMS sessions separated by at least 5 days. spTMS was applied to the right pIPS 30 ms after the detection of the primary horizontal saccade for one session, 60 ms after saccade detection for another session, and 90 ms after saccade detection in a third session (Fig. 1). In the fourth session, spTMS was applied over the vertex. During this control stimulation condition, the timing of spTMS (relative to the detection of the primary horizontal saccade) was set at 30 ms for four subjects, 60 ms for four other subjects, and 90 ms for the remaining four subjects. A four-way ANOVA (with phase: pre × adaptation × post, saccade direction, saccade type, and stimulus timing as factors) showed that, for this control session, there was no effect of timing on saccadic gain change ($F_{2,18} < 2.34$; $P > 0.12$). Accordingly, the data collected during the control session were pooled across the three timing conditions,

separately for VS experiment and for RS experiment. The order of the four sessions was counterbalanced across subjects.

Figure 1 about here

Each spTMS session involved three phases: a pre-adaptation phase; an adaptation phase; and a post-adaptation phase. During the adaptation phase, adaptation was elicited using a classical double-step target procedure for reactive saccades (McLaughlin 1967; Alahyane et al. 2007) or for voluntary saccades (Alahyane et al. 2007). The differences between adaptation protocols were maximally reduced, given the objective to elicit reactive and voluntary saccades. For both saccades types, three points were presented in each trial (see Figure 2) and subjects had to discriminate a letter located inside one of them. Trials always started by the production of a vertical saccade from the upper to the central point, followed by a horizontal (reactive or voluntary) saccade from the central to the lateral point. Therefore, the main differences between protocols reside on the mode of saccade triggering and on the number of targets present when the second saccade started, as detailed in the following. In both cases, the visual scene was shifted at the onset of the horizontal saccade and in the direction opposite to that of the saccade. This intra-saccadic "backward step" of the visual scene induced an error between the saccade endpoint and the target position. For the VS experiment (Fig 2a), subjects had to explore a display containing three targets. Each adaptation trial started with the presentation of a fixation point, 4° above the center of the screen. After 1600 ms, a circle surrounding the fixation point and two targets appeared. One target (central target) was located immediately below the fixation point, and another target (lateral target) was located in the left or the right hemifield, at ±8°. The extinction of the circle 500 ms later indicated to the subjects that they had to make, first, a vertical saccade toward

the central target, and then, a horizontal saccade toward the lateral target. The second saccade was initiated voluntarily, at the subject's own pace. Once this horizontal voluntary saccade was detected (velocity threshold: 80-90°/s), the fixation point and the two targets were displaced in the direction opposite to that of the saccade. For the RS experiment (Fig 2b), each trial started with the presentation of the fixation point, 4° above the center of the screen. Then, after 1700 ms, the fixation point suddenly jumped toward the center of the screen. Subjects were required to make a vertical saccade toward this central target. Then, after a random delay (800-1200 ms) following the end of this saccade, the central target was switched off and, simultaneously, a lateral target appeared in the left or the right hemifield, at ±8°. Subjects had to move their eyes toward this new target as soon as it appeared. Once this horizontal reactive saccade was detected (velocity threshold: 80-90°/s), the target was displaced backward. In both RS and VS experiments, the intra-saccadic step corresponded to 25% of the initial target eccentricity for adaptation blocks 1 and 2 (48 trials each), and to 40% of the initial target eccentricity for adaptation blocks 3 and 4 (48 trials each). spTMS was applied for all trials of the adaptation phase. The visual display disappeared 50 ms after the end of the horizontal saccade (Fig. 1). The 50 ms duration was based on two considerations. First, given that the effects of spTMS are usually short-lived, the use of short visual stimulus durations would restrict the temporal window over which the stepped target is visible and could thus increase the likelihood of interfering with adaptation. Second, it has been previously shown that a 50 ms target duration is sufficient to induce an optimal adaptation of both reactive and voluntary saccades (Panouilleres et al. 2011).

Both pre-adaptation and post-adaptation phases consisted of a block of 24 trials without spTMS and a block of 24 trials with spTMS; in the latter block, the same spTMS timing as in the corresponding adaptation phase was used. In the pre-adaptation phase, the no spTMS block was performed before the spTMS block, whereas in the post-adaptation phase the

sequence was reversed. Each 24-trial block comprised 12 rightward-saccade trials, and 12 leftward-saccade trials, in random order. The design of the pre- and post-adaptation trials was the same as for the adaptation phase, except that the visual display was switched off as soon as the horizontal saccade was detected.

To keep subjects attentive during sessions, we required them to perform a discrimination task. After every trial, they had to indicate (by pressing a key) whether the letter "E" (not shown in Fig 2), which was displayed on the fixation point (for reactive trials) or the central target (for voluntary trials), was complete or truncated.

To evaluate if our two protocols were triggering the two different types of saccades, a separate, complementary experiment, ran without spTMS, was conducted on age-matched neurologically healthy participants (N=5). In this experiment, we assessed the proportion in which adaptation transferred from RS to VS and vice versa. Results revealed that the transfers of adaptation between saccades elicited in the two protocols were similar to those reported in previous studies both for reactive and voluntary saccades, hence validating our protocols as eliciting these different saccade categories (Supplementary Fig 1).

Figure 2 about here

TMS data Analysis:

The eye-movement data were analyzed using a custom program developed in Matlab v.7.1 (MathWorks Inc., Natick, MA, USA). Data from the left and right eyes were averaged and all subsequent analyses were performed on the horizontal and vertical components of cyclopean eye position. The start and end times of all saccades were identified based on a velocity threshold of 50°/s. Trials for which a primary saccade was not correctly detected on-line, or

was contaminated by eye blinks, were eliminated; 4.8 ±3.7% of all trials were eliminated in this way.

Each primary horizontal saccade was described by its latency, amplitude and gain. Saccade latency was defined as the delay between horizontal saccade onset and the time of lateral target presentation for reactive saccades and between horizontal saccade onset and the time of vertical saccade completion (i.e. central target fixation time) for voluntary saccades. Saccade amplitude was computed as the difference between the initial and final positions of the eye. Saccade gain was obtained by dividing horizontal saccade amplitude by retinal error, the latter being defined as the difference between the target position and the starting position of the saccade. In each spTMS session, the mean saccadic gain was computed separately for rightward and leftward saccades and for the eight blocks of trials (two pre-adaptation blocks, four adaptation blocks, and two post-adaptation blocks). For each block, saccades with a gain which differed from the mean by at least three standard deviations were excluded from analysis. The gain change of each saccade of the spTMS blocks following the pre-adaptation phase (four adaptation blocks and one post-adaptation block) was calculated as follow:

$$Gain\,change\,of\ \ saccaden\,(spTMS) = \frac{Gain\,of\ \ saccaden - Mean\,gain\,of\ \ pre\,spTMS\,block}{Mean\,gain\,of\ \ pre\,spTMS\,block}$$

Similarly, the gain change of each saccade of the no spTMS block of post-adaptation phase was calculated as follow:

$$Gain\,change\,of\ \ saccaden\,(no\,spTMS) = \frac{Gain\,of\ \ saccaden - Mean\,gain\,of\ \ pre\,no\,spTMS\,block}{Mean\,gain\,of\ \ pre\,no\,spTMS\,block}$$

Negative (positive) values of gain changes corresponded to a decrease (increase) of saccade amplitude relative to pre-adaptation.

During the adaptation phase, secondary corrective saccades were identified as saccades directed toward the stepped target position, and initiated within 500 ms after the offset of the

primary saccade. The gain of these corrective saccades was calculated in the same way as for primary saccades. Their latency was computed as the duration of fixation since the preceding primary saccade. The proportion of corrective saccades (out of the total number of adaptive trials) was also measured.

Statistical analyses were performed with Statistica 9 (Statsoft Inc., Tulsa, OK, USA). The latency and the gain of saccades measured during the pre-adaptation phase were submitted to a four-way ANOVA with three within-subject factors (TMS: On or Off; Saccade Direction: leftward or rightward; and TMS Type: pIPS 30 ms, pIPS 60 ms, pIPS 90 ms, or vertex) and one between-subject factor (Experiment: VS or RS). Gain changes during the adaptation phase, which were computed relative to the gain measured during the pre-adaptation phase with TMS, were analyzed using a four-way ANOVA with three within-subjects factors (Block of trials: 1 to 4; Saccade Direction; and TMS Type) and one between-subject factor (Experiment). The same four-way ANOVA was also used to analyze the latency, the proportion, and the gain of corrective saccades. Gain changes in post-adaptation with and without TMS, which were computed relative to the gain measured during the pre-adaptation (with and without TMS, respectively), were submitted to a four-way ANOVA with three within-subject factors (TMS, Saccade Direction and TMS Type) and one between-subject factor (Experiment). ANOVAs yielding significant results were followed by post-hoc Tukey's HSD tests. The significance level was set at $P < 0.05$.

Results

This study was aimed at evaluating the involvement of the parietal cortex in saccadic adaptation. First, the oculomotor region of the pIPS was localized by fMRI. Then, in two separate experiments, spTMS was applied in each trial of an adaptation paradigm, to assess

the implication of pIPS in the adaptation of voluntary saccades (VS experiment) and of reactive saccades (RS experiment).

Localizer scans

The fMRI saccade localizer scans revealed a cluster of activated voxels in the posterior part of the intra-parietal sulcus (pIPS) in each subject. A representative individual example is illustrated in Figure 3. Over all subjects, the average Talairach coordinates corresponding to the location of the peak of activity in pIPS were: x = 13 ±5, y = -63 ±6, and z = 52 ±5.

Figure 3 about here

In the following, we present the results of the two experiments. The results of the pre-adaptation phase will be presented first, followed by the results of the adaptation and post-adaptation phases.

No spTMS effect on pre-adaptation saccade parameters

To assess whether spTMS could modify baseline saccadic parameters, we compared the latency and gain of saccades measured during pre-adaptation between spTMS and no spTMS blocks. A repeated-measure ANOVA (see Methods) revealed that, as expected, saccade latency differed depending on the saccade category (effect of Experiment: VS vs. RS – $F_{1,22}$ = 43.7, $P = 1.2\times10^{-6}$) but also on the presence of TMS (On vs. Off – $F_{1,22}$ = 34.0, $P = 7.2\times10^{-6}$). The significant interaction between these two factors ($F_{1,22}$ = 19.5, $P = 2.2\times10^{-4}$), indicated that spTMS had a stronger effect on the latency of voluntary saccades (430 ±14.3 ms without spTMS vs. 378 ±13.5 ms with spTMS) than on the latency of reactive saccades (196 ±2.6 ms without spTMS vs. 189 ±2.8 ms with spTMS). Note that this facilitatory effect of spTMS on

saccade initiation was unspecific, as it occurred independently of the stimulation site (no effect of TMS Type: $F_{3,66} < 1.43$, $P > 0.24$). Note further that this latency decrease was larger for voluntary saccades (characterized by their long latency) than for reactive saccades, which is compatible with a non specific alerting effect of the TMS pulses. Alternatively, since the pre-adaptation with spTMS was always performed after the pre-adaptation without spTMS, the decrease of saccade latency might also originate from a non specific training effect. Concerning the saccadic gain, no effect of spTMS was found, either for reactive saccades or for voluntary saccades, irrespective of the stimulation site (pIPS or vertex) and of the timing (30 to 90 ms – no effect of TMS Type: $F_{3,66} < 2.47$, $P > 0.07$, Fig 4a and Fig 4b). Thus, any specific effect of spTMS over pIPS on saccade latency and gain can be ruled out.

Figure 4 about here

Effect of spTMS over the right pIPS on saccadic adaptation

The gain of reactive and voluntary saccades decreased progressively during the adaptation phase in all spTMS sessions (Fig 5). This saccade shortening is consistent with the direction of the intra-saccadic target step, opposite to the primary saccade. To test whether spTMS over the right pIPS influenced the adaptation, the mean saccadic gain change calculated relative to the mean gain in pre-adaptation with spTMS was submitted to a four-way ANOVA with the following factors: Block (1 to 4), Saccade Direction (left vs. right), Experiment (VS vs. RS), TMS Type (pIPS 30 ms, 60ms, 90 ms and vertex). A significant effect of Block on saccadic gain change was observed ($F_{3,66} = 195.9$, $P < 0.001$), consistent with a gradual adaptation of saccades. As expected (Alahyane et al. 2007; Panouilleres et al. 2012b), no difference in gain changes was observed between the two experiments in the vertex session (post-hoc Tukey's HSD tests, $P > 0.73$). Interestingly, gain changes were affected differently depending on

spTMS timing and on experiments (Experiment × TMS Type interaction: $F_{3,66}$ = 3.0, P = 0.038) and also depending on the adaptation blocks (Block × Experiment × TMS Type interaction: $F_{9,198}$ = 2.0, P = 0.038). Post-hoc tests revealed that, in VS experiment, the application of spTMS over the right pIPS at 60 ms reduced the gain change of voluntary saccades, as compared to the vertex session. Specifically, for leftward voluntary saccades (Fig 3a, left panel), a significant decrease in adaptation compared to the vertex session was observed for the last three adaptation blocks (post-hoc Tukey's HSD tests, $P < 0.019$). For rightward voluntary saccades (Fig 5a, right panel), a significant decrease of adaptation was observed for the last adaptation block (post-hoc Tukey's HSD test, $P = 0.004$). In contrast, in RS experiment (Fig 5b), a significant difference of gain changes between the right-pIPS and the vertex sessions was observed only for the 90 ms spTMS timing and for the rightward saccades during the last adaptation block (post-hoc Tukey's HSD test, $P = 0.0004$). In this case, the adaptation of reactive saccades was larger for the pIPS session than for the vertex session. For reactive leftward saccades, there was also a trend toward larger gain changes when spTMS is applied over the pIPS at 90 ms than when applied over the vertex (Fig 5 b, left panel). Notwithstanding, this trend failed to reach significance (post-hoc Tukey's HSD test, $P > 0.07$). No difference of gain change was observed between the session where spTMS was applied over pIPS at 30 ms and the vertex session, regardless of experiments ($P > 0.26$).

In sum, the application of spTMS over the right pIPS 60 ms after saccade detection resulted in less adaptation of voluntary saccades in both directions (VS experiment). In contrast, the application of spTMS over the right pIPS at 90 ms enhanced the gain change of rightward reactive saccades at the end of the adaptation phase (RS experiment).

Figure 5 about here

No effect of spTMS over the right pIPS on the production of corrective saccades

Progressive changes in primary-saccade gain induced by repeated perturbations, such as intra-saccadic target steps, reflect the operation of an adaptive mechanism. The error signals induced by these perturbations also trigger secondary corrective saccades. Since the application of spTMS over the right pIPS was found to affect saccadic adaptation, we thought it important to assess whether it interfered also with corrective saccades. In principle, spTMS could influence the initiation of corrective saccades, thus affecting their latency. It could also interfere with the detection of the post-saccadic visual feedback, and as a result, affect the rate of occurrence of corrective saccades. Lastly, spTMS could affect the processing of the size of the visual error, and thus modify the gain of corrective saccades. All of these parameters of corrective saccades (latency, rate, and gain; see Table 1) were analyzed separately using four-way ANOVAs with the same factors as above (Block, Saccade Direction, Experiment, and TMS Type). No significant effect of TMS Type factor was observed ($F_{3,526} < 1.8$, $P > 0.14$), indicating that the production of corrective saccades remained unchanged regardless of the site (pIPS and vertex) and timing (30, 60 or 90 ms) of the spTMS.

Thus, the effects of spTMS over the right pIPS on saccadic gain changes reported in the previous section are not accompanied by spTMS effects on corrective saccades.

Table 1 about here

Effect of spTMS over the right pIPS on adaptation after-effects

During the post-adaptation phase, subjects performed saccades toward targets that disappeared at saccade onset. This allowed us to assess the extent to which saccadic gain changes persisted after the adaptation phase, when tested in the absence of any error signal. The gain difference between these saccades and those generated during the pre-adaptation

phase is called “adaptation after-effect”, a typical measure of the retention of adaptation. This adaptation after-effect was computed separately for the post-adaptation spTMS block (Fig 6a and 6b, left panels), and for the post-adaptation no spTMS block (Fig 6a and 6b, right panels). After-effects were analyzed using a four-way ANOVA with three within-subject factors (TMS: On vs. Off, Saccade Direction and TMS Type) and one between-subject factor (Experiment). As revealed by this ANOVA (TMS Type × Experiment interaction, $F_{3,66} = 3.0$, $P = 0.038$), the adaptation after-effects were differently affected by the TMS Type and the Experiment factors. For voluntary saccades (VS experiment, Fig 6a, left panel), after-effects measured in the post-adaptation spTMS block were significantly smaller in the session with spTMS over the right pIPS at 60 ms than in the vertex session (post-hoc Tukey’s HSD test, $P < 0.048$). This indicates that the inhibitory effect of right pIPS-TMS on the adaptation of voluntary saccades, which was reported above, persisted in the post-adaptation spTMS block. This inhibitory effect of TMS on adaptation was still observed in the post-adaptation no spTMS block (Fig 6a, right panel). Indeed, the after-effect measured in the session with spTMS over pIPS at 60 ms was significantly reduced relative to the vertex session for rightward saccades (post-hoc Tukey’s HSD test, $P = 0.03$) and this reduction approached significance for leftward saccades (post-hoc Tukey’s HSD test, $P = 0.057$).

By contrast, for reactive saccades, no significant effect of spTMS on after-effects was observed, whether measured in post-adaptation with spTMS (Fig 6b, left panel, post-hoc Tukey’s HSD tests, $P > 0.91$), or without spTMS (Fig 6b, right panel, post-hoc Tukey’s HSD test, $P > 0.67$). Despite a trend for larger after-effects at this timing than for the vertex session, this negative outcome indicates that the facilitatory effect of pIPS-TMS with a 90-ms delay, which was observed during the adaptation phase, was not maintained in the post-adaptation phase.

To summarize, for voluntary saccades, adaptation after-effects were significantly smaller in the session with spTMS applied over the pIPS at 60 ms than in the vertex session (VS experiment). In contrast, for reactive saccades, spTMS never affected the after-effect (RS experiment).

Figure 6 about here

Discussion

Single-pulse TMS applied over the right pIPS, 60 ms after the onset of leftward and rightward voluntary saccades, largely reduced the amount of adaptation and the size of the after-effect, as compared to the application of TMS over the vertex. A markedly different pattern of results was found for reactive saccades: right pIPS-TMS applied 90 ms after the onset of rightward saccades led to larger adaptation at the end of the adaptation phase, with no persistent change in the after-effect. Given the lack of specific modifications of baseline saccade parameters, this pattern of TMS effects clearly results from the modification of different adaptation or error processing mechanisms engaged by the reactive-saccade and voluntary-saccade protocols.

To the best of our knowledge, the results of this study provide the first direct evidence that parietal regions are causally involved in saccadic plasticity. Consistent with this finding, the results of two recent fMRI studies suggest a role of the cerebral cortex in saccadic adaptation. The first study showed an involvement of the Supplementary Eye Fields and of the temporo-insular cortex in the adaptation of reactive saccades (Blurton et al. 2011). The second study found that a network of cerebellar and cerebral areas is implicated in the adaptive processes of reactive and voluntary saccades. In particular, the right pIPS was specifically involved in adaptation of voluntary saccades (Gerardin et al. 2012). Here, by using fMRI-guided spTMS

over this area we could perturb selectively the adaptation of voluntary saccades, whereas adaptation of reactive saccades was not impaired, but rather enhanced. The present study thus shows that the pIPS is necessary for the optimal adaptation of voluntary saccades and may mediate the strengthening of the adaptation of reactive saccades.

An important methodological aspect of the present study is that the intra-parietal area targeted by spTMS was functionally localized on a single subject basis using fMRI. The localizer task was designed to allow precise determination of the oculomotor region of the pIPS. This region is currently thought to correspond to the Parietal Eye Fields, which are known to play a crucial role in the production of saccades (for review see: (Muri 2006). This area is also believed to be the human homolog of the Lateral Intra-Parietal (LIP) area in the monkey–consistent with the results of a recent fMRI study in humans (Galati et al. 2011). It is commonly accepted that the parietal cortex contributes more to the generation of reactive than voluntary saccades. This view is supported by data showing that permanent or reversible lesions of the parietal cortex specifically delay the initiation of reactive saccades (Pierrot-Deseilligny et al. 1991; Rivaud et al. 1994; Pierrot-Deseilligny et al. 2004; Muri and Nyffeler 2008). From this perspective, the finding that the pIPS is necessary for the adaptation of voluntary saccades might seem unexpected. However, the contradiction is only apparent, as the notion that the parietal cortex is more involved in reactive than voluntary saccades has been challenged and amended by recent studies. First, data from non-human primate models indicate that saccade deficits induced by inactivation of the LIP are related specifically to selection and/or attentional mechanisms, and not to saccade execution processes *per se* (Wardak et al. 2002). Similarly, saccade deficits of neurological patients suffering from lesions of the intra-parietal region have been linked to impairments of visuomotor, or saccade-programming processes, rather than to saccade initiation processes (Rafal 2006). Second, fMRI studies have shown that parietal areas are more activated for voluntary saccades

generation than for reactive saccades generation (for review see: (McDowell et al. 2008). Event-related fMRI studies suggest that this stronger activation may be associated with saccade-preparation processes (Brown et al. 2004; Brown et al. 2008). Altogether, these studies indicate that the parietal cortex is involved both in the initiation processes of reactive saccades and in the visuo-motor programming processes of voluntary saccades. Consistent with the latter notion, the presently demonstrated effect of spTMS over pIPS on voluntary saccades adds sensorimotor adaptation to the multiple functions of the parietal cortex in saccadic control.

A major finding of the present study is the opposite effects of spTMS over the pIPS for the adaptation of the two categories of saccades. Indeed, spTMS at the 60 ms timing strongly impaired adaptation of voluntary saccades, whereas spTMS at the 90 ms timing improved the adaptation of reactive saccades. A recent spTMS study showed that TMS applied over the lateral cerebellum can also have opposite effects on reactive saccade adaptation, but this time in relation to the direction of adaptation (Panouilleres et al. 2012a). Indeed, irrespective of the timing of application, TMS over the cerebellar lobule Crus I potentiated the adaptive lengthening and depressed the adaptive shortening of saccades. The authors of this study proposed that different neuronal populations located in the lobule Crus I may be specifically involved in the two adaptive processes. Another study reported the existence of inhibitory and excitatory effects depending on the timing of spTMS and on the behavioural task (Nyffeler et al. 2004). The authors found that spTMS applied over the Frontal Eye Field (FEF) at target onset, decreased the latency of saccades in a gap task (reactive saccades) but not in an overlap task (voluntary saccades). In contrast, spTMS applied over FEF after target disappearance, significantly increased saccade latency in both tasks. The authors proposed that a direct spTMS interference with the FEF was responsible for the inhibitory effect on saccade initiation and that an indirect TMS interference with the superior colliculus was responsible

for the facilitatory effect. In the next paragraph, we will consider whether direct/local versus indirect/remote TMS effects could explain the present pattern of findings.

Irrespective of its nature (inhibitory of facilitatory), the mere presence of an effect of spTMS over pIPS on reactive saccades adaptation could not be predicted based on previous works. There is a large consensus that the adaptation of reactive saccades involves motor stages of the sensorimotor transformation at the brainstem-cerebellar level (for reviews see: (Hopp and Fuchs 2004; Tian et al. 2009; Pelisson et al. 2010; Prsa and Thier 2011). Comparatively, suggestions that saccadic adaptation may involve sensory stages in the cerebral cortex are based on sparse and indirect evidence, and concern voluntary saccades (Deubel 1995; Gancarz and Grossberg 1999; Cotti et al. 2007; Cotti et al. 2009), or the adaptive lengthening of reactive saccades (Semmlow et al. 1989; Hernandez et al. 2008). To our knowledge, only two behavioural studies implied cerebral structures in the adaptive shortening of reactive saccades, one reporting adaptation deficits in two patients with thalamic lesion (Gaymard et al. 2001), the other one showing a visual mislocalization in healthy subjects when adaptation was induced in a new protocol (Zimmermann and Lappe 2010), which differs from the classical double-step protocol used here. Therefore, we consider that a note of caution should be taken in interpreting our findings on reactive-saccade adaptation as evidence that the parietal cortex is the site where adaptive changes develop. Rather, the parietal cortex could be involved in the processing of error signals that lead to saccadic adaptation. However, the fact that the processing of error signals occurs earlier for reactive saccades than for voluntary saccades (Panouilleres et al. 2011) is not compatible with the relatively late timing in which spTMS was effective for reactive (90 ms) compared to voluntary saccades (60 ms). Further, the effect of pIPS-TMS applied with a delay of 90 ms on reactive saccade gain changes was not maintained in the post-adaptation phase. Finally, spTMS facilitated, rather than impaired, adaptation of reactive saccades. Thus, contrary to the

case of voluntary saccades, TMS might not disrupt an on-going neural activity specifically related to saccadic adaptation, but could remotely alter neural activity in the cerebellum (see e.g. Nyffeler et al. 2004), via existing parietal-cerebellar connections (for reviews, see Glickstein 2003; Ramnani 2012), leading to a facilitation of reactive-saccades adaptation. Indeed, effects of TMS on remote but connected areas have been largely documented using TEP (Paus et al. 1997), fMRI (Ruff et al. 2006), EEG (Fuggetta et al. 2005; Taylor et al. 2007), or a second 'test' TMS pulse (Ugawa et al. 1995; Pascual-Leone and Walsh 2001; Silvanto et al. 2006; Ruff et al. 2008).

The application of spTMS over the right pIPS modified the adaptation of voluntary saccades in both directions (left and right). Previous studies have shown that the right parietal cortex is dominant for both visual hemifields in visual, attentional, and/or motor processes (Corbetta et al. 1993; Mangun et al. 1994; van Koningsbruggen et al. 2009). The bilateral effect of spTMS on saccade adaptation could then be due to this dominance of right parietal cortex. For the voluntary saccades, a significant impairment on the development and the retention of adaptation was found when the spTMS was applied 60 ms after saccade onset. In this case, the pulse occurred approximately 20 ms after saccade completion (mean saccade duration: 40 ms). This indicates that the adaptation of voluntary saccades critically depends on functions taking place in the right pIPS almost immediately after saccade termination.

What could be the nature of these post-saccadic functions? One possibility is that spTMS may have interfered with post-saccadic visual-information processing in the pIPS. Visual responses organised according to retinotopic maps in IPS have indeed been described in several reports (Schluppeck et al. 2005; Medendorp et al. 2005; Swisher et al. 2007). In the light of the strong dissociation between the mechanisms leading to adaptation and those leading to corrective saccades (see e.g. Wallman and Fuchs 1998; Bahcall and Kowler 2000; Noto and Robinson 2001; Panouilleres et al. 2011), our study may help understand whether

these parietal responses encode "early" visual information, driving both adaptation and corrective saccades, or encode visuo-motor signals specialized for each type of correction. If the effect of spTMS was due to an interference with early visual processes, then it should not depend on the type of saccade (reactive or voluntary), and it should also be observed for corrective saccades. The present results invalidate both of these predictions**.** Thus, the most parsimonious conclusion is that spTMS did not act at such early sensory level, but more likely interfered with visuo-motor processes that specifically lead to saccadic adaptation. Both error signals processing and enduring changes of oculomotor commands take place during the adaptation phases. Although conceptually distinct, these two components of adaptation cannot be dissociated in our study, like in most previous studies (including the fMRI study of Gerardin et al. 2012). The question of whether spTMS on pIPS has altered the "error signal" and/or the "oculomotor commands" component of adaptation can nevertheless be discussed in relation to the available literature. The "error signal" hypothesis is coherent with the proposed contribution of IPS in error processing for adaptation of arm-reaching movements to a velocity-dependent force field (Della-Maggiore et al. 2004), or to optical prisms (Luaute et al. 2009). Concerning saccadic adaptation, it is believed that error signals result from a comparison between the expected post-saccadic error, which is predicted based on a copy of the motor command (efference copy), and the actual error, which is sampled after saccade completion (Bahcall and Kowler 2000; Wong and Shelhamer 2011; Collins and Wallman 2012). Interestingly, the parietal cortex is known to be involved in remapping the representation of visuo-spatial information through eye movements (Duhamel et al. 1992; Medendorp et al. 2003; Merriam et al. 2003), a mechanism that also requires the use of efference copy. Along this line, TMS studies have further indicated that the right posterior parietal cortex is causally involved in the spatial remapping of visual targets for perception (Chang and Ro 2007; Prime et al. 2008; van Koningsbruggen et al. 2009), or sequential

saccades programming (Van Donkelaar and Muri 2002; Morris et al. 2007). The present findings suggest that the role of the parietal cortex in spatial remapping could also serve an error signals monitoring function in the context of voluntary-saccades adaptation. Note that the different effect of TMS on the right pIPS in the adaptation of voluntary and reactive saccades is consistent with the dissociation in the processing of error signals between these saccade types (Panouilleres et al. 2011). In contrast, according to the "oculomotor commands" hypothesis, plastic changes underlying the adaptation of voluntary saccades could take place in pIPS, as suggested in previous behavioural studies (Cotti et al. 2007; Cotti et al. 2009). Thus, the application of TMS to the right pIPS 60 ms after saccade onset may have interfered with these plastic changes, resulting in a slower development and a smaller after-effect of adaptation. To conclude, the critical involvement of the right pIPS in voluntary saccadic adaptation depends either on error-signal processing, or on plastic changes related to adaptation, and further studies are necessary to tease apart these two possibilities.

In conclusion, we demonstrate the right pIPS is causally involved in saccadic adaptation. Interestingly, we found that spTMS affected adaptation differently depending on the type of saccades. Both adaptation and retention of voluntary saccades were impaired with spTMS applied over the pIPS 60 ms after saccade onset. On the contrary, adaptation of reactive saccades was facilitated when spTMS was applied 90 ms after saccade onset. We propose that these differential effects may respectively emerge from a direct effect of the TMS over the pIPS and from an indirect effect over the cerebellum. Thus, this study provides direct evidence consistent with the hypothesis that the adaptation of voluntary and reactive saccades involves different neural mechanisms.

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Table

TMS Type	**pIPS 30 ms**	**pIPS 60 ms**	**pIPS 90 ms**	**Vertex**
Latency	282 ±7.9 ms	284 ±7.8 ms	295 ± 7.3 ms	270 ±7.6 ms
Rate	27.5 ±2.0%	29.3 ±2.1%	31.9 ±2.2%	32.9 ±2.1%
Gain	1.15 ±0.06	1.38 ±0.13	1.28 ±0.09	1.17 ±0.10

Table 1: Latency, rate and gain of corrective saccades measured during the adaptation phase. Mean parameter values (±SEMs) are depicted separately for the four TMS Types. No significant effect of the TMS Type factor was observed (four-way ANOVA, $F_{3,526} < 1.8$, $P > 0.14$).

Figure captions

Figure 1: Schematics of an adaptation trial

Eye (black line) and target (grey bars) positions are represented as a function of time. When the saccade is detected (velocity threshold: 80-90°/s), the visual display jumped toward the fixation point and spTMS occurred at a certain timing (30, 60 or 90 ms) after saccade detection (these 3 spTMS timings were used in separate sessions). Target was switched off 50 ms after saccade completion.

Figure 2: Schematic illustration of the experimental protocols used to induce voluntary-saccade (a) and reactive-saccade (b) adaptation.

The long horizontal arrows indicate primary saccades. The short horizontal arrows indicate corrective saccades. When a horizontal primary saccade was detected (velocity threshold: 80-90°/s), the target (for reactive saccades), or the visual display (for voluntary saccades), jumped. spTMS occurred at 30 ms or 60 ms or 90 ms after detection of the horizontal primary saccade. Fifty milliseconds after saccade termination, a blank screen replaced the visual display. Note that only trials involving rightward saccades are illustrated in this figure.

Figure 3: Representative example of fMRI localizer-scan results showing the oculomotor area of the right pIPS in one subject (Talairach coordinates: x = 9; y = -63; z = 48).

The parietal-area activation measured in the fMRI saccade localizer scan was overlaid onto two-dimensional anatomical slices. In the sagittal (SAG) slice (left panel), anterior (A) is shown on the left and posterior (P) is shown on the right. In the coronal (COR) and transversal (TRA) slices (middle and right panels), the right hemisphere (R) is shown on the left. Cortical activation of the pIPS is shown in white color.

Figure 4: Saccadic gain in the pre-adaptation phase of the VS experiment (a) and the RS experiment (b)

Mean values of saccade gain are plotted as a function of the different spTMS sessions: pIPS at 30 ms (dark grey bars), pIPS at 60 ms (black bars), pIPS at 90 ms (light grey bars) and vertex (white bars). Error bars are SEMs. The ANOVA with three within-subject factors (TMS presence, Saccade Direction and TMS Type) and one between-subject factor (Experiment) did not reveal any significant effect (spTMS factor, $F_{3,66}<2.47$, $P>0.07$).

Figure 5: **Development of adaptation for the VS experiment (a) and the RS experiment (b) in the different spTMS sessions.**

Gain changes relative to the gain in pre-adaptation with spTMS are plotted separately for rightward and leftward saccades as a function of adaptation blocks (1, …, 4). The grey shaded areas represent mean values ± 1 standard error of the mean (SEM) gain change measured during the vertex sessions. The dark-grey, black, and light-grey lines correspond to gain changes for sessions during which spTMS was applied over the right pIPS with a delay of 30, 60, or 90 ms after saccade onset, respectively. The error bars show SEMs. The asterisks

indicate significant differences in gain changes between the pIPS-TMS and vertex-TMS sessions, as follows: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (post-hoc HSD Tukey's tests).

Figure 6: Adaptation after-effects in the post-adaptation blocks for the VS experiment (a) and the RS experiment (b).

After-effects were calculated as gain changes in post-adaptation blocks relative to the mean gain measured during pre-adaptation blocks, separately for the spTMS block (rightward panels) and for the no spTMS block (leftward panels). Mean after-effect values are plotted separately for the different spTMS sessions: pIPS at 30 ms (dark grey bars), pIPS at 60 ms (black bars), pIPS at 90 ms (light grey bars) and vertex (white bars). Error bars show SEMs. Significant differences in adaptation after-effects between pIPS and vertex sessions are indicated by asterisks: * $P < 0.05$ and *** $P < 0.001$ (post-hoc HSD Tukey's tests).