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J Neurophysiol 101:1550-1559, 2009. First published Dec 17, 2008; doi:10.1152/jn.90988.2008

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Behavioral Evidence of Separate Adaptation Mechanisms Controlling Saccade Amplitude Lengthening and Shortening

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Submitted 2 September 2008; accepted in final form 9 December 2008

Panouillères M, Weiss T, Urquizar C, Salemme R, Munoz DP, Pélisson D. Behavioral evidence of separate adaptation mechanisms controlling saccade amplitude lengthening and shortening. *J Neurophysiol* 101: 1550–1559, 2009. First published December 17, 2008; doi:10.1152/jn.90988.2008. The accuracy of saccadic eye movements is maintained over the long term by adaptation mechanisms that decrease or increase saccade amplitude. It is still unknown whether these opposite adaptive changes rely on common mechanisms. Here, a double-step target paradigm was used to adaptively decrease (backward second target step) or increase (forward step) the amplitude of reactive saccades in one direction only. To test which sensorimotor transformation stages are subjected to these adaptive changes, we measured their transfer to antisaccades in which sensory and motor vectors are spatially dissociated. In the backward adaptation condition, all subjects showed a significant amplitude decrease for adapted prosaccades and a significant transfer of adaptation to antisaccades performed in the adapted direction, but not to oppositely directed antisaccades elicited by a target jump in the adapted direction. In the forward adaptation condition, only 14 of 19 subjects showed a significant amplitude increase for prosaccades and no significant adaptation transfer to antisaccades was detected in either the adapted or nonadapted direction. These findings suggest that, whereas the level(s) of forward adaptation cannot be resolved, the mechanisms involved in backward adaptation of reactive saccades take place at a sensorimotor level downstream from the vector inversion process of antisaccades and differ markedly from those involved in forward adaptation.

INTRODUCTION

Ocular saccades are fast and accurate movements of both eyes. Dedicated adaptation mechanisms are known to modulate the amplitude and/or direction of saccades to help maintain their accuracy and thus optimize visual perception of our environment, despite progressive physiological and/or pathological modifications (Hopp and Fuchs 2004). Sensorimotor adaptation of saccades can be induced in the laboratory non-invasively with the double-step target paradigm (McLaughlin 1967), which uses a midsaccade displacement of a target to induce an increase in saccade gain (forward target step) or a decrease in saccade gain (backward target step). Previous studies have shown that adaptation of a single saccade transfers

to other saccades whose vector is close to the adapted saccade vector but not to orthogonal or oppositely directed vectors (Alahyane et al. 2008; Frens and van Opstal 1994; Noto et al. 1999). Also, different adaptation mechanisms seem to operate for reactive (i.e., visually triggered) saccades compared with voluntary (i.e., intentionally triggered) saccades. In particular, tests of the adaptation transfer between the two types of saccade have not found the strong and symmetrical transfer expected from the common mechanism hypothesis (Alahyane et al. 2007; Collins and Doré-Mazars 2006; Cotti et al. 2007; Deubel 1995; Erkelens and Hulleman 1993; Fujita et al. 2002).

Despite numerous studies of the *adaptive shortening* of reactive saccades, the neural substrates of adaptation mechanisms are still not clearly established (Hopp and Fuchs 2004). The brain stem premotor areas are likely involved, but the whole extent of the participating network is still debated (Edelman and Goldberg 2002; Takeichi et al. 2007; see references in Alahyane et al. 2007). The mechanisms controlling the *adaptive lengthening* of saccades are even less understood because, despite their stronger functional significance in the compensation of saccade hypometria due to neuromuscular pathological conditions or aging, they have been much less studied. Recent studies in the monkey (Kojima et al. 2004) and in cerebellar patients (Golla et al. 2008) have suggested that these adaptive lengthening mechanisms differ from those of adaptive shortening.

In the present study, we compare in healthy human subjects the adaptive mechanisms subtending the lengthening (forward adaptation) and the shortening (backward adaptation) of reactive saccades. We seek to determine in each case which sensorimotor transformation stages are subjected to adaptive changes. Indeed, whereas backward adaptation has often been suggested to affect motor stages of saccade generation (see Alahyane et al. 2007 for references), this issue is still debated, and the same issue concerning forward adaptation has not yet been tested. To this aim, we used the double-step target paradigm to adaptively increase or decrease the amplitude of saccades (hereafter called prosaccades [pro-s]) performed along one horizontal direction (“adapted direction”) and then tested subjects in an antisaccade task. Antisaccades (anti-s) are triggered by the appearance of a target but are directed toward

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the opposite position (Hallett 1978). Thus the anti-s task allows a spatial dissociation between the sensory vector pointing to the target and the motor vector pointing in the opposite direction and thus allows testing whether pro-s adaptation takes place at a processing stage that precedes or follows this vector inversion process. On the one hand, if the adaptation of pro-s involves early sensorimotor processes located upstream of vector inversion, then a transfer is expected to the anti-s triggered by a target in the “adapted direction” and performed in the “nonadapted direction” (here called “*nonadapted* direction antisaccades”). On the other hand, if the adaptation of pro-s occurs at sensorimotor levels located downstream of vector inversion, a transfer is expected to the anti-s performed in the “adapted direction” (here called “*adapted* direction antisaccades”).

Note that a recent study also tested the transfer of saccadic adaptation to antisaccades (Collins et al. 2008). However, contrary to ours, this study was not aimed at investigating the locus of saccadic adaptation but, conversely, to use saccadic adaptation as a tool for contrasting alternative hypotheses about the programming of antisaccades. In addition, the prosaccades were submitted only to backward adaptive training and fell in a category different from the reactive saccade category studied here (see DISCUSSION). In the present study, using this original approach to compare backward and forward adaptations of reactive saccades, we identified different patterns of pro-s adaptation transfers between the forward and the backward conditions. Together with the observed marked differences in adaptation efficiency, these results demonstrate the existence of separate adaptive mechanisms for forward and backward adaptations.

TABLE 1. Summary design of all experiments

Experiment	Condition	Direction	Sessions	
			Adaptation	Pre and Post
Main $n = 33$ (5 subjects performed both conditions)	Backward $n = 14$	Rightward $n = 8$	144 rightW: 3×24 with target step of -25% 3×24 with target step of -40%	72 saccades: 18 rightW pro-s 18 leftW pro-s 18 rightW anti-s 18 leftW anti-s
		Leftward $n = 6$	144 leftW: 3×24 with target step of -25% 3×24 with target step of -40%	
	Forward $n = 19$	Rightward $n = 12(8)$	144 rightW: 3×24 with target step of 25% 3×24 with target step of 40%	
		Leftward $n = 7(6)$	144 leftW: 3×24 with target step of 25% 3×24 with target step of 40%	
Control $n = 17$ (1 subject performed both conditions)	Backward $n = 7$	Rightward	144 rightW: 3×24 with target step of -25% 3×24 with target step of -40%	72 saccades: 18 rightW pro-s 18 leftW pro-s 18 rightW anti-s 18 leftW anti-s
	Forward $n = 10$	Rightward	144 rightW: 3×24 with target step of 25% 3×24 with target step of 40%	

n , numbers of subjects completing each condition. Some subjects were tested in both conditions and eight subjects performed both main and control experiments. The number of subjects who showed a significant gain increase of adapted pro-s in the forward condition of the main experiment is indicated in parentheses. pro-s, prosaccade; anti-s, antisaccade; rightW, rightward; leftW, leftward.

METHODS

We conducted one main experiment and one control experiment. The main experiment tested the adaptation of rightward or leftward pro-s separately in different groups of subjects. Because no significant difference was highlighted between the two groups, the data collected for the two directions were pooled. The aim of this experiment was to contrast backward and forward adaptations and to look for a potential transfer of adaptation to both adapted direction anti-s (anti-s with the saccadic movement in the adapted direction) and nonadapted direction anti-s (anti-s with the saccadic movement in the nonadapted direction and elicited by a target in the adapted direction). The control experiment used a pseudoadaptation procedure to test the potential contribution of unspecific factors to the saccadic gain changes observed in the main experiment. The basic procedure was identical to that of the main experiment except that the second target step did not occur until >1 s after the saccade, a delay that was previously shown to prevent saccadic adaptation (Bahcall and Kowler 2000; Fujita et al. 2002).

Subjects

Thirty-six volunteers participated in the experiments (21 women, 22 fully naïve subjects; mean age: 29.2 ± 8.5 yr). All subjects had a normal or corrected-to-normal vision and gave their consent to participate. The study conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Twenty-eight and 16 subjects took part in the main experiment and in the control experiment (pseudoadaptation of rightward pro-s), respectively, including 8 subjects who participated twice, with a minimum interval of 7 days between recording sessions (see Table 1 for more details).

Apparatus

Participants sat in a dark room with head maintained on a chin rest and cheekbone rests. They were required to follow visual targets (0.6

cm black disks on a gray background) shown on a 140 Hz computer screen (distance: 57 cm; size: $30 \times 40^\circ$ of visual angle) controlled by a Visual Stimuli Generation system (Cambridge Research Systems, Cambridge, UK).

Subjects wore a helmet where two infrared sensors of the video eye tracker (Eyelink II, SR Research, Mississauga, Ontario, Canada) were mounted, allowing continuous recording of the horizontal and vertical positions of each eye with a frequency of 500 Hz and a resolution of 0.05° . The eye tracker was calibrated before each experiment by asking the subject to look at nine targets constituting a 28° high \times 38° wide rectangle. Software developed in the laboratory allowed us to monitor eye-movement data both for off-line analysis and for on-line modification of the visual display during primary saccades (detected based on a horizontal eye velocity threshold of $85\text{--}95^\circ/\text{s}$).

Procedures

MAIN EXPERIMENT. *Adaptation session (Fig. 1).* Saccadic adaptation was induced using the double-step target protocol (McLaughlin 1967). At the beginning of a trial, the subject gazed at a central fixation point (FP). After 1,600, 1,800, or 2,000 ms, this FP was switched off and a target appeared at $+8^\circ$ (adaptation of rightward pro-s) or at -8° (adaptation of leftward pro-s) along the horizontal meridian. During the saccadic response, when the ocular velocity reached the $85\text{--}95^\circ/\text{s}$ threshold, the target switched position. This intrasaccadic step corresponded to 25% of the initial target eccentricity for the first 72 adaptation trials (first three blocks of 24 trials) and to 40% for the remaining 72 trials (last three blocks of 24 trials). The intrasaccadic target step was directed toward the fixation point (backward condition) or away from the fixation point (forward condition) and the target thereafter remained visible for 800 ms. After 500 ms a sound required subjects to shift their gaze back to the center of the screen in preparation for the next trial.

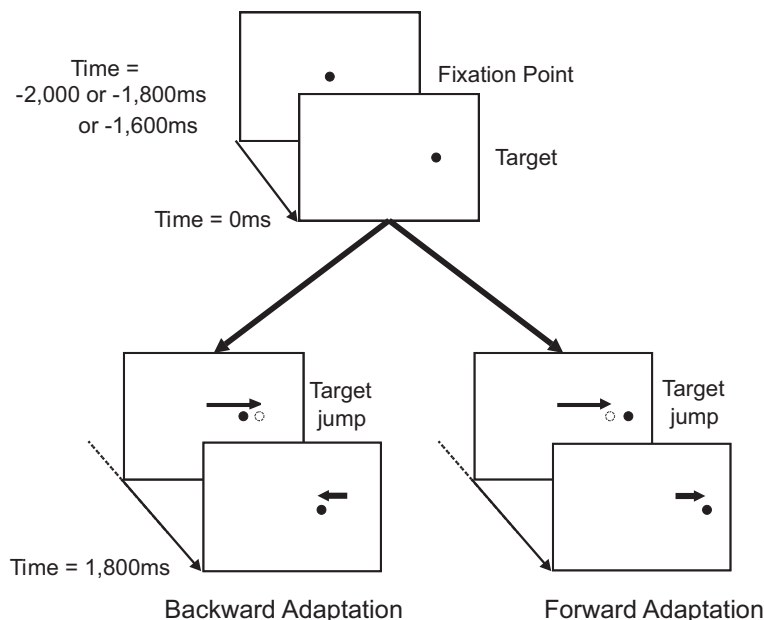
Test sessions. Prosaccades and antisaccades were recorded before (preadaptation) and after (postadaptation) each adaptation session. A green or red fixation point (FP) was shown at the center of the screen for 1,600, 1,800, or 2,000 ms. When the FP was switched off, a target appeared randomly at $+8^\circ$ (right) or -8° (left) on the horizontal meridian. If the FP was green, the subject had to look at the target (prosaccade), whereas a red FP required the subject to look away from the target toward its opposite position (antisaccade). When saccade velocity reached $85\text{--}95^\circ/\text{s}$, the target was extinguished. This was achieved to prevent any deadaptation in the postadaptation session and, for the sake of comparison, this procedure was followed in both pre- and postadaptation sessions. At 500 ms after the target extinction, a sound signaling the end of the trial indicated the subject to look at the center of the screen.

Each test session (preadaptation and postadaptation) was divided into three blocks of 24 trials, each block corresponding to 12 prosaccades and 12 antisaccades, six in each direction. These trials were presented in a random sequence.

Before the beginning of an experiment, subjects performed 24 pro-s and anti-s to become familiar with the task. Then, data collection started with a preadaptation session (three blocks of pro-s and anti-s), an adaptation session (six blocks of pro-s in one direction), and a postadaptation session (identical to the preadaptation session) (see Table 1).

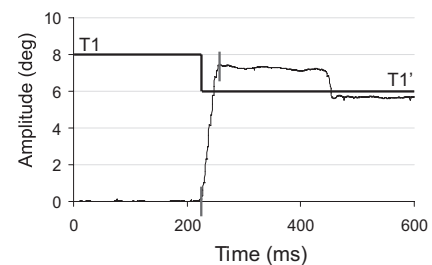
CONTROL EXPERIMENT. This experiment was identical to the main experiment except for the adaptation session, hereafter called the "pseudoadaptation session." During this session, only rightward saccades were elicited and the target step occurred only 1,800 ms after target onset, i.e., ≥ 1 s after the end of the saccade. This delayed target step was directed to the left in 7 subjects (backward condition) and to the right in 10 subjects (forward condition). Because the analyses of pro-s and anti-s gain changes in postadaptation relative to preadaptation did not reveal any statistical difference between the backward and

A Adaptation sessions: Backward or Forward



B Examples of rightward pro-s during adaptation sessions

Backward Adaptation (subject R17)



Forward Adaptation (subject R13)

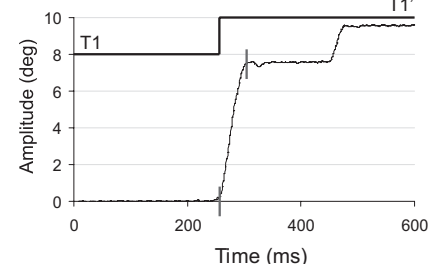


FIG. 1. *A:* the sequence of events in the adaptation session (examples illustrating the case of rightward prosaccade [pro-s]). Long horizontal arrows represent the required primary saccades and short arrows represent corrective saccades. The control experiment differed from the main experiment only by the timing of the second target step (1,800 ms after trial onset in control experiment). *B:* single trial examples of rightward pro-s during the adaptation session. Time course of horizontal eye position aligned on the appearance of the primary target (T1). T1 = primary target position (8° , right visual field); T1' = position of the target (6 or 10°) after a 25% step. The gray cursors indicate the beginning and the end of the saccade as defined automatically by our analysis software.

forward conditions, we pooled the two groups of subjects into a single pseudoadaptation control group with 17 subjects.

Data analysis

Horizontal movements of the two eyes were analyzed off-line with a custom program developed in the Matlab v.7.1 environment (The MathWorks, Natick, MA). The position and time of the beginning and end of each primary saccade (the first saccade after target appearance) were detected on the basis of a velocity threshold of 50°/s (Fig. 1B). Only primary saccades with a reaction time between 100 and 1,000 ms were analyzed. Moreover, saccades contaminated by a blink and erroneous movements (prosaccade for an antisaccade trial and vice versa) were eliminated. Excluded trials represented $4.3 \pm 2.8\%$ of total trials. The following parameters were extracted from the mean data of the right and left eyes.

Saccade amplitude was computed as the difference between the final and the initial positions and saccade duration as the difference between the termination and onset times. Saccade gain was calculated as the ratio between primary saccade amplitude and retinal error, retinal error representing the difference between target position and initial eye position. Mean gain values were calculated separately for prosaccades and antisaccades, for the leftward and rightward directions, for preadaptation and postadaptation sessions as well as for the different blocks of adaptation or pseudoadaptation. Saccades with a gain outside the range $\text{mean} \pm 3\text{SD}$ were eliminated from the study (0.4% of the trials). Gain changes between pre- and postadaptation were calculated separately not only for adapted and nonadapted prosaccades but also for adapted direction and nonadapted direction antisaccades with the following formula

Gain change (%)

$$= \frac{\text{Mean postadaptation gain} - \text{Mean preadaptation gain}}{\text{Mean preadaptation gain}} \times 100$$

We use the difference of saccadic gains computed between the pre- and postadaptation as a conservative estimate of the changes induced by adaptation (adaptation aftereffects).

Statistical analyses were performed with the STATISTICA 7 software package. Student's *t*-test compared the gain between preadaptation and postadaptation, for each subject, both for rightward and leftward prosaccades and for rightward and leftward antisaccades. Mean values of gain are presented with SEs. Repeated-measures ANOVAs were used (as indicated in text) and were followed by post hoc Fisher's least significant difference (LSD) tests. Significance level was set at $P < 0.05$.

RESULTS

General observations

BASILINE CHARACTERISTICS IN PREADAPTATION. Table 2 shows that significantly more numerous direction errors (saccades in the wrong direction for a given instruction) occurred in the antisaccade task than in the prosaccade task as previously described (see references in Munoz and Everling 2004). All

these erroneous trials were discarded for the rest of the study. The mean saccadic latency computed over all subjects was significantly shorter for prosaccades than that for antisaccades, in agreement with previous studies (Awater and Lappe 2004; Brown et al. 2006; Dafoe et al. 2007; Everling and Fischer 1998; Seidlits et al. 2003). In addition, we found that prosaccades reached a significantly faster peak velocity than antisaccades. This velocity difference was compensated by a significant lengthening of the duration of antisaccades with respect to prosaccades such that the amplitude of both saccade types remained similar (see Table 2).

QUALITATIVE OBSERVATIONS OF PROSACCADE MODIFICATIONS DURING ADAPTATION SESSIONS. The time course of the gain of adapted pro-s in the main experiment is plotted for two representative subjects in Fig. 2, A and B. Adapted pro-s gain decreased during the adaptation session for the backward condition (Fig. 2A), whereas it increased for the forward condition (Fig. 2B). The gain changes induced during the adaptation sessions were maintained in postadaptation but note that this aftereffect was smaller in the forward condition than that in the backward condition (see following text).

Main experiment: adaptation of rightward or leftward prosaccades

TIME COURSE OF ADAPTED PROSACCADES GAIN. The time courses of mean absolute gain changes relative to the preadaptation are superimposed for the backward and forward conditions (Fig. 2C). For the backward condition, the mean gain across 14 subjects shows two phases of variation during the adaptation session, corresponding to the two different target steps (25 and 40%). A one-way repeated-measures ANOVA revealed a significant effect of the "blocks of trials" factor on gain change ($P < 0.001$). This effect is related to a statistically significant decrease of gain, relative to preadaptation, in the postadaptation and in all adaptation blocks (post hoc Fisher's LSD test, $P < 0.001$). For the forward condition, the time course of mean absolute gain change across 19 subjects was slower compared with that for the backward condition. A one-way repeated-measures ANOVA detected a main effect on gain change of the "blocks of trials" factor ($P < 0.001$), corresponding to a significant increase of gain, relative to preadaptation, in the postadaptation and in all adaptation blocks except the first one (post hoc Fisher's LSD test, $P < 0.001$).

GAIN CHANGES OF PROSACCADES BETWEEN PRE- AND POSTADAPTATIONS. We next quantified the gain changes between pre- and postadaptation (adaptation aftereffects), excluding any effect of nonspecific factors that could be linked to the intrasaccadic target step during the adaptation session (see METHODS).

TABLE 2. Baseline saccade parameters (preadaptation)

	Correct Response Rate, %	Latency, ms	Duration, ms	Peak Velocity, deg/s	Amplitude, deg
pro-s	97 ± 0.3	241 ± 52.2	45 ± 6.9	266 ± 29.6	7.31 ± 0.40
anti-s	$92 \pm 0.8^{***}$	$304 \pm 62.8^{***}$	$49 \pm 11.1^{***}$	$248 \pm 46.6^{***}$	7.36 ± 1.78

Values are means \pm SD. Mean correct response rate, latency, duration, peak velocity, and amplitude were calculated for all subjects of the different experiments for both prosaccade (pro-s) and antisaccade (anti-s). Asterisks represent significant differences between pro-s and anti-s (*t*-test, $^{***}P < 0.001$).

Backward condition. Figure 3A plots the gain of adapted pro-s in preadaptation and postadaptation for all 14 subjects who completed the backward condition. There was a significant decrease of adapted pro-s gain in postadaptation relative to preadaptation (unpaired *t*-test, $P < 0.05$). On average, this

reduction reached $18.1 \pm 1.4\%$ across subjects and was highly significant (paired *t*-test, $P < 0.001$). In contrast, the changes of nonadapted pro-s gain varied substantially between the 14 subjects (Fig. 3B). Across all subjects, a small but statistically significant gain decrease was disclosed ($3.2 \pm 1.3\%$, unpaired *t*-test, $P = 0.03$). Comparing between the adapted and nonadapted saccade directions revealed, as predicted from the direction selectivity of saccadic adaptation (Albano 1996; Deubel et al. 1986; Miller et al. 1981), a much larger gain decrease for pro-s performed in the adapted direction (paired-samples *t*-test, $P < 0.001$).

Forward condition. Among the 19 subjects tested in the forward condition, 5 did not show any significant gain increase for adapted pro-s in postadaptation relative to preadaptation (unpaired *t*-test, $P > 0.05$). Because a significant level of adaptation was required to test a potential adaptation transfer to anti-s, the results of these 5 subjects were removed from subsequent analyses. From the remaining 14 subjects, a significant mean gain increase in postadaptation relative to preadaptation was found for adapted pro-s (Fig. 4A, $10.7 \pm 1.5\%$, paired *t*-test, $P < 0.001$), whereas a weak, but significant, gain decrease was observed for nonadapted pro-s (Fig. 4B, $2.4 \pm 1.1\%$, paired *t*-test, $P = 0.044$). The difference of variation between nonadapted and adapted pro-s was highly significant (paired-samples *t*-test, $P < 0.001$).

Thus exposure to systematic intrasaccadic target steps successfully modified the amplitude of adapted prosaccades in a statistically reliable and direction-specific way in all of the 28 subjects who were retained for the measurement of antisaccade gain changes.

ANTISACCADE GAIN CHANGES. **Backward condition.** At the individual level, 12 of 14 participants subjected to the backward adaptation protocol presented a significant gain decrease for adapted direction anti-s in postadaptation relative to preadaptation (unpaired *t*-test, $P < 0.05$; Fig. 3C). Comparatively for nonadapted direction anti-s, only four subjects showed a significant difference of gain (decrease in one subject and increase in three, unpaired *t*-test, $P < 0.05$; Fig. 3D).

At the group level, the gain of adapted direction anti-s significantly decreased in postadaptation relative to preadaptation by $18.7 \pm 1.8\%$ on average (paired *t*-test, $P < 0.001$), whereas the gain of nonadapted direction anti-s increased slightly ($3.4 \pm 3.0\%$, paired *t*-test, $P = 0.53$). These observations were confirmed by a significant effect of the direction factor (adapted direction vs. nonadapted direction) of a one-way ANOVA ($P < 0.001$). Thus the adaptation of pro-s transferred to adapted direction anti-s, but not to nonadapted direction anti-s. We quantified this transfer of adaptation with the following transfer index

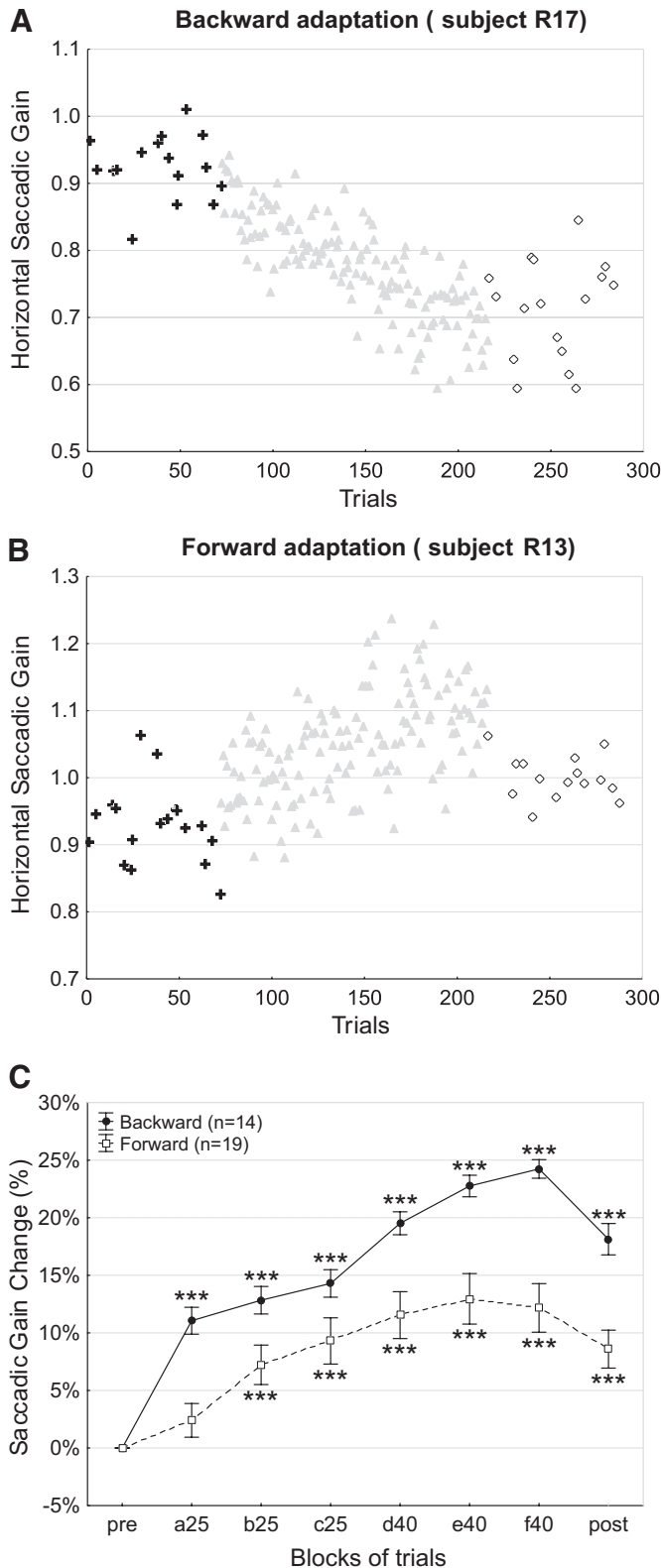


FIG. 2. *A* and *B*: time course of adapted prosaccades gain for 2 representative subjects, plotted as a function of trial number. Different symbols indicate preadaptation (✦), adaptation phase (▴), and postadaptation (◇). *C*: the mean values of absolute gain change as a function of trial blocks for the backward (●) and the forward (□) conditions. The blocks of trials are: preadaptation (pre), adaptation blocks with an intrasaccadic step of 25% of the initial target eccentricity (a25, b25, c25) or of 40% (d40, e40, f40), and postadaptation (post). Errors bars are SEs. Significant differences of gain change relative to preadaptation (post hoc Fisher's LSD test) are indicated by *** ($P < 0.001$).

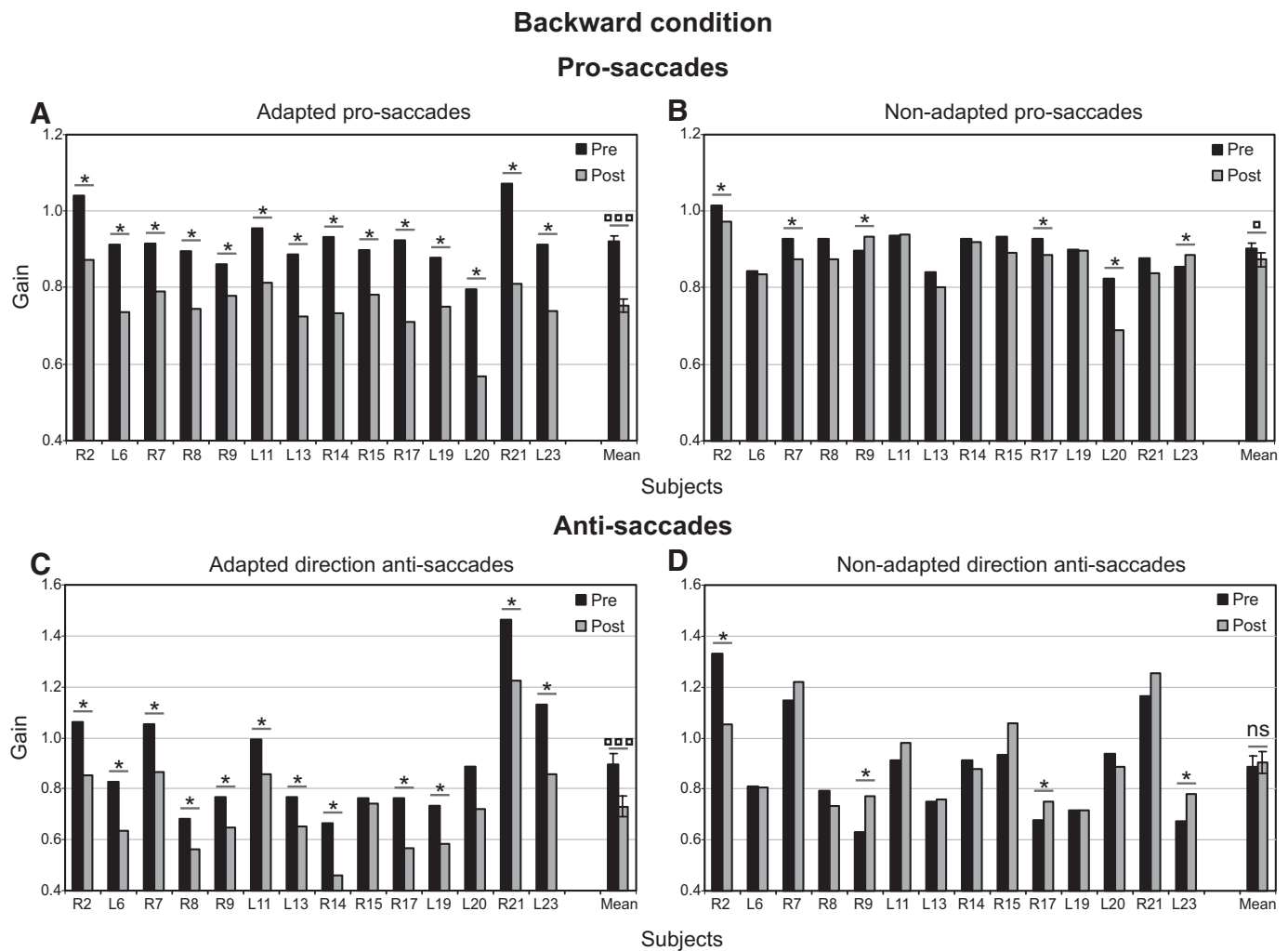


FIG. 3. Preadaptation and postadaptation gain in the backward condition for all subjects. *A* and *B*: adapted pro-s and the nonadapted pro-s data, respectively. *C* and *D*: adapted direction antisaccade (anti-s) and the nonadapted direction anti-s data, respectively. Asterisks (*) indicate for each subject statistically significant gain changes in postadaptation relative to preadaptation (unpaired *t*-test, $P < 0.05$). At the group level, paired *t*-tests were used to measure significant gain changes in postadaptation relative to preadaptation and these significant changes are indicated by □ ($P < 0.05$) and □□ ($P < 0.001$). Each subject is identified by L or R to indicate the direction of adapted pro-s (leftward and rightward, respectively).

$$\text{Transfer index} = \frac{\text{Adapted direction antisaccade gain change}}{\text{Adapted prosaccade gain change}} \times 100$$

The index of adaptation transfer averaged over all subjects was $106.5 \pm 9.9\%$. This mean value is statistically different from 0 (*t*-test, $P < 0.001$) but not from 100% ($P = 0.52$).

Thus for the backward condition, the results indicate a full transfer of adaptation from adapted pro-s to adapted direction anti-s without any significant change of nonadapted direction anti-s.

Forward condition. At the individual level, few subjects showed a significant modification of anti-s gain in postadaptation relative to preadaptation: five subjects for adapted direction anti-s and two for nonadapted direction anti-s (Fig. 4, *C* and *D*, respectively). At the group level, the mean gain of adapted direction anti-s increased by $2.0 \pm 3.4\%$, whereas that of nonadapted direction anti-s decreased by $1.12 \pm 3.1\%$. These small changes were not statistically significant (paired *t*-test, $P = 0.45$ and 0.47 , respectively). In addition, a one-way ANOVA failed to reveal any significant effect of the direction factor (adapted direction vs. nonadapted direction, $P = 0.50$).

In conclusion, during forward adaptation, there was no reliable transfer of pro-s adaptation to either type of anti-s.

Control experiment: pseudoadaptation of rightward saccades

To control for nonspecific factors (e.g., fatigue, attention) that may have contributed to the effects revealed in the main experiment, we conducted a control experiment involving a pseudoadaptation session (see METHODS).

The rightward pro-s gain remained unchanged during the pseudoadaptation phase because a one-factor ANOVA failed to detect a significant effect of the “blocks of trials” factor on saccadic gain change. On average, the postadaptation gain of saccades made in the pseudoadapted direction increased by $1.2 \pm 1.2\%$ relative to preadaptation, a change that did not reach statistical significance (paired *t*-test, $P = 0.31$). The postadaptation gain of pro-s made in the nonpseudoadapted direction slightly but significantly decreased by $2.2 \pm 1.1\%$ relative to preadaptation (paired *t*-test, $P = 0.045$). Moreover, the mean variations of anti-s gain in postadaptation relative to preadaptation were small and did not reach significance (right-

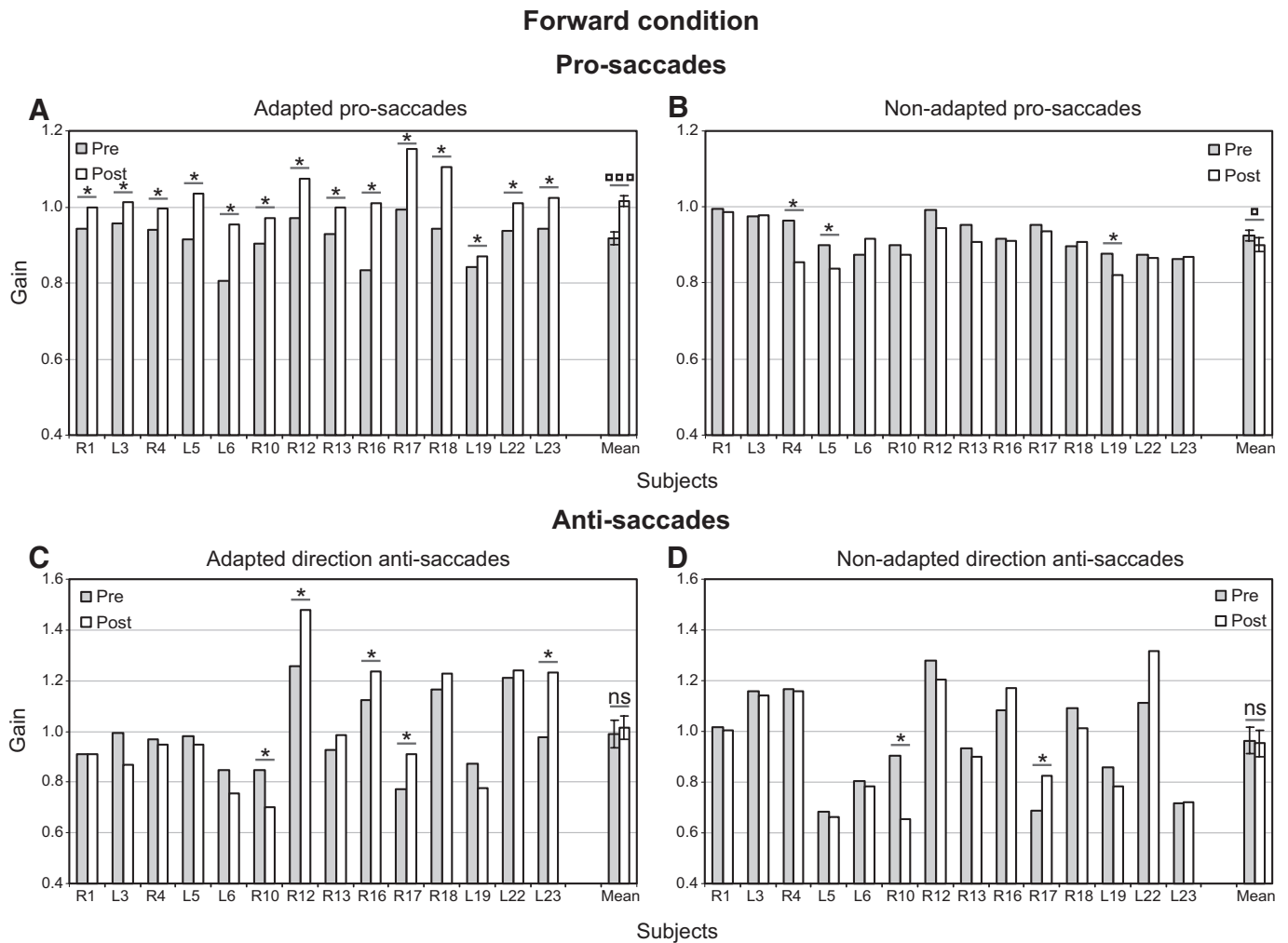


FIG. 4. Preadaptation and postadaptation gains in the forward condition for all subjects. Same conventions as in Fig. 3.

ward and leftward anti-s: -0.1 ± 3.8 and $+0.7 \pm 4.4\%$, paired *t*-test, $P > 0.66$).

Thus the variations of pro-s and anti-s gain due to nonspecific factors were weak during the pseudoadaptation session.

Summary of results

COMPARISON BETWEEN MAIN EXPERIMENT AND CONTROL EXPERIMENT. Figure 5 illustrates the mean gain changes for the control and main experiments, separately for the forward and backward conditions. In the main experiment, gain changes in postadaptation relative to preadaptation were highly significant for the adapted pro-s and were weak, but significant, for nonadapted pro-s. To quantitatively evaluate whether the gain changes for the nonadapted pro-s were similar to those induced in the control experiment, pro-s gain changes between pre- and postadaptations were submitted separately for the backward and forward conditions to a two-way ANOVA with the factors experiment (main vs. control) and saccadic direction (adapted vs. nonadapted). For both backward and forward conditions, the effects of the experiment and direction factors and of the interaction were all significant ($P < 0.001$). This interaction indicated that the difference of pro-s gain changes between the main experiment and the control experiment reached signifi-

cance only for the adapted pro-s, but not for the nonadapted pro-s (post hoc Fisher's LSD test, $P < 0.001$ and $P > 0.60$). This latter result showed that the slight gain changes of nonadapted pro-s observed in the main experiment resulted from a nonspecific effect.

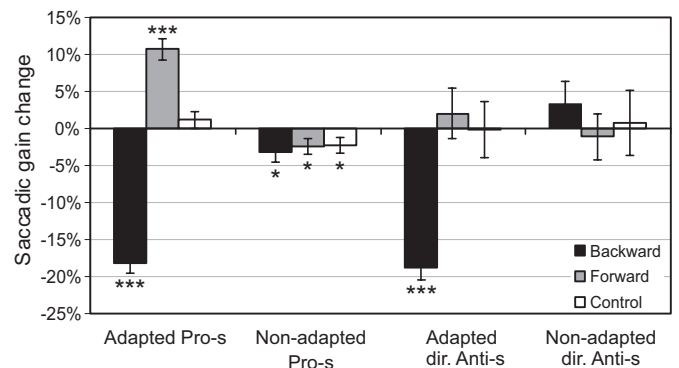


FIG. 5. Summary of results. Mean saccadic gain changes in the main experiment and in the control experiment. Results of backward adaptation condition are shown with black bars; data of forward adaptation condition are shown with gray bars and data of control experiment are shown with white bars. Statistically significant differences of gain changes with respect to 0 are indicated by * ($P < 0.05$) and *** ($P < 0.001$).

COMPARISON BETWEEN BACKWARD CONDITION AND FORWARD CONDITION IN THE MAIN EXPERIMENT. Finally, we tested the differences between the backward and forward conditions using two two-way ANOVAs (condition \times saccade direction) on gain changes of pro-s and anti-s, separately. Both factors had a significant effect ($P < 0.001$) but no interaction was identified ($P = 0.48$) on pro-s gain changes. This analysis confirmed that, in both forward and backward conditions, pro-s gain changes were higher for the adapted direction than those for the nonadapted direction (post hoc Fisher's LSD test, $P < 0.001$). The analysis also demonstrated that the backward adaptation session induced a greater gain change than that of the forward adaptation (18.1 ± 1.4 vs. $10.7 \pm 1.5\%$, post hoc Fisher's LSD test, $P < 0.001$).

Moreover, the effects of the condition factor ($P < 0.05$), the saccade direction factor ($P < 0.001$) and the interaction ($P < 0.01$) were all significant on anti-s gain changes. These results showed that modifications of adapted direction anti-s in the backward adaptation condition differed strongly from the adapted direction and nonadapted direction anti-s gain changes in forward condition (post hoc Fisher's LSD test, $P < 0.001$).

DISCUSSION

This study revealed two appreciable differences between backward adaptation and forward adaptation of reactive saccades. The first, which has been identified in previous studies with monkeys (Noto et al. 1999; Straube et al. 1997), is that backward adaptation induced stronger adaptive changes in pro-s gain than did forward adaptation. The second difference is that backward adaptation transferred fully to adapted direction anti-s but not to nonadapted direction anti-s, whereas forward adaptation did not produce any significant transfer to either adapted direction or to nonadapted direction anti-s. These findings were specifically related to adaptation processes because no such amplitude changes were observed in the control experiment.

Comparisons between backward and forward adaptations

TIME COURSE OF ADAPTATION AND AMOUNT OF GAIN CHANGE. Forward adaptation was more difficult to induce than backward adaptation: 100% of the subjects (14/14) adapted to backward steps but only 74% (14/19) adapted to forward steps. In addition, for the backward condition, the changes in pro-s gain developed quickly and followed an exponential time course (Deubel et al. 1986; Straube et al. 1997). In comparison, for the forward condition, gain changes followed a slower time course with higher intersubject variability. Even after excluding subjects that did not show any significant gain change in the forward condition, the mean rate of forward adaptation remained much smaller ($10.7 \pm 1.5\%$) than that of backward adaptation ($18.1 \pm 1.4\%$).

Note that in both conditions and, as already reported in several studies (see Alahyane et al. 2007 for references), there was some decrease of the adaptation effect in the postadaptation relative to the end of the adaptation phase. This apparent reduction of adaptation could be related to the involvement of strategic—conscious or unconscious—factors that add their effect to the true effect of adaptation. In the present study, all analyses were based on the aftereffect measured during the

postadaptation phase, to minimize the contribution of these nonspecific factors.

TRANSFER OF ADAPTATION TO ANTISACCADES. One of the most remarkable findings of the present study is the strong difference of the patterns of adaptation transfer to anti-s between backward and forward conditions and, notably, the absence of any significant modification of anti-s after forward adaptation. Could this lack of transfer to both adapted and nonadapted direction anti-s be simply explained by an insufficient amount of forward adaptation? According to this hypothesis, a transfer of adaptation to anti-s could have been obtained if a longer adaptation session and/or a larger target step was used. However, this hypothesis is not supported by our data. First, among the five subjects who showed an amount of adaptation greater than the group mean value (subjects L5, L6, R16, R17, and R18 in Fig. 4A), only one demonstrated a significant transfer to adapted direction anti-s and only one showed a significant transfer to both adapted direction and nonadapted direction anti-s. Second, at the group level, the mean amount of forward adaptation ($10.7 \pm 1.5\%$) was theoretically sufficient to induce a significant gain change of adapted direction anti-s. Indeed, applying the ratio of the amounts of adaptation obtained between the backward and forward conditions ($18.1 / 10.7$) to the amount of backward adaptation transfers predicts a $+11.1\%$ gain change of adapted direction anti-s after forward adaptation, which is more than fivefold larger than the actual gain change ($+2.0\%$). Thus altogether, these observations support our conclusion that the forward adaptation readily failed to significantly transfer to either adapted direction or nonadapted direction antisaccades.

POSSIBLE INTERPRETATION. The differences between backward and forward adaptations we identified are compatible with—and complement—some other previously reported differences. Indeed, it has been shown that backward adaptation is easier to achieve than forward adaptation (Noto et al. 1999; Straube et al. 1997) and that forward adaptation has a weaker eye-position-related specificity than that of backward adaptation (Alahyane and Péliouss 2004).

A possible explanation of the differences between these two kinds of adaptation is related to the natural tendency of the saccadic system to generate hypometric primary saccades (Henson 1978). The physiological role of this hypometria could be to allow the neural representation of the target to stay in the same hemisphere following the production of the primary saccade. Alternatively, this hypometria tendency would allow minimizing the total saccadic flight time to reach a peripheral target (Harris 1995). In any case, backward adaptation might have acquired an evolutionary advantage over forward adaptation because it reestablishes and/or maintains saccade hypometria. Indeed, if the saccadic system tolerates hypometria, the error induced by the intrasaccadic target step in forward adaptation might not be a very powerful signal to drive adaptation. Note also that the observed advantage of the backward adaptation relative to the forward adaptation is compatible with the hypothesis that error signals involved in saccadic adaptation are not simply the postsaccadic retinal input (Bahcall and Kowler 2000). Indeed, if it were the case, forward adaptation would be instead favored by a larger postsaccadic retinal input because of the natural hypometria tendency.

The strong differences between backward and forward adaptations revealed by our study are particularly highlighted by the different patterns of transfer to anti-s. These differences suggest that separate mechanisms are involved in these two adaptation conditions. The findings that separate plasticity mechanisms subtend gain increase and gain decrease are consistent with recent studies (monkey: Catz et al. 2008; Kojima et al. 2004; humans: Golla et al. 2008; Hernandez et al. 2008) and should be taken into consideration when designing new paradigms to address the neural mechanisms underlying saccadic plasticity. Note that a similar dissociation between adaptive increase and decrease of eye movement amplitude has also been observed for other oculomotor behaviors, such as the vestibuloocular reflex (Kimpo et al. 2005; Li et al. 1995) and the smooth pursuit response (Ono and Mustari 2007). Interestingly, adaptation of all these eye movements is under cerebellar control.

Do adaptation mechanisms affect early or late sensorimotor processes?

The full transfer of backward adaptation from pro-s to the adapted direction anti-s and the lack of transfer to the non-adapted direction anti-s allow us to functionally localize the site of adaptation with respect to the spatial inversion process, which takes place in the antisaccade task (Munoz and Everling 2004). Two cortical areas have been proposed to participate in this spatial inversion of a sensory vector into a motor vector. In monkeys, the lateral intraparietal area (LIP) contains some visual neurons showing an activity time-locked to the appearance of the target in the ipsilateral visual hemifield during a memory-delayed antisaccade task (Zhang and Barash 2000). This neural response has been qualified "paradoxical activity" because it is, based on its timing, a visual activity associated with a target that does not fall in the receptive field of the neurons but in its mirror location in the "opposite" hemifield, thus representing a possible neural signature of the vector inversion process. In humans a case study of a parietal patient (Nyffeler et al. 2007) and a magnetoencephalography (MEG) study in healthy subjects (Van Der Werf et al. 2008) recently pointed out that this visual vector inversion for antisaccade generation could occur in the posterior parietal cortex (in a putative homologous area to the monkey LIP). The second structure that could be involved in vector inversion is the frontal eye field (FEF), as suggested by a recent MEG study in normal human subjects (Moon et al. 2007). Therefore based on these studies and on our findings, we propose that backward adaptation of reactive saccades occurs downstream from the vector inversion process, that is, in subcortical areas involved in the encoding of saccadic motor commands.

This hypothesis is in line with previous proposals that saccadic adaptation involves motor stages and may take place under cerebellar control at the level of the superior colliculus or the brain stem (Alahyane et al. 2004, 2007; Edelman and Goldberg 2002; Frens and van Opstal 1994, 1997; Hopp and Fuchs 2002; Kojima et al. 2008; Melis and Van Gisbergen 1996; Takeichi et al. 2005, 2007; Wallman and Fuchs 1998). However, such a mechanism cannot be extended to voluntary saccades. Studies of reciprocal adaptation transfer have shown that saccadic adaptation mechanisms are partially segregated between reactive and voluntary saccades (Alahyane 2007;

Collins 2006; Deubel 1995; Erkelens 1993; Fujita 2002). Moreover, Cotti et al. (2007) demonstrated that the adaptation of voluntary saccades transfers to hand movements, whereas adaptation of reactive saccades does not. These results suggest that the neural substrates of adaptation of voluntary saccades, but not of reactive saccades, include early stages of saccade preparation devoted to the encoding of the visual target. This conclusion, however, seems to be refuted by a recent study showing that backward adaptation of so-called *intentional saccades* transfers to motor, but not sensory, antisaccades (Collins et al. 2008). However, this apparent contradiction can be related to the fact that the overlap paradigm used by these authors may have elicited saccades that actually belong to the reactive saccade category of the present study (similar latencies), explaining that the same pattern of transfer to antisaccades was found. Thus the findings of Collins et al. (2008) may actually reinforce our hypothesis that the neural substrates of the backward adaptation of reactive saccades takes place downstream from the vector inversion process.

However, in forward adaptation, the lack of significant transfer to either type of anti-s prevents us from making any inference about the neural control of adaptive lengthening of saccades. In particular, this finding does not allow us to localize the site of forward adaptation with respect to the spatial inversion involved in anti-s generation. Besides providing strong evidence of separate neural substrates for forward adaptation and for backward adaptation, this observation unexpectedly suggests that the former are not recruited for anti-saccade generation as well. Thus the disclosure of neural centers involved in forward adaptation of reactive saccades awaits further behavioral and neurophysiological investigation.

In conclusion, this study demonstrates different properties for backward and forward adaptations. These findings strongly support the hypothesis of separate mechanisms for the two kinds of adaptation of reactive saccades. The pattern of transfer to anti-s suggests that the principal site of backward adaptation is located at a sensorimotor level downstream from the vector inversion process of antisaccades, whereas the complete lack of transfer of forward adaptation fails to supply any additional argument on its neural site.

ACKNOWLEDGMENTS

We thank all the subjects who participated in the study. Experiments were performed in the "Mouvement et Handicap" Institut Fédératif de Neurosciences de Lyon platform (Lyon, France).

GRANTS

This work was supported by an Agence National pour la Recherche grant and Institut National de la Santé et de la Recherche Médicale U864. D. Pélisson was supported by Centre National de la Recherche Scientifique. D. P. Munoz was supported by the Canada Research Chair Program.

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