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

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**Title: Behavioural evidence of separate adaptation mechanisms controlling saccade amplitude  
lengthening and shortening**

**Running Title:** Adaptive lengthening and shortening of saccades

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## **Abstract**

The accuracy of saccadic eye movements is maintained over the long term by adaptation mechanisms which 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 sensory-motor transformation stages are subjected to these adaptive changes, we measured their transfer to anti-saccades in which sensory and motor vectors are spatially dissociated. In the backward adaptation condition, all subjects showed a significant amplitude decrease for adapted pro-saccades and a significant transfer of adaptation to anti-saccades performed in the adapted direction but not to oppositely-directed anti-saccades elicited by a target jump in the adapted direction. In the forward adaptation condition, only 14 out of 19 subjects showed a significant amplitude increase for pro-saccades, and no significant adaptation transfer to anti-saccades was detected in either the adapted or non-adapted 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 sensory-motor level downstream from the vector inversion process of anti-saccades 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 therefore optimize visual perception of our environment, despite progressive physiological and/or pathological modifications (Hopp and Fuchs 2004). Sensory-motor adaptation of saccades can be induced in the laboratory non-invasively with the double-step target paradigm (McLaughlin 1967) which uses a mid-saccade 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 (Frens and van Opstal 1994; Noto et al.

1999; Alahyane et al. 2008). Also, different adaptation mechanisms seem to operate for reactive (i.e., visually-triggered) saccades compared to 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 Dore-Mazars 2006; Cotti et al. 2007; Deubel 1995; Fujita et al. 2002; Erkelens and Hulleman 1993).

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 brainstem pre-motor 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 sensory-motor 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 (thereafter called pro-saccades, pro-s) performed along one horizontal direction ('adapted direction'), and then tested subjects in an anti-saccade task. Anti-saccades (anti-s) are triggered by the appearance of a target but are directed toward 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 hence allows testing whether pro-s adaptation takes place at a processing stage which precedes or follows this vector inversion process. On the one hand, if the adaptation of pro-s

involves early sensory-motor 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 “non-adapted direction” (here called “non-adapted direction anti-saccades”). On the other hand, if the adaptation of pro-s occurs at sensory-motor levels located downstream of vector inversion, a transfer is expected to the anti-s performed in the “adapted direction” (here called “adapted direction anti-saccades”).

Note that a recent study also tested the transfer of saccadic adaptation to anti-saccades (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 anti-saccades. In addition, the pro-saccades were only submitted to backward adaptive training and fell in a different category than the reactive saccade category studied here (see Discussion). In the present study, using this original approach to compare backward and forward adaptation 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 adaptation.

## **Materials and 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 adaptation 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 non-adapted direction anti-s (anti-s with the saccadic movement in the non-adapted direction and elicited by a target in the adapted direction). The control experiment used a pseudo-adaptation 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 more than one second after the saccade, a delay which has been shown previously to prevent saccadic adaptation (Fujita et al. 2002; Bahcall and Kowler 2000).

## **1. Subjects**

Thirty-six volunteers participated in the experiments (21 women, 22 fully naïve subjects; mean age:  $29.2 \pm 8.5$  years). 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 (pseudo-adaptation 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).

## **2. Apparatus**

Participants sat in a dark room with the head maintained on a chin rest and cheekbone rests. They were required to follow visual targets (0.6cm black disks on a grey background) shown on a 140 Hz computer screen (distance 57 cm, size:  $30^\circ \times 40^\circ$  of visual angle) controlled by a Visual Stimuli Generation system (CRS Cambridge, UK).

Subjects wore a helmet where two infrared sensors of the video eye tracker (Eyelink II, SR Research, Canada) were mounted, allowing continuous recording of the horizontal and vertical position of each eye with a frequency of 500Hz and a resolution of  $0.05^\circ$ . The eye tracker was calibrated before each experiment by asking the subject to look at 9 targets constituting a  $28^\circ$  high  $\times$   $38^\circ$  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 85-95°/sec).

## **3. Procedures**

### *3.1. Main experiment*

### *3.1.1. 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 1600, 1800 or 2000 ms, this FP was switched off and a target appeared at  $+8^\circ$  (adaptation of rightward pro-s) or at  $-8^\circ$  (adaptation of leftward pro-s) along the horizontal meridian. During the saccadic response, when the ocular velocity reached the 85-95°/sec threshold, the target switched position. This intrasaccadic step corresponded to 25% of the initial target eccentricity for the first 72 adaptation trials (first 3 blocks of 24 trials) and to 40% for the remaining 72 trials (last 3 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 800ms. Five hundred ms later a sound indicated the subject to shift their gaze back to the center of the screen in preparation of the next trial.

**Insert Figure 1 here**

### *3.1.2. Test sessions*

Pro-saccades and anti-saccades were recorded before (pre-adaptation) and after (post-adaptation) each adaptation session. A green or red fixation point (FP) was shown at the center of the screen for 1600, 1800 or 2000ms. When the FP was switched off, a target appeared randomly at  $+8^\circ$  (right) or  $-8^\circ$  (left) on the horizontal meridian. If the FP was green, the subject had to look at the target (pro-saccade), whereas a red FP required the subject to look away from the target toward its opposite position (anti-saccade). When saccade velocity reached 85-95°/sec, the target was extinguished. This was achieved to prevent any de-adaptation in the post-adaptation session, and for the sake of comparison, this procedure was followed in both pre- and post-adaptation sessions. Five hundred ms after the target extinction, a sound signalling the end of the trial indicated the subject to look at the center of the screen.

Each test session (pre-adaptation and post-adaptation) was divided into 3 blocks of 24 trials, each block corresponding to 12 pro-saccades and 12 anti-saccades, 6 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 pre-adaptation session (3 blocks of pro-s and anti-s), adaptation session (6 blocks of pro-s in one direction) and post-adaptation session (identical to pre-adaptation session) (see Table 1).

**Insert Table 1 here**

### *3.2. Control experiment*

This experiment was identical to the main experiment except for the adaptation session, hereafter called the ‘pseudo-adaptation session’. During this session, only rightward saccades were elicited and the target step occurred only 1800 ms after target onset, i.e. at least one second 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 post-adaptation relative to pre-adaptation did not reveal any statistical difference between the backward and forward conditions, we pooled the two subjects groups into a single pseudo-adaptation control group with 17 subjects.

## **4. Data analysis**

Horizontal movements of the 2 eyes were analyzed off-line with a custom program developed in the Matlab v.7.1 environment (Mathworks, MA., U.S.A.). 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°/sec (Fig. 1B). Only primary saccades with a reaction time between 100 and 1000ms were analyzed. Moreover, saccades contaminated by a blink and erroneous movements (pro-saccade for an anti-saccade trial and vice versa) were eliminated. Excluded trials represented 4.3



±2.8% of total trials. The following parameters were extracted from the mean data of the right and the left eye.

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 pro-saccades and anti-saccades, for the leftward and rightward directions, for pre-adaptation and post-adaptation sessions as well as for the different blocks of adaptation or pseudo-adaptation. Saccades with a gain outside the range mean ± 3 standard-deviations were eliminated from the study (0.4% of the trials). Gain changes between pre- and post-adaptation were calculated separately for adapted and non-adapted pro-saccades as well as for adapted direction and non-adapted direction anti-saccades with the following formula:

$$\text{Gain change (\%)} = \frac{\text{Mean postadaptation gain} - \text{Mean preadaptation gain}}{\text{Mean preadaptation gain}}$$

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

Statistical analyses were performed with the STATISTICA 7 software package. Student t tests compared the gain between pre-adaptation and post-adaptation, for each subject, for rightward and leftward pro-saccades as well as for rightward and leftward anti-saccades. Mean values of gain are presented with standard error of the mean. Repeated measures analyses of variances (ANOVA) were used (as indicated in text) and were followed by post-hoc LSD Fischer tests. Significance level was set at  $p < 0.05$ .

## **Results**

### **1. General observations**

#### *1.1. Baseline characteristics in pre-adaptation*

Table 2 shows that significantly more numerous direction errors (saccades in the wrong direction for a given instruction) occurred in the anti-saccade task than in the pro-saccade 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 pro-saccades than for anti-saccades, in agreement with previous studies (Awater and Lappe 2004; Brown et al. 2006; Everling and Fischer 1998; Seidlits et al. 2003; Dafoe et al. 2007). In addition, we found that pro-saccades reached a significantly faster peak velocity than anti-saccades. This velocity difference was compensated by a significant lengthening of anti-saccades duration with respect to pro-saccades such that the amplitude of both saccade types remained similar (see Table 2).

**Insert Table 2 here**

### *1.2. Qualitative observations of pro-saccade modifications during adaptation sessions*

The time-course of the gain of adapted pro-s in the main experiment is plotted for 2 representative subjects in Fig. 2A 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 post-adaptation but note that this after-effect was smaller in the forward condition than in the backward condition (see below).

**Insert Figure 2 here**

## **2. Main experiment: adaptation of rightward or leftward pro-saccades**

### *2.1. Time-course of adapted pro-saccades gain*

The time-courses of mean absolute gain changes relative to the pre-adaptation are superimposed for the backward and forward conditions (Fig. 2C). For the backward condition, the mean gain across 14 subjects shows 2 phases of variation during the adaptation session, corresponding to the 2 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 pre-adaptation, in the post-adaptation and in all adaptation blocks (post-hoc LSD Fischer test,  $p < 0.001$ ). For the forward condition, the time-course of mean absolute gain change across 19 subjects was slower compared to 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 pre-adaptation, in the post-adaptation and in all adaptation blocks except the first one (post-hoc LSD Fisher test,  $p < 0.001$ ).

## *2.2 Changes of pro-saccades gain between pre- and post-adaptations*

We next quantified the gain changes between pre- and post-adaptation (adaptation after-effects), excluding any effect of non specific factors which could be linked to the intrasaccadic target step during the adaptation session (see Methods).

### *2.2.1. Backward condition*

Figure 3A plots the gain of adapted pro-s in pre-adaptation and post-adaptation for all 14 subjects who completed the backward condition. There was a significant decrease of adapted pro-s gain in post-adaptation relative to pre-adaptation (unpaired t tests,  $p < 0.05$ ). 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 non-adapted 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 non-adapted saccade directions revealed, as predicted from the direction-selectivity of saccadic adaptation (Albano 1996; Miller et al. 1981; Deubel et al. 1986), a much larger gain decrease for pro-s performed in the adapted direction (paired samples t test,  $p < 0.001$ ).

### *2.2.2. Forward condition*

Among the 19 subjects tested in the forward condition, 5 did not show any significant gain increase for adapted pro-s in post-adaptation relative to pre-adaptation (unpaired t tests,  $p > 0.05$ ). 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 post-adaptation relative to pre-adaptation was found for adapted pro-s (Fig. 4A,  $10.7 \pm 1.5\%$ , paired t tests,  $p < 0.001$ ), whereas a weak, but significant, gain decrease was observed for non-adapted pro-s (Fig. 4B,  $2.4 \pm 1.1\%$ , paired t tests,  $p = 0.044$ ). The difference of variation between non-adapted 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 pro-saccades in a statistically reliable and direction-specific way in all the 28 subjects who were retained for the measurement of anti-saccades gain changes.

**Insert Figure 3 and 4 here**

### *2.3. Changes in anti-saccades gain*

#### *2.3.1. Backward condition*

At the individual level, 12 out of 14 participants subjected to the backward adaptation protocol presented a significant gain decrease for adapted direction anti-s in post-adaptation relative to pre-adaptation (unpaired t tests,  $p < 0.05$ ; Fig. 3C). Comparatively for non-adapted direction anti-s, only 4 subjects showed a significant difference of gain (decrease in one subject and increase in three, unpaired t tests  $p < 0.05$ ; Fig. 3D).

At the group level, the gain of adapted direction anti-s significantly decreased in post-adaptation relative to pre-adaptation by  $18.7 \pm 1.8\%$  on average (paired t test,  $p < 0.001$ ) while the gain of non-adapted 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 versus non-adapted direction) of a one-way ANOVA ( $p < 0.001$ ). Thus, the adaptation of pro-s transferred to adapted direction anti-s, but not to non-adapted direction anti-s. We quantified this transfer of adaptation with the following transfer index:

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

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 non adapted direction anti-s.

### *2.3.2. Forward condition*

At the individual level, few subjects showed a significant modification of anti-s gain in post-adaptation relative to pre-adaptation: 5 subjects for adapted direction anti-s and 2 for non adapted direction anti-s (Fig 4C and Fig. 4D, respectively). At the group level, the mean gain of adapted direction anti-s increased by  $2.0 \pm 3.4\%$  while that of non-adapted direction anti-s decreased by  $1.12 \pm 3.1\%$ . These small changes were not statistically significant (paired t tests,  $p = 0.45$  and  $0.47$ , respectively). In addition, a one-way ANOVA failed to reveal any significant effect of the direction factor (adapted direction versus non-adapted direction,  $p = 0.50$ ).

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

### **3. Control experiment: pseudo-adaptation of rightward saccades**

To control for non specific factors (e.g., fatigue, attention) which may have contributed to the effects revealed in the main experiment, we conducted a control experiment involving a pseudo-adaptation session (see Methods).

Rightward pro-s gain remained unchanged during the pseudo-adaptation phase as a one-factor ANOVA failed to detect a significant effect of the “blocks of trials” factor on saccadic gain change. On average, the post-adaptation gain of saccades made in the pseudo-adapted direction increased by  $1.2 \pm 1.2\%$  relative to pre-adaptation, a change which did not reach statistical significance (paired t test,  $p = 0.31$ ). The post-adaptation gain of pro-s made in the non pseudo-adapted direction slightly but significantly decreased by  $2.2 \pm 1.1\%$  relative to pre-adaptation (paired t test,  $p = 0.045$ ). Moreover, the

mean variations of anti-s gain in post-adaptation relative to pre-adaptation were small and did not reach significance (rightward and leftward anti-s:  $-0.1 \pm 3.8\%$  and  $+0.7 \pm 4.4\%$ , paired t tests,  $p > 0.66$ ).

Thus, the variations of pro-s and anti-s gain due to non specific factors were weak during the pseudo-adaptation session.

#### **4. Results summary**

##### *4.1. 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 post-adaptation relative to pre-adaptation were highly significant for the adapted pro-s and were weak, but significant, for non-adapted pro-s. To quantitatively evaluate if the gain changes for the non-adapted pro-s was similar to the one induced in the control experiment, pro-s gain changes between pre- and post-adaptations were submitted separately for backward and forward condition to a two-way ANOVA with the factors experiment (main versus control) and saccadic direction (adapted versus non-adapted). 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 significance only for the adapted pro-s, but not for the non-adapted pro-s (post-hoc Fisher test,  $p < 0.001$  and  $p > 0.60$ ). This latter result showed that the slight gain changes of non-adapted pro-s observed in the main experiment resulted from a non-specific effect.

##### *4.2. Comparison between backward condition and forward condition in the main experiment*

Finally, we tested the differences between the backward and forward condition using 2 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 for the non-adapted direction (post-hoc LSD Fischer test,

$p < 0.001$ ). The analysis also demonstrated that the backward adaptation session induced a greater gain change than the forward adaptation ( $18.1 \pm 1.4\%$  versus  $10.7 \pm 1.5\%$ , post-hoc LSD Fischer,  $p < 0.001$ ).

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 non-adapted direction anti-s gain changes in forward condition (post-hoc LSD Fischer test,  $p < 0.001$ ).

**Insert Figure 5 here**

## **Discussion**

This study revealed two marked differences between backward 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 forward adaptation. The second difference is that backward adaptation transferred fully to adapted direction anti-s but not to non-adapted direction anti-s, whereas forward adaptation did not produce any significant transfer to either adapted direction or to non-adapted direction anti-s. These findings were specifically related to adaptation processes because no such amplitude changes were observed in the control experiment.

### **1. Comparisons between backward and forward adaptation**

#### *1.1. 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 inter-subject 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 post-adaptation 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 after-effect measured during the post-adaptation phase, in order to minimize the contribution of these non-specific factors.

### *1.2. Transfer of adaptation to anti-saccades*

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 non-adapted 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 5 subjects who showed an amount of adaptation larger than the group mean value (subjects L5, L6, R16, R17, R18 in Fig. 4A), only 1 demonstrated a significant transfer to adapted direction anti-s and only 1 showed a significant transfer to both adapted direction and non-adapted 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 five times as large as 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 non-adapted direction anti-saccades.



### *1.3. Possible interpretation*

The differences between backward and forward adaptation 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 backward adaptation (Alahyane and Pelisson 2004).

A possible explanation of the differences between these 2 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 re-establishes 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 post-saccadic retinal input (Bahcall and Kowler 2000). Indeed, if it were the case, forward adaptation would be instead favoured by a larger post-saccadic retinal input because of the natural hypometria tendency.

The strong differences between backward and forward adaptation 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 2 adaptation conditions. The findings that separate plasticity mechanisms subtend gain increase and gain decrease are consistent with recent studies (monkey: (Kojima et al. 2004; Catz et al. 2008), 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 vestibulo-ocular reflex (Li et al. 1995; Kimpo et al. 2005) and the smooth pursuit response (Ono and Mustari 2007). Interestingly, adaptation of all these eye movements is under cerebellar control.

## **2. Do adaptation mechanisms affect early or late sensory-motor 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 localise the site of adaptation with respect to the spatial inversion process which takes place in the anti-saccade 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 anti-saccade task (Zhang and Barash 2000). This neural response has been qualified “paradoxical activity” as 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” hemi-field, 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 MEG study in healthy subjects (Van Der Werf et al. 2008) recently pointed out that this visual vector inversion for anti-saccade generation could occur in the posterior parietal cortex (in a putative homologous area to the monkey LIP). The second structure which 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, namely 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; Alahyane et al. 2007; Edelman and Goldberg 2002; Frens and van Opstal 1994; Hopp and Fuchs 2002; Takeichi et al. 2007; Wallman and Fuchs 1998; Frens and van Opstal 1997; Melis and Van Gisbergen 1996; Takeichi et al. 2005; Kojima et al. 2008). 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) have 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 seems however to be refuted by a recent study showing that backward adaptation of so-called “intentional saccades” transfers to motor, but not sensory, anti-saccades (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 which actually belong to the reactive saccade category of the present study (similar latencies), explaining that the same pattern of transfer to anti-saccades 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 localise the site of forward adaptation with respect to the spatial inversion involved in anti-s generation. Beside 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 adaptation. 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 sensory-motor level downstream from the vector inversion process of anti-saccades whereas the complete lack of transfer of forward adaptation fails to supply any additional argument on its neural site.

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## References

- Alahyane N, Devauchelle AD, Salemm R and Pelisson D.** Spatial transfer of adaptation of scanning voluntary saccades in humans. *Neuroreport* 19: 37-41, 2008.
- Alahyane N, Koene A and Pelisson D.** Transfer of adaptation from visually guided saccades to averaging saccades elicited by double visual targets. *Eur J Neurosci* 20: 827-836, 2004.
- Alahyane N and Pelisson D.** Eye position specificity of saccadic adaptation. *Invest Ophthalmol Vis Sci* 45: 123-130, 2004.
- Alahyane N, Salemm R, Urquizar C, Cotti J, Guillaume A, Vercher JL and Pelisson D.** Oculomotor plasticity: Are mechanisms of adaptation for reactive and voluntary saccades separate? *Brain Res* 1135: 107-121, 2007.
- Albano JE.** Adaptative changes in saccade amplitude: oculocentric or orbitocentric mapping? *Vision Res* 36: 2087-2098, 1996.
- Awater H and Lappe M.** Perception of visual space at the time of pro- and anti-saccades. *J Neurophysiol* 91: 2457-2464, 2004.
- Bahcall DO and Kowler E.** The control of saccadic adaptation: implications for the scanning of natural visual scenes. *Vision Res* 40: 2779-2796, 2000.
- Brown MRG, Goltz HC, Vilis T, Ford KA and Everling S.** Inhibition and generation of saccades: Rapid event-related fMRI of prosaccades, antisaccades, and nogo trials. *NeuroImage* 33: 644-659, 2006.

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

**Collins T and Dore-Mazars K.** Eye movement signals influence perception: Evidence from the adaptation of reactive and volitional saccades. *Vision Res* 46: 3659-3673, 2006.

**Collins T, Vergilino-Perez D, Delisle L and Doré-Mazars K.** Visual versus motor vector inversions in the antisaccade task: a behavioral investigation with saccadic adaptation. *J Neurophysiol* 99: 2708-2718, 2008.

**Cotti J, Guillaume A, Alahyane N, Pelisson D and Vercher JL.** Adaptation of voluntary saccades, but not reactive saccades, transfers to hand pointing movements. *J Neurophysiol* 98: 602-612, 2007.

**Dafoe JM, Armstrong IT and Munoz DP.** The influence of stimulus direction and eccentricity on pro-s and anti-saccades in humans. *Exp Brain Res* 179: 563-570, 2007.

**Deubel H.** Separate adaptive mechanisms for the control of reactive and volitional saccadic eye movements. *Vision Res* 35: 3529-3540, 1995.

**Deubel H, Wolf W and Hauske G.** Adaptive gain control of saccadic eye movements. *Hum Neurobiol* 5: 245-253, 1986.

**Edelman JA and Goldberg ME.** Effect of short-term saccadic adaptation on saccades evoked by electrical stimulation in the primate superior colliculus. *J Neurophysiol* 87: 1915-1923, 2002.

**Erkelens CJ and Hulleman J.** Selective adaptation of interally triggered saccades made to visual targets. *Exp Brain Res* 93: 157-164, 1993.

- Everling S and Fischer B.** The antisaccade: a review of basic research and clinical studies. *Neuropsychologia* 36: 885-899, 1998.
- Frens MA and van Opstal AJ.** Transfer of short-term adaptation in human saccadic eye movements. *Exp Brain Res* 100: 293-306, 1994.
- Frens MA and van Opstal AJ.** Monkey superior colliculus activity during short-term saccadic adaptation. *Brain Res Bull* 43: 473-483, 1997.
- Fujita M, Amagai A, Minakawa F and Aoki M.** Selective and delay adaptation of human saccades. *Cogn Brain Res* 13: 41-52, 2002.
- Golla H, Konstantin T, Haarmeier T, Catz N, Barash S and Thier P.** Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. *Eur J Neurosci* 27: 132-144, 2008.
- Hallett PE.** Primary and secondary saccades to goals defined by instructions. *Vision Res* 18: 1279-1796, 1978.
- Harris CM.** Does saccadic undershoot minimize saccadic flight-time? A Monte-Carlo study. *Vision Res* 35: 691-701, 1995.
- Henson D.** Corrective saccades: effects of altering visual feedback. *Vision Res* 18: 63-67, 1978.
- Hernandez TD, Levitan CA, Banks MS and Schors CM.** How does saccade adaptation affect visual perception. *J Vision* 8: 1-16, 2008.
- Hopp JJ and Fuchs AF.** Investigating the site of human saccadic adaptation with express and targeting saccades. *Exp Brain Res* 144: 538-548, 2002.

- Hopp JJ and Fuchs AF.** The characteristics and neuronal substrate of saccadic eye movement plasticity. *Progr Neurobiol* 72: 27-53, 2004.
- Kimpo RR, Boyden ES, Katoh A, Ke MC and Raymond JL.** Distinct patterns of stimulus generalization of increases and decreases in VOR gain. *J Neurophysiol* 94: 3092-3100, 2005.
- Kojima Y, Iwamoto Y, Robinson FR, Noto CT and Yoshida K.** Premotor inhibitory neurons carry signals related to saccade adaptation in the monkey. *J Neurophysiol* 99: 220-230, 2008.
- Kojima Y, Iwamoto Y and Yoshida K.** Memory of learning facilitates saccadic adaptation in the monkey. *J Neurosci* 24: 7531-7539, 2004.
- Li J, Smith SS and McElligott JG.** Cerebellar nitric oxide is necessary for vestibulo-ocular reflex adaptation, a sensorimotor model of learning. *J Neurophysiol* 74: 489-494, 1995.
- McLaughlin SC.** Parametric adjustment in saccadic eye movements. *Percept Psychophys* 2: 359-362, 1967.
- Melis BJ and Van Gisbergen JA.** Short-term adaptation of electrically induced saccades in monkey superior colliculus. *J Neurophysiol* 76: 1744-1758, 1996.
- Miller JM, Anstis T and Templeton WB.** Saccadic plasticity: parametric adaptive control feedback. *J Exp Psychol Hum Percept Perform* 7: 356-366, 1981.
- Moon SY, Barton JJS, Mikulski S, Polli FE, Cain MS, Vangel M, Hamalainen MS and Manoch DS.** Where left becomes right: A magnetoencephalographic study of sensorimotor transformation for antisaccades. *NeuroImage* 36: 1313-1323, 2007.



**Munoz DP and Everling S.** Look away: the anti-saccade task and the voluntary control of the eye movement. *Nature* 5: 218-228, 2004.

**Noto C, Watanabe S and Fuchs AF.** Characteristics of Simian adaptation fields produced by behavioral changes in saccadic gain and direction. *J Neurophysiol* 81: 2798-2813, 1999.

**Nyffeler T, Rivaud-Péchox S, Pierrot-Deseignilly C, Diallo R and Gaymard B.** Visual vector inversion in the posterior parietal cortex. *Neuroreport* 18: 917-920, 2007.

**Ono S and Mustari MJ.** Horizontal smooth pursuit adaptation in macaques after muscimol inactivation of the dorsolateral pontine nucleus (DLPN). *J Neurophysiol* 98: 2918-2932, 2007.

**Seidlits SK, Reza T, Briand KA and Sereno AB.** Voluntary spatial attention has different effects on voluntary and reflexive saccades. *ScientificWorldJOURNAL* 3: 881-902, 2003.

**Straube A, Fuchs AF, Usher S and Robinson FR.** Characteristics of saccadic gain adaptation in Rhesus macaques. *J Neurophysiol* 77: 874-895, 1997.

**Takeichi N, Kaneko CR and Fuchs AF.** Discharge of monkey nucleus reticularis tegmenti pontis neurons changes during saccade adaptation. *J Neurophysiol* 94: 1938-1951, 2005.

**Takeichi N, Kaneko CR and Fuchs AF.** Activity changes in monkey superior colliculus during saccade adaptation. *J Neurophysiol* 97: 4096-4107, 2007.

**Van Der Werf J, Jensen O, Fries P and Medendorp WP.** Gamma-band activity in human posterior parietal cortex encodes the motor goal during delayed prosaccades and antisaccades. *J Neurosci* 28: 8397-8405, 2008.

**Wallman J and Fuchs AF.** Saccadic gain modification: visual error drives motor adaptation. *J Neurophysiol* 80: 2405-2416, 1998.

**Zhang M and Barash S.** Neuronal switching of sensorimotor transformations for antisaccades. *Nature* 408: 971-975, 2000.

## Figure Legends

**Figure 1:** (A) The sequence of events in the adaptation session (examples illustrating the case of rightward 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 (1800 msec 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 grey cursors indicate the beginning and the end of the saccade as defined automatically by our analysis software.

**Figure 2:** (A) and (B) Time-course of adapted pro-saccades gain for 2 representative subjects, plotted as a function of trial number. Different symbols indicate pre-adaptation (+), adaptation phase (▲) and post-adaptation (◇). (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: pre-adaptation (pre), adaptation blocks with an intrasaccadic step of 25% of the initial target eccentricity (a25, b25, c25) or of 40% (d40, e40, f40), and post-adaptation (post). Errors bars are standard error of the mean. Significant differences of gain change relative to pre-adaptation (post-hoc LSD Fischer test) are indicated by \*\*\* (p<0.001).

**Figure 3:** Pre-adaptation and post-adaptation gain in the backward condition for all subjects. (A) and (B) Adapted pro-s and the non-adapted pro-s data, respectively. (C) and (D) Adapted direction anti-s and the non-adapted direction anti-s data, respectively. Asterisks (\*) indicate for each subject statistically significant gain changes in post-adaptation relative to pre-adaptation (unpaired t test, p<0.05). At the group level, paired t tests were used to measure significant gain changes in post-adaptation relative to pre-adaptation 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).

**Figure 4:** Pre-adaptation and post-adaptation gain in the forward condition for all subjects. Same conventions as in Fig. 3.

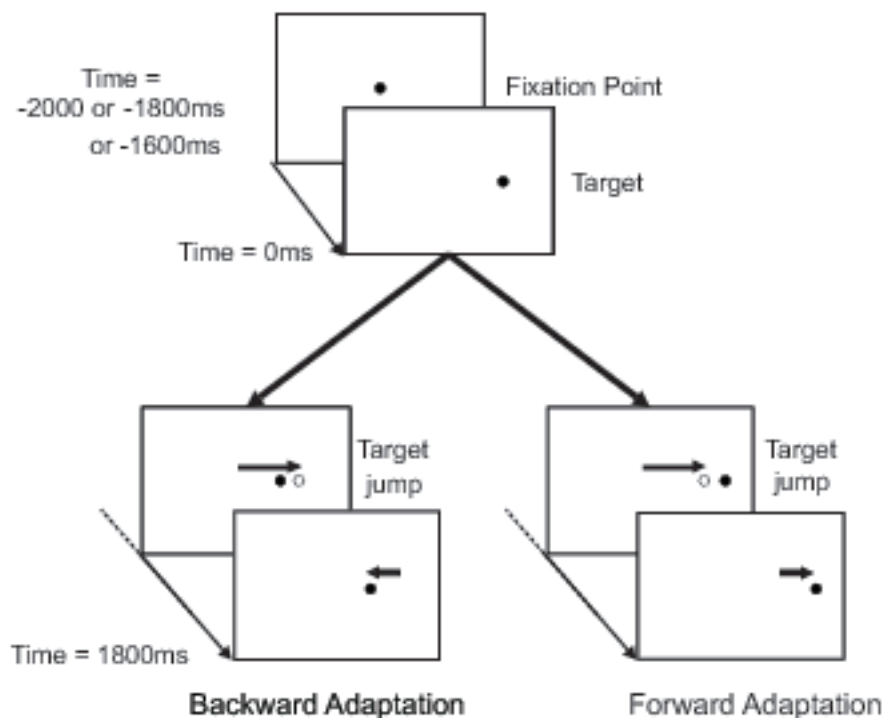
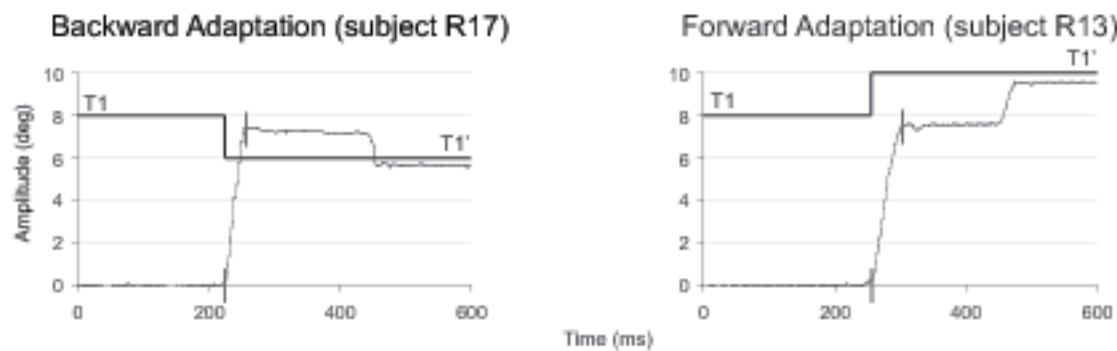
**Figure 5:** Summary of results. Mean saccadic gain changes in the main experiment and in the control experiment. Results of backward adaptation condition are shown with black bars, data of forward adaptation condition are shown with grey bars and data of control experiment are shown with white bars.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

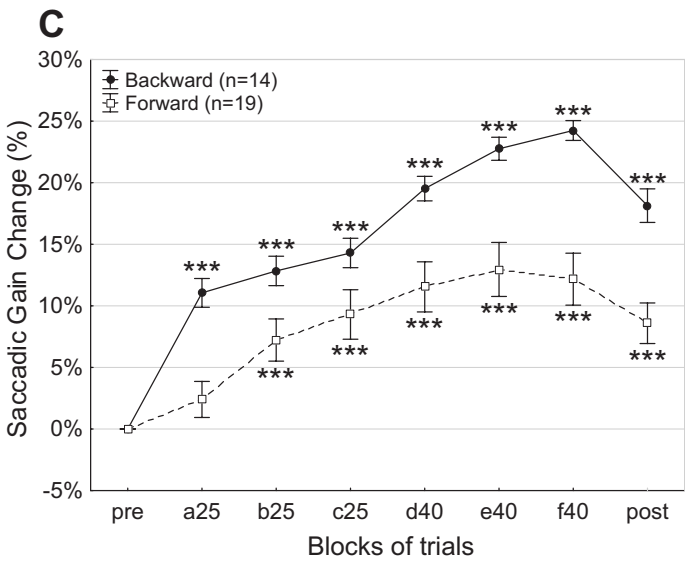
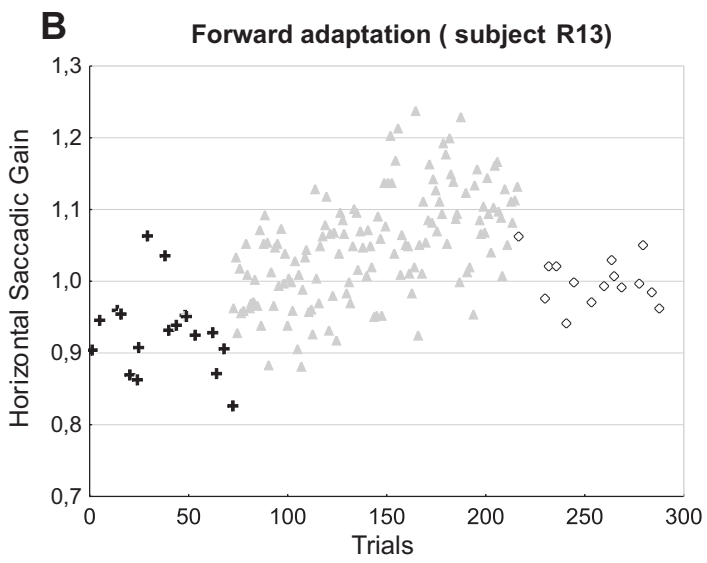
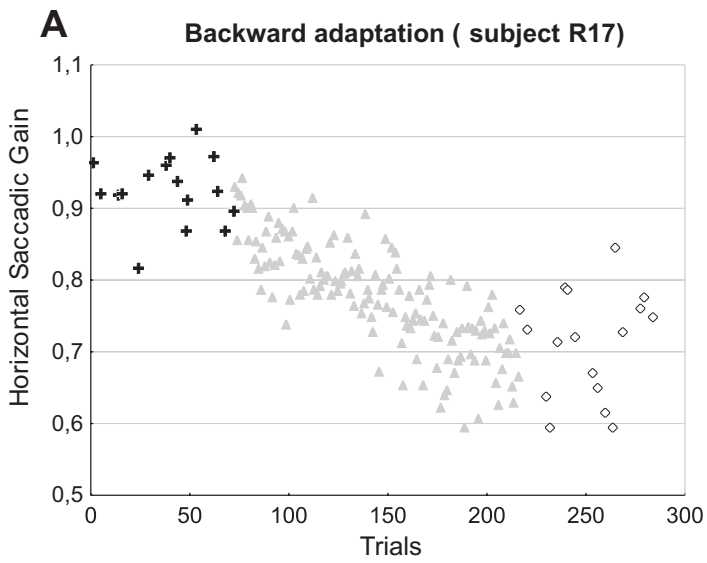
**Table 1:** Summary design of all experiments. N = numbers of subjects completing each condition. Some subjects were tested in both conditions and 8 subjects performed both main and control experiments. The number of subjects who showed a significant gain increase of adapted pro-s in the forward condition of the main experiment is indicated in parenthesis.

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

**Table 2:** Baseline saccade parameters (pre-adaptation). Mean correct response rate, latency, duration, peak velocity and amplitude calculated for all subjects of the different experiments for both pro-s and anti-s ( $\pm$  standard deviation of the mean). Asterisks represent significant differences between pro-s and anti-s (t test, \*\*\*:  $p < 0.001$ ).

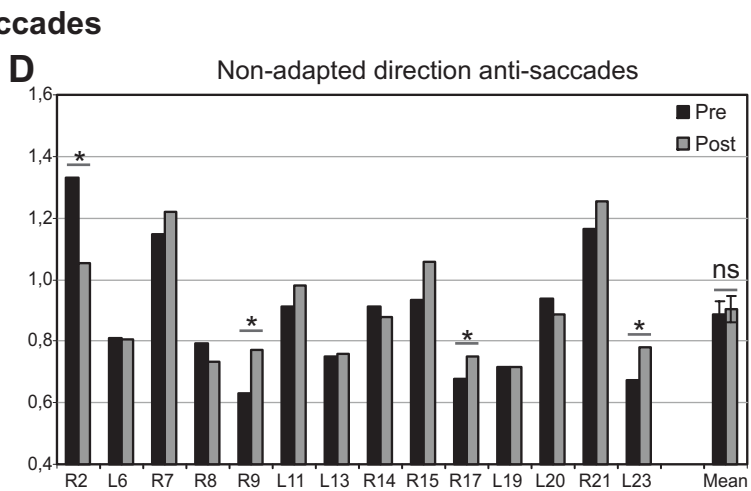
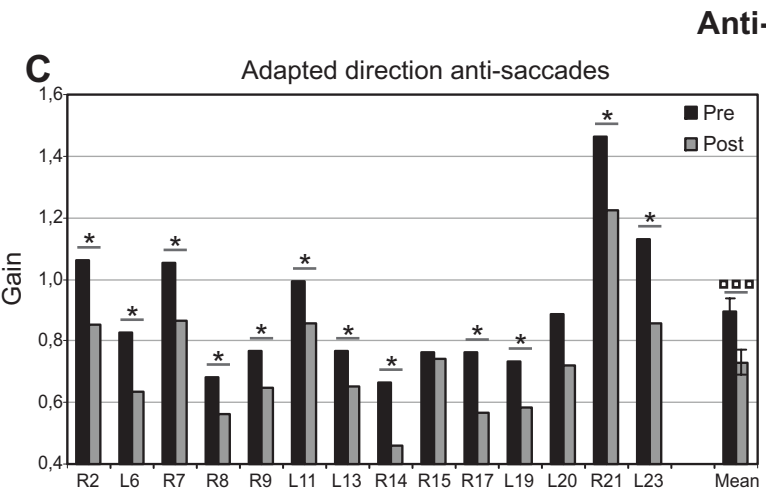
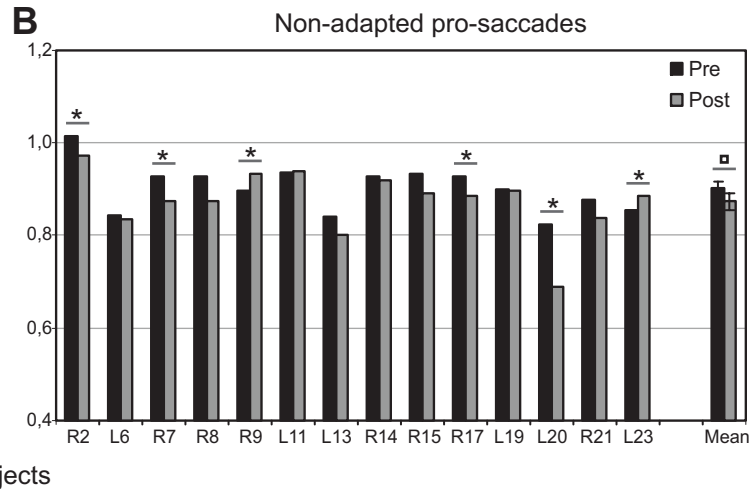
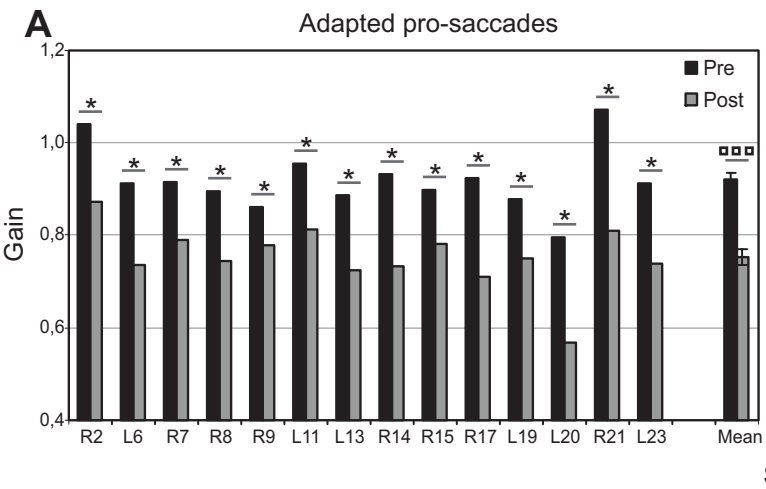
	Correct response rate (%)	Latency (ms)	Duration (ms)	Peak velocity (°/sec)	Amplitude (°)
<b>pro-s</b>	97 $\pm$ 0.3	241 $\pm$ 52.2	45 $\pm$ 6.9	266 $\pm$ 29.6	7.31 $\pm$ 0.40
<b>anti-s</b>	92 $\pm$ 0.8 ***	304 $\pm$ 62.8 ***	49 $\pm$ 11.1 ***	248 $\pm$ 46.6 ***	7.36 $\pm$ 1.78

**A****Adaptation sessions: Backward or Forward****B****Examples of rightward pro-s during adaptation sessions**



# Backward condition

## Pro-saccades



Subjects



# Forward condition

## Pro-saccades

