Adaptation of reactive and voluntary saccades: different patterns of adaptation revealed in the antisaccade task

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Sensorimotor adaptation restores and maintains the accuracy of goal-directed movements. It remains unclear whether these adaptive mechanisms modify actions by controlling peripheral premotor stages that send commands to the effectors and/or earlier processing stages involved in registration of target location. Here, we studied the effect of adaptation of saccadic eye movements, a well-established model of sensorimotor adaptation, in an antisaccade task. This task introduces a clear spatial dissociation between the actual target direction and the requested saccade direction because the correct movement direction is in the opposite direction from the target location. We used this requirement of a vector inversion to assess the level(s) of saccadic adaptation for two different types of adapted saccades. In two different experiments, we tested the transfer to antisaccades of the adaptation in one direction of reactive saccades to jumping targets and of scanning voluntary saccades within a target array. In the first experiment, we found that adaptation of reactive saccades transferred only to antisaccades in the adapted direction. In contrast, in the second experiment, adaptation of scanning voluntary saccades transferred to antisaccades in both the adapted and non-adapted directions. We conclude that adaptation of reactive saccades acts only downstream of the vector inversion required in the antisaccade task, whereas adaptation of voluntary saccades has a distributed influence, acting both upstream and downstream of vector inversion.

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Goal-directed behaviours require the central nervous system to assess the position of the object of interest (sensory stages) and based on this information, to generate commands for the effector (motor stages). Processes of sensorimotor adaptation guarantee the high precision of these sensory-to-motor transformations (Wolpert *et al.* 2001; Bock & Schneider, 2002; Gauthier *et al.* 2007). A central question in the neural control of movement is which stages of sensorimotor transformation are controlled by these adaptive processes (Raymond, 1998).

An excellent model of sensorimotor adaptation is the adaptive control of saccadic eye movements (Hopp & Fuchs, 2004). Numerous studies have tested saccades produced automatically in reaction to the sudden appearance of a visual target (reactive saccades) and concluded that saccadic adaptation modifies mainly neural structures near the output where signals are encoded in motor coordinates (for review see Hopp & Fuchs, 2004). However, this conclusion may not be valid for all saccade types. In everyday life, a large number of saccades are made between stationary objects within the visual environment (scanning voluntary saccades, referred to as voluntary saccades in the rest of the paper). We recently demonstrated that adaptation of voluntary saccades, but not of reactive saccades, transfers to hand pointing movements (Cotti *et al.* 2007). This pattern of results indicates that the adaptation of voluntary saccades modifies neural signals used by both the ocular and the manual systems, and thus suggests an involvement of early stages of processing where neural signals may be encoded in sensory coordinates.

In the present article, we report the results of two behavioural experiments conducted separately in two different laboratories to determine which stage(s) of saccade production are modified by the adaptation of

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reactive saccades (experiment 1) and of voluntary saccades (experiment 2). Both experiments evaluated the effect of saccade adaptation in a single direction on the production of antisaccades. These two experiments share the same rationale based on two points.

First, it is well known that saccadic adaptation is spatially restricted to fields of adaptation (Miller *et al.* 1981; Deubel, 1987; Frens & Van Opstal, 1994; Noto *et al.* 1999). In particular, saccadic adaptation is *direction specific*. Inducing an amplitude adaptation of saccades generated in a given direction does not modify the amplitude of saccades directed in the opposite direction (see Hopp & Fuchs, 2004 for a review on reactive saccades; Alahyane *et al.* 2008 for voluntary saccades). This simply reflects the lateralized organization of both visual and saccadic systems relative to the vertical meridian of the visual field, whereby opposite visual and saccadic movement directions are encoded in neural structures located in opposite sides of the brain.

Second, the antisaccade task requires the production of an eye movement away from a visual target toward the opposite position (Hallet, 1978; Munoz & Everling, 2004). Compared to the pro-saccade task that requires saccades directed toward the target, the antisaccade task introduces a clear spatial dissociation between the vector pointing to the target and the vector pointing to the 'anti' position. Anatomically, antisaccade generation specifically requires a transfer of information from one hemisphere (contralateral to target vector) to the other hemisphere (contralateral to movement vector), a transfer also called vector inversion. Theoretically this vector inversion could take place at early stages of sensori-motor transformation, where the stimulus is registered in sensory coordinates, or later when saccadic signals are registered in motor coordinates. The following studies favour the first possibility by suggesting that the visually registered target vector is reversed at the level of the posterior parietal cortex (PPC). Zang & Barash (2000, 2004) recorded in area LIP of the monkey neuronal responses in an antisaccade task. In addition to the classical visual response evoked by a contralateral target presentation, some LIP neurons also showed, some 50 ms later, an activity time-locked to the appearance of the visual target in the ispilateral field. The authors called this activity '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. They interpreted this paradoxical activity as the result of the inversion of the visual target vector (a remapped visual response) leading to the generation of the contraversive antisaccade. In addition in humans, indirect evidence implicates the intraparietal sulcus (IPS, human homologue of LIP) in the inversion of the visual target vector in the antisaccade task (Medendorp *et al.* 2005; Nyffeler *et al.* 2007; Moon *et al.* 2007).

Regardless of the exact nature of the inverted signal in antisaccade generation and of the precise neural substrates of this vector inversion, the aim of the present study was to determine, separately for reactive and voluntary saccades, whether saccadic adaptation acts upstream or downstream of vector inversion. These two hypotheses generate two opposite sets of predictions which can be tested by measuring the transfer to antisaccades of an adaptive amplitude reduction of pro-saccades generated in a single direction.

If saccadic adaptation acts upstream of vector inversion, then a transfer of this adaptive amplitude reduction will be observed for antisaccades performed in the non-adapted direction. Indeed, these antisaccades result from inversion of a target vector which points toward the adapted field and which, according to the upstream hypothesis, has been modified by adaptation mechanisms. Conversely, antisaccades in the adapted direction will not be modified, because in this case, the target vector points toward the non-adapted hemifield and thus elicits activity in neural structures completely immune to adaptive changes.

If saccadic adaptation acts downstream of vector inversion, the amplitude of antisaccades in the non-adapted direction will this time not be affected. This is because the underlying neural signals, by changing of brain hemisphere (vector inversion) before encountering adaptive modification, involve neural structures completely immune to adaptive changes. Conversely, the amplitude of antisaccades in the adapted direction will be modified, because after inversion, the signals underlying antisaccade generation will be transmitted to neural stage(s) influenced by saccadic adaptation.

The results presented reveal different patterns of adaptation transfer to antisaccades, depending on the type of saccade that was submitted to adaptation. Reactive saccade adaptation transferred only to antisaccades in the adapted direction, whereas voluntary saccade adaptation transferred to antisaccades in both adapted and non-adapted directions.

Methods

Subjects

Two separate experiments were conducted. Sixteen subjects volunteered to take part in the reactive saccade adaptation experiment (median age, 30 years) and a different group of 20 subjects participated in the voluntary saccade experiment (median age, 26 years). All were healthy, with normal or corrected-to-normal vision. They were naïve as to the purpose of the study and gave their informed consent to participate. The study was performed in accordance with the ethical standards laid down in the *Declaration of Helsinki* (last modified 2004).

Table 1. Experimental design: temporal arrangement of experimental phases in each condition (test and control) of the two experiments

		pre-adaptation phases			adaptation	post-adaptation phases			
Experiment 1: Reactive saccades	Test (N = 8)	reactive pro-saccades AS non-adapted direction AS adapted direction			reactive pro-saccade adaptation	reactive pro-saccades AS non-adapted direction AS adapted direction			
	Control (N = 8)	reactive pro-saccades AS non-adapted direction AS adapted direction			reactive pro-saccade *pseudo-adaptation*	reactive pro-saccades AS non-adapted direction AS adapted direction			
Experiment 2: Voluntary saccades	Test (N = 10)	AS adapted direction	AS non-adapted direction	voluntary pro-saccades	voluntary pro-saccade adaptation	voluntary pro-saccades	AS non-adapted direction	AS adapted direction	voluntary pro-saccades
	Control (N = 10)	AS adapted direction	AS non-adapted direction	voluntary pro-saccades	voluntary pro-saccade *pseudo-adaptation*	voluntary pro-saccades	AS non-adapted direction	AS adapted direction	voluntary pro-saccades

AS, antisaccades. *N*, number of subjects. See Methods for further details.

General experimental design and experimental set-up

The reactive and voluntary saccade experiments were conducted separately in two laboratories. Despite minor differences (see below), the protocols used in the two laboratories were designed specifically to test which stages of sensorimotor transformation were modified during saccadic adaptation. In both cases, the experiments consisted of a test condition and a control condition (Table 1). The test condition assessed the effect of saccadic adaptation induced by systematic perturbation of target position (i.e. an intrasaccadic backward step of the target) on antisaccades. Eight and 10 subjects participated in the test conditions of reactive and voluntary experiments, respectively. Importantly, similar average gain decreases were obtained for reactive saccade and voluntary saccade test conditions (18.1% and 18.3%, respectively, see Results). The control condition was designed to evaluate non-specific effects (e.g. fatigue or attentional effects), differing from the test condition only by the absence of target perturbation during the adaptation phase. Eight and 10 subjects different from the subjects of the test conditions participated in control conditions for the reactive and voluntary experiments, respectively.

In both reactive saccade and voluntary saccade experiments, a helmet-mounted infrared sensor allowed recording of left eye position at 250 Hz (EyeLink video-oculographic system, SR Research, Mississauga, Ontario, Canada) with a spatial resolution better than 0.1 deg. The calibration that allowed precise measurements of horizontal and vertical eye position was performed using a nine-point calibration grid. The two experiments were performed in the dark, so as to limit the use of any visual reference not related to the visual stimuli of the task.

Protocol

Experiment 1: reactive saccades. During the reactive saccade experiment, visual targets were presented on a fast video screen (140 Hz) controlled by a VSG (Visual Stimuli Generation) system (Cambridge Research Systems, Cambridge, UK).

The adaptation phase ($n = 144$ trials) and the pre- and post-adaptation phases ($n = 72$ trials each) have been described in detail elsewhere (Alahyane *et al.* 2007; see Table 1 for experimental phases arrangement). Briefly, each trial began with a variable period of fixation on a central fixation point (FP). Simultaneously with extinction of the FP, a visual target was presented on the horizontal meridian at 8 deg to the right of the FP. The subject was instructed to react as quickly and accurately as possible to target appearance by producing a saccade toward the target (reactive saccades).

On adaptation trials, reactive saccade adaptation was induced by the classical double-step paradigm (McLaughlin, 1967), in which the visual target systematically steps in the opposite direction during the primary saccadic response. This intrasaccadic backward step of the target was triggered around the time of peak saccade velocity (based on an online saccade detection using a velocity threshold fixed at 30 deg. s^{-1}). This intrasaccadic backward target step corresponded to 25% of the initial step for the first 72 adaptation trials. This step was increased to 40% for the remaining 72 adaptation trials. Hence, the gain reduction required at the end of the adaptation phase was 0.4.

In the pre- and post-adaptation phases, the subjects were required to produce reactive saccades and anti-saccades in a mixed design. After the fixation period, the target appeared on the horizontal meridian at 8 deg to

the right or left of the FP. Depending on FP colour, the subject had to produce a saccade toward the target or an antisaccade toward the mirror position of the target. On half of the antisaccade trials, the target was presented at the non-adapted location, thus requiring a saccade in the adapted direction (Fig. 2*A*). On the other half of the trials, the target was presented at the adapted location, thus requiring a saccade in the non-adapted direction (Fig. 2*B*). Based on the velocity threshold, the target was extinguished at saccade onset, depriving the subject of any visual feedback about saccade accuracy and avoiding any potential de-adaptation in the post-adaptation phase. In each pre- and post-adaptation phase, 36 antisaccade trials (18 in each direction) were pseudo-randomly intermingled with 36 reactive saccade trials.

Experiment 2: voluntary saccades. During the voluntary saccade experiment, visual targets were presented with an LCD projector (85 Hz), illuminating a backprojection screen.

The adaptation phase ($n = 75$ trials) and the pre- and post-adaptation phases ($n = 40$ and $n = 80$ trials, respectively) are detailed elsewhere (Cotti *et al.* 2007; see Table 1 for experimental phases arrangement). Briefly, each trial began with a variable period of FP fixation. In the adaptation trials (Fig. 1*A* and *B*), subjects were required to scan, at their own pace, a visual scene made of four targets following a predetermined visual path (protocol modified from Deubel, 1995). Each trial required two leftward saccades of 20 deg. Online detection of each leftward saccade (based on a velocity threshold fixed at 30 deg. s^{-1}) triggered a 6 deg backward step of the whole visual scene requiring a 0.3 gain reduction in saccade amplitude. Hence, during the voluntary saccade adaptation phase, subjects produced 150 leftward saccades with an intrasaccadic target step.

In the pre- and post-adaptation phases ($n = 40$ trials and $n = 80$ trials, respectively), subjects were required to make a single saccade per trial between the FP and a target that were both presented at the time of trial onset. Both FP and target were extinguished at saccade onset. To reinforce the voluntary nature of saccades produced in adaptation and pre- and post-adaptation phases, subjects were instructed to voluntarily change the moment of saccade triggering from trial-to-trial. Before and after voluntary saccade adaptation, subjects were also required in a block design to produce antisaccades directed either to the adapted direction or to the non-adapted direction ($n = 20$ for each type; Fig. 2*A* and *B*). After a variable delay, the FP disappeared and simultaneously a target was flashed for 250 ms, 20 deg to either the left or right of the FP. The appearance of this target served as the trigger signal to perform the antisaccade, i.e. a saccade in the opposite direction.

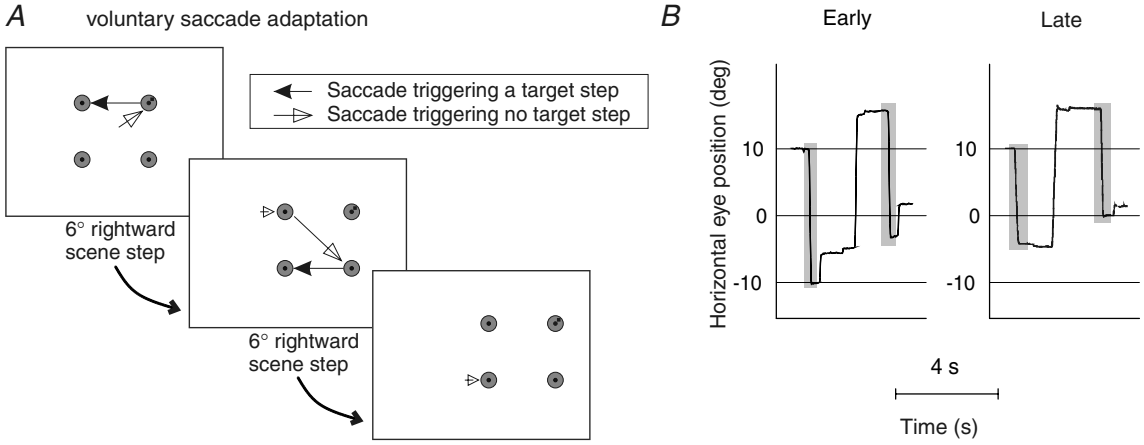

Figure 1. Voluntary saccades adaptation protocol
A, schematics of whole scene double-step protocol. Subjects were required to explore a scene made of four targets (0.5 deg diameter red circles with a black centre) presented simultaneously from trial onset, following a predetermined but self-paced scan-path. Each leftward saccade made the whole visual scene step rightward by 30% of the initially required amplitude. To enhance the voluntary nature of the saccades produced in this adaptation phase, subjects were required to additionally: (i) vary the moment of each saccade onset during this visual exploration; and (ii) perform a discrimination task: a random number of targets (zero to four) were modified (the red circle of the target was truncated by black pixels) and subjects had to report this number by means of button-presses at the end of each trial (one modification on the top right target in the illustrated case). *B*, representative horizontal eye displacements obtained from early and late trials of the voluntary saccade adaptation phase. Each trial required the production of two leftward saccades (grey shading). Note the amplitude reduction of these leftward primary saccades associated with a reduced number of backward correction saccades in the late trial.

Data analysis

Saccade amplitude was computed and transformed into gain values. The saccadic gain was defined as the ratio between the eccentricity of the target relative to the FP and the amplitude of the primary saccade (first saccade after target appearance). Mean gains computed in the pre-adaptation phases of the reactive and voluntary saccade experiments were used to determine baseline saccade properties.

Student's *t* test for independent samples was used to compare the amounts of adaptation obtained in the reactive saccade experiment and in the voluntary saccade experiment. For each subject participating in the test conditions of the reactive and voluntary experiments, Student's *t* test for independent samples was used to compare (i) pre- and post-adaptation gain of antisaccades in the adapted direction and (ii) pre- and post-adaptation gain of antisaccades in the non-adapted direction.

Two ANOVAs were conducted separately for each of these experiments to assess changes in saccadic gain at the population level. The design of these ANOVAs was as follows: one between-subjects factor, 'Experimental Condition' (test *versus* control; $n = 8$ and $n = 8$, respectively, for reactive saccade experiment; $n = 10$ and $n = 10$, respectively, for voluntary saccade experiment); and two within-subjects factors, 'Experimental Phase' (pre- *versus* postadaptation) and 'Saccade Type' (saccades *versus* antisaccades in the adapted direction *versus* anti-saccades in the non-adapted direction).

Significant interactions revealed by the analyses of variance were submitted to *post hoc* breakdown analyses (Newman–Keuls *post hoc* tests).

Significance threshold was fixed to $P < 0.05$ for all statistical analyses.

Results

Reactive and voluntary saccade adaptation

For both reactive and voluntary saccade adaptation experiments, only one saccade direction was adapted. The intrasaccadic backward target step mimicked a systematic overshoot of the primary saccade, and required subjects to produce backward corrective saccades. When repeated, this paradigm led to a progressive shortening of the primary saccade. This progressive decrease of gain during the course of the adaptation phase is illustrated for two representative subjects in Experiment 1 (Fig. 3*A*, black stars) and Experiment 2 (Fig. 4*A*, black stars). The gain of saccades produced in the post-adaptation phase was also reduced. For both reactive saccades and voluntary saccades, this gain decrease between pre-adaptation and post-adaptation phases was statistically significant. ANOVAs performed separately for the two experiments (see Methods) revealed significant interactions between Experimental Condition, Experimental Phase and Saccade Type for both the reactive saccade experiment ($F_{2,26} = 8.5$, $P < 0.01$) and the voluntary saccade experiment ($F_{2,34} = 5.9$, $P < 0.01$). For both experiments, the post-adaptation gain values of saccades performed in the Test Condition were significantly lower than baseline gain values observed before adaptation (Newman–Keuls *post hoc* tests, $P < 0.001$; Figs 3*C* and 4*C*). Furthermore, these gain decreases were due to the adaptive protocol and not to

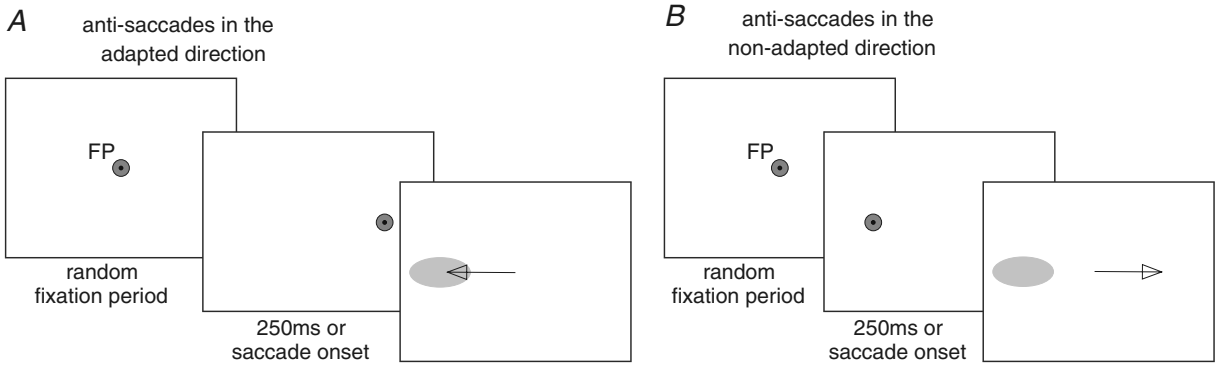

Figure 2. Antisaccades tasks
In the reactive experiment and in the voluntary experiment, antisaccades in the adapted direction (*A*) and anti-saccades in the non-adapted direction (*B*) were tested to determine stage(s) of sensorimotor processing influenced by saccadic adaptation. Subjects were required to produce a saccade directed toward the mirror position of the target with respect to the FP. The FP was turned off simultaneously with the appearance of the target. The target was then either extinguished at saccade onset (reactive experiment) or flashed for 250 ms (voluntary experiment). In each panel, the shaded area designates – only for the sake of illustration, not shown to the subjects – the screen position where the backward target step occurred during the adaptation phase.

non-specific effects (e.g. fatigue or attentional processes). Indeed, no statistically significant change in reactive or voluntary saccade gains occurred for the Control Condition in which no intrasaccadic backward step of the visual stimulus occurred during the pseudo-adaptation phase (Newman–Keuls *post hoc* tests; $P = 0.77$ and $P = 0.48$, respectively). Following adaptation, the gain change of reactive saccades reached −0.17 (S.E.M. 0.02; $n = 8$), corresponding to a reduction of 18.1% of the initial amplitude. The gain change of voluntary saccades reached –0.19 (S.E.M. 0.02; $n = 10$; gain reduction of 18.3%). These gain decreases were not statistically different from each other (Student's *t* test for independent samples; $P = 0.26$).

Experiment 1

Reactive saccade adaptation acts downstream of vector inversion. In the reactive saccade experiment, the gain of antisaccades in the adapted direction decreased between the pre-adaptation phase and the post-adaptation phase for all tested subjects. This gain reduction was statistically significant for 7 out of the 8 subjects (Student's *t* test for independent samples; Fig. 3*B*, empty to filled boxes).

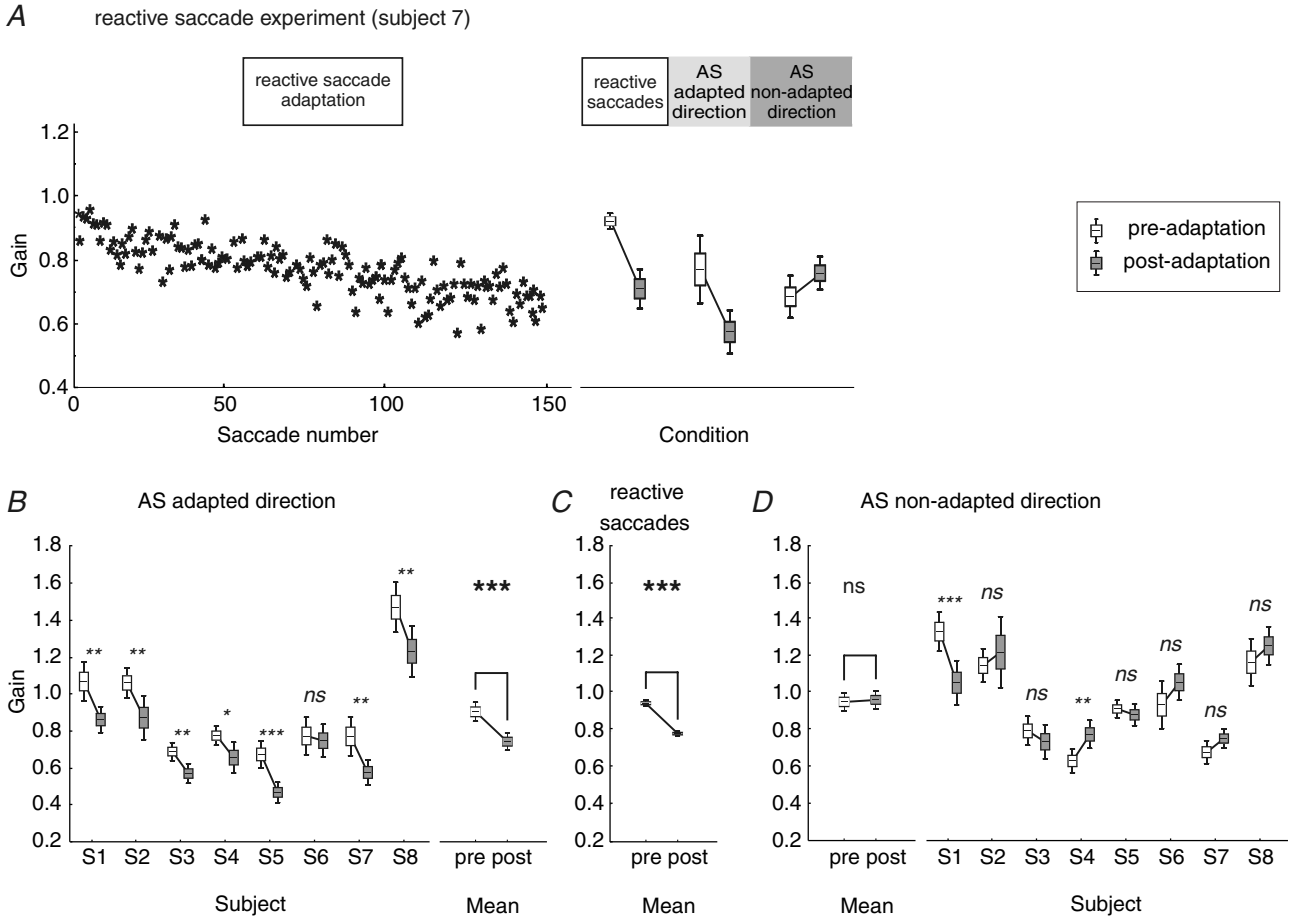

Figure 3. Individual and mean results of the reactive saccade experiment
Empty boxes and filled boxes in *A*, *B* and *C* correspond to pre- and post-adaptation data. *A*, left panel, time course of the reactive saccade gain of a representative subject (S7) during the adaptation phase. Each symbol represents one primary reactive saccade (black star). Right panel, mean gains of reactive saccades, of antisaccades in the adapted direction and of antisaccades in the non-adapted direction, tested in subject S7 before and after the reactive saccade adaptation phase. Boxes represent the standard error of the mean and whiskers represent the 95% confidence interval. *B*, mean gains of antisaccades in the adapted direction tested before and after adaptation for each subject (S1 . . . S8) and for the group (Mean, $n = 8$). Results of Student's *t* test for independent samples for each subject and of ANOVA for means (see text for design) are indicated by asterisks (***$P < 0.001$, **$P < 0.01$, *$P < 0.05$) and ns ($P > 0.05$). *C*, grand means of reactive saccade gains before and after adaptation ($n = 8$). *D*, mean gains of antisaccades in the non-adapted direction tested before and after adaptation for the group (Mean, $n = 8$) and for each subject (S1 . . . S8). Results of ANOVA (see text for design) are indicated by asterisks (***$P < 0.001$) and ns ($P > 0.05$).

On average, this gain change reached −0.16 (S.E.M. 0.02, $n = 8$; gain decrease of 18.0%). At the population level, this gain reduction was statistically significant, as revealed by the *post hoc* breakdown of the interaction between Experimental Condition, Experimental Phase and Saccade Type (ANOVA, Newman–Keuls *post hoc* test; $P < 0.001$). This effect was specifically related to adaptation because no statistically significant change in antisaccade gain occurred in the Control Condition (Newman–Keuls *post hoc* test; $P = 0.75$). Because these antisaccades were initiated by a target presented in the non-adapted direction but were performed in the adapted direction, our results demonstrate that reactive saccade adaptation acts downstream of vector inversion.

Reactive saccade adaptation does not act upstream of vector inversion. After the adaptation of reactive saccades, the gain changes of the antisaccades in the non-adapted direction were very variable. Only 3 out of 8 subjects presented a gain decrease congruent with the adaptive procedure (statistically significant in only one case; Student's *t* test for independent samples; Fig. 3*D*). On average, the gain of antisaccades in the non-adapted direction did not change significantly between the pre- and post-adaptation phases (−0.02, S.E.M. 0.05, $n = 8$; gain *increase* of 1.8%; ANOVA, Newman–Keuls *post hoc* test; $P = 0.96$; Fig. 3*D*). Similarly the gain of these antisaccades did not change after the pseudo-adaptation phase of the Control Condition (Newman–Keuls *post hoc* test; $P = 0.49$). These antisaccades were initiated by a target presented along the adapted direction, but were produced toward the opposite, non-adapted direction. The absence of an average gain change thus shows that reactive saccade adaptation does not act upstream of vector inversion.

Experiment 2

Voluntary saccade adaptation acts downstream of vector inversion. In the voluntary saccade experiment, the gain of antisaccades in the adapted direction decreased between the pre- and the post-adaptation phases for 9 out of the 10 subjects. This gain reduction was statistically significant for 6 out of these 9 subjects (Student's *t* test for independent samples; Fig. 4*B*). On average, this gain decrease reached −0.14 (S.E.M. 0.04, $n = 10$; gain reduction of 18.5%) and was statistically significant, as revealed by the *post hoc* breakdown of the interaction between Experimental Condition, Experimental Phase and Saccade Type (ANOVA, Newman–Keuls *post hoc* test; $P < 0.001$). This effect was specifically related to adaptation because no statistically significant change of antisaccade gain occurred in the control condition (Newman–Keuls *post hoc* test;

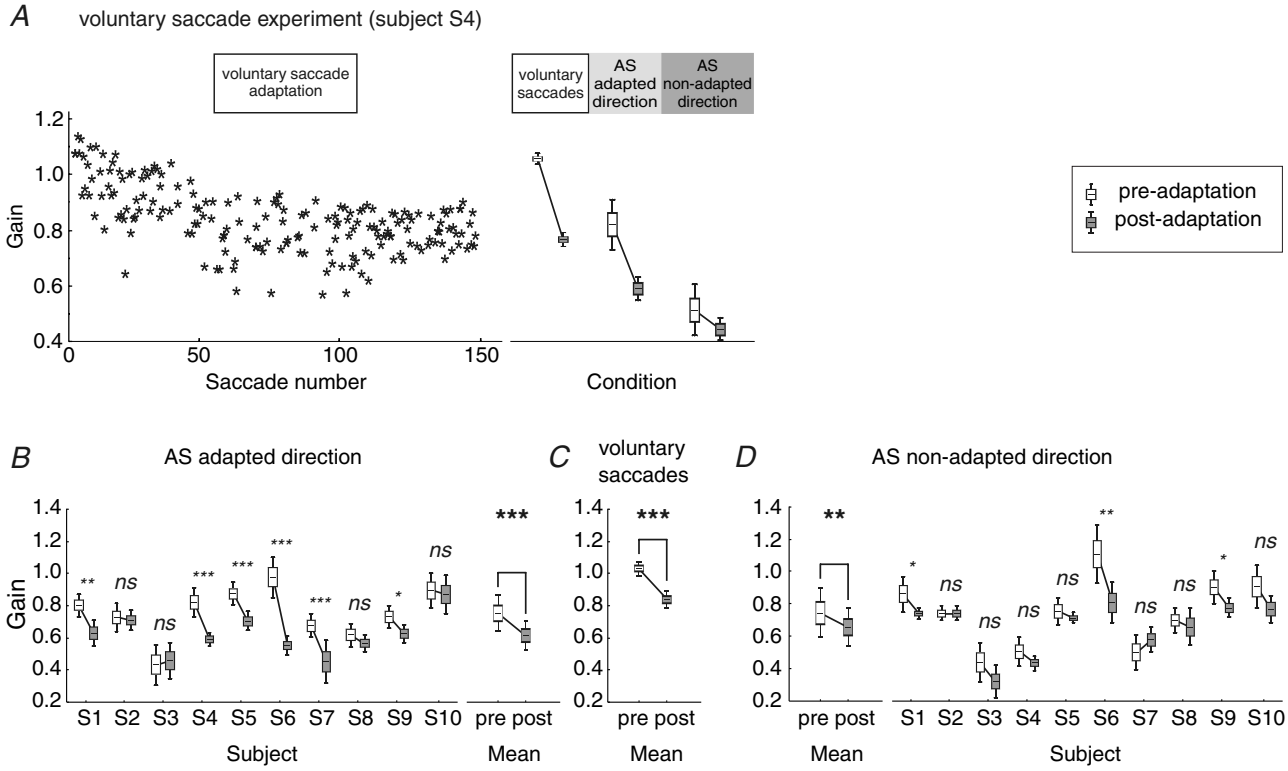

Figure 4. Individual and mean results of the voluntary saccade experiment
Same conventions as for Fig. 3.

$P = 0.31$). This result demonstrates that voluntary saccade adaptation acts downstream of vector inversion.

Voluntary saccade adaptation also acts upstream of vector inversion. The results of the experimental condition testing the effect of voluntary saccade adaptation on the gain of antisaccades in the non-adapted direction are presented in Fig. 4*D*. For 8 of the 10 subjects tested in this condition, the gain of antisaccades in the non-adapted direction decreased. This gain reduction was of a smaller magnitude than the gain reduction reported above for the antisaccades in the adapted direction for both reactive and voluntary experiments. When tested at the individual level, the gain reduction reached significance for 3 of the 8 subjects (Student's *t* test for independent samples; Fig. 4*D*). Nevertheless, on average over the group of subjects, this decrease was statistically significant (ANOVA, Newman–Keuls *post hoc* test; $P = 0.01$; Fig. 4*D*), and reached −0.09 (S.E.M. 0.03, $n = 10$; gain reduction of 11.7%). This effect was specifically related to adaptation, as no statistically significant change in antisaccade gain occurred in the Control Condition (Newman–Keuls *post hoc* test; $P = 0.12$). These antisaccades were initiated by a target presented along the adapted direction, but produced in the opposite, non-adapted, direction. The statistically significant gain change of these antisaccades revealed at the population level implies that voluntary saccade adaptation does not act only downstream but also upstream of vector inversion.

Discussion

The production of antisaccades requires a vector inversion that represents a clear landmark in the sensorimotor transformation (Hallett, 1978; Munoz & Everling, 2004). Additionally, saccadic adaptation is a direction specific phenomenon (Hopp & Fuchs, 2004; Alahyane *et al.* 2008). Taking advantage of these features, the present study allows determining whether saccadic adaptation acts upstream or downstream of the vector inversion underlying the antisaccade task. We show that adaptive shortening of voluntary saccades performed in a single direction leads to amplitude shortening of antisaccades in both directions, whereas adaptation of reactive saccades only affects antisaccades in the adapted direction. We conclude that the adaptation of voluntary saccades has a distributed influence on sensorimotor transformation, acting upstream and downstream of vector inversion whereas the adaptation of reactive saccades acts only downstream of vector inversion.

Reactive and voluntary saccade experiments lead to clearly distinct pattern of results. As previously mentioned these two experiments were performed independently and used slightly different protocols. The first difference is the amplitude of adapted saccades and of antisaccades (8 deg in the reactive saccade experiment *versus* 20 deg in the voluntary saccade experiment). Although the gain reductions achieved after adaptation were very similar for reactive saccades (18.1%) and voluntary saccades (18.3%), one may ask whether this amplitude difference could have influenced the present results? In the monkey, Straube *et al.* (1997) showed that the rate and amount of adaptation were similar when saccades of different amplitudes were adapted (5 deg, 10 deg and 15 deg). Additionally, in our previous study (Cotti *et al.* 2007) which also addressed the sensorimotor stages modified by saccadic adaptation, different amplitudes were tested. For both reactive and voluntary saccades, the patterns of transfer of saccadic adaptation to hand movements did not depend on saccadic amplitude. The second difference between the two experiments lies in the pre- and post-tests performed to evaluate the transfer of adaptation to antisaccades. Whereas the reactive saccade experiment used a mixed design, i.e. saccades and antisaccades in the adapted and non-adapted directions were presented in a pseudo-random order, the voluntary saccade experiment used a blocked design (pro-saccades and antisaccades were performed in separate blocks of trials). Additionally, whereas in both experiments antisaccades were triggered in reaction to the sudden onset of the target, target offset slightly differed: in the reactive saccade experiment, saccade onset extinguished the target whereas in the voluntary saccade experiment, the target was flashed for a fixed duration (250 ms). Several analyses were carried out to control for any effect of these paradigm differences. First, it is worth noting that no gain change occurred for antisaccades in the control condition of the two experiments. Thus the different patterns of gain changes observed in the Test (adaptation) Condition between the two experiments are not likely to originate from a difference of experimental design. Second, the antisaccades produced using different designs (mixed *versus* blocked) proved to have the same characteristics. Comparisons (Student's *t* test for independent samples) of the pre-adaptation antisaccades gain and latency between the reactive and voluntary experiments revealed no significant difference ($P > 0.05$), for both antisaccades produced in the adapted and non-adapted directions. For all these reasons, we are confident that the different patterns of results obtained in the two experiments were specifically related to the type, i.e. reactive and voluntary, of the saccade that was submitted to adaptation.

The first experiment showed that adaptation of reactive saccades acts downstream of the vector inversion required by the antisaccade task. This confirmed and extended previous proposals that the adaptive processes act at the level of the superior colliculus or downstream (e.g. brainstem reticular formation) (Frens & Van Opstal, 1997; Edelman & Goldberg, 2002; Hopp & Fuchs, 2002, 2006;

Alahyane *et al.* 2004, 2007; Takeichi *et al.* 2007). The second part of this experiment, i.e. the test of antisaccades in the non-adapted direction, further suggests that the adaptation of reactive saccades do not involve early stages of information processing. This is in agreement with the absence of transfer of reactive saccade adaptation to hand pointing movements demonstrated previously (Kröller *et al.* 1999; Cotti *et al.* 2007; Hernandez *et al.* 2008).

Several studies nevertheless reported visual mislocalizations after reactive saccadic adaptation (Bahcall & Kowler, 1999; Awater *et al.* 2005; Collins *et al.* 2007; Bruno & Morrone, 2007; Georg & Lappe, 2009). (We discuss below the fact that, from our point of view, the 'volitional' saccades studied by Collins *et al.* (2007) could be considered as sharing more properties with reactive saccades than voluntary saccades.) Since all the reported mislocalizations occurred only when the localization task required the production of a saccade (Awater *et al.* 2005; Collins *et al.* 2007; Georg & Lappe, 2009), these mislocalizations cannot originate in changes of purely perceptual processes. Furthermore, Collins *et al.* (2007) reported that the pattern of localization shifts was very similar to the structure of the non-uniform adaptation field thus rendering unlikely an influence of signals related to the executed saccade (e.g. efference copy) that would have induced a uniform shift. Collins *et al.* then proposed that the metrics of the saccade required to acquire a target contribute to the localization of that target in space (see also the detailed analysis of this adaptation-induced shift in Georg & Lappe, 2009). If these studies allow the conclusion that sensorimotor transformations involved in saccade generation participate in target localization, the perceptual or motor origin of the adaptively induced mislocalization remains undetermined. Indeed the pro-saccade task used in these studies implies the spatial overlap of perceptual and motor processes. Our present study brings further insight into this question by demonstrating that antisaccades in the non-adapted direction are not modified by reactive saccade adaptation. This result indicates that the estimate of the upcoming saccade metrics is provided by processes performed downstream of vector inversion.

Moidell & Bedell (1988) nevertheless reported a significant error in target localization without saccade execution. It has to be noted that this target mislocalization was very small (about 15−20% of the adaptive change of saccade amplitude) and reached significance potentially because the statistical comparison was performed between adaptive shortening and lengthening of saccadic amplitude (see Table 1 in Moidell & Bedell, 1988). Another problem with the rationale of this comparison method is that numerous studies have now demonstrated differences in shortening and lengthening adaptive processes (e.g. Semmlow *et al.* 1989; Straube *et al.* 1997; Scudder *et al.* 1998; Noto *et al.* 1999; Alahyane *et al.* 2004; Kojima *et al.* 2004; Golla *et al.* 2008). Thus, at best the study of Moidell & Bedell (1988) only suggests a possible minor effect on target localization of the shortening amplitude adaptation. This explanation agrees with the results and conclusions of Hernandez *et al.* (2008) stating that adaptive shortening (in contrast to adaptive lengthening) of reactive saccades can be fully accounted for by sensorimotor transformation changes, i.e. acting downstream of visual registration of the stimulus.

During the second experiment, the gain change of antisaccades in the non-adapted direction observed after adaptation of voluntary saccades suggests that adaptation acts upstream of the vector inversion required by the antisaccade task. This change in an early stage of sensorimotor transformation is consistent with the change in hand pointing movements that we have demonstrated previously using a voluntary saccade adaptation protocol identical to that used in the present study (Cotti *et al.* 2007). Interestingly, the gain change of the hand pointing movements observed in this previous study was not significantly different from the gain change of antisaccades in the non-adapted direction observed in the present study (Student's t test for independent samples; $P = 0.54$). This result provides strong evidence that voluntary saccade adaptation modifies a stage participating in target localization processes that are common to different effectors (i.e. eye and hand). In addition, voluntary saccade adaptation also transferred to antisaccades in the adapted direction. This has to be paralleled by the fact that the transfer of voluntary saccade adaptation to hand movements and to antisaccades in the non-adapted direction was only partial. These two sets of observations suggest that voluntary saccade adaptation not only acts upstream of vector inversion but also affects downstream stages of the sensorimotor transformation.

The recent study of Collins *et al.* (2008) provided results that could apparently lead to the interpretation – opposite to our conclusion – that no change occurs upstream of vector inversion after voluntary saccade adaptation. Indeed, in this study, adaptation of saccades that were considered to be of the 'volitional type' did not modify antisaccades produced in the non-adapted direction. However, this apparent discrepancy may be explained by the type of saccades these authors have actually tested. The overlap paradigm used in this study may not be the most appropriate for eliciting internally triggered saccades (i.e. voluntary saccades). In this paradigm, saccade initiation is based on an exogenous 'go' signal (extinction of the fixation point) rather than on an endogenous decision signal as in our study. The possibility that this paradigm favoured the production of reactive externally triggered saccades is first supported by the gain values reported for saccades tested before adaptation. Latency values provide a second indication, although not a strict criterion, because voluntary saccades

latency includes the period of previous eye fixation, whereas reactive saccades latency does not. The values reported by Collins *et al.* (2008; average gain: 0.89 and average latency: 198 ms; see also their Fig. 2) are much closer to the range of reactive saccades than to the range of voluntary saccades (Smit *et al.* 1987; Collewijn *et al.* 1988; Deubel, 1995; Walker & McSorley, 2006; Alahyane *et al.* 2007; see also values given by the same authors in Collins & Dore-Mazars, 2006). The possibility that the saccades studied by Collins *et al.* (2008) share properties of reactive saccades is entirely consistent with the full transfer of adaptation to antisaccades in the adapted direction that is reported both in their study and in our reactive saccade experiment. This statement concerning the type of saccade actually adapted also holds for the study of Collins *et al.* (2007; see the discussion part concerning reactive saccades).

What could be the neurophysiological substrates of the influence of voluntary saccade adaptation upstream of the vector inversion? Theoretically voluntary saccade adaptation could influence the frontal oculomotor areas which are strongly involved in the antisaccade task (see Munoz & Everling, 2004, for a review). The dorso-lateral prefrontal cortex (DLPFC) and frontal eye fields (FEF) are postulated to participate in the preparatory set for the antisaccade task, namely inhibition of the reactive pro-saccade (Guitton *et al.* 1985; Pierrot-Deseilligny *et al.* 1991; Everling & Munoz, 2000; Condy *et al.* 2007) and control of sensorimotor transformation performed in parietal areas (Funahashi *et al.* 1993; Barash, 2003). The supplementary eye fields (SEF) could be particularly concerned with the generation of the antisaccade motor commands (Schlag-Rey *et al.* 1997). Furthermore, interactions occur between eye- and hand-related signals in these structures, particularly in the FEF (see Thura *et al.* 2008), which would account for the transfer of voluntary saccade adaptation to hand movements observed in our previous study (Cotti *et al.* 2007). However, although not definitive, current knowledge about the neural bases of antisaccade generation suggests that these frontal areas are likely to be situated downstream of vector inversion (see Introduction, Barash, 2003). This would rule out a potential effect of voluntary saccade adaptation at the level of these frontal areas. Supporting this assertion, voluntary saccade adaptation transfers to reactive saccades (from 30 to 40%: Deubel, 1995; Erkelens & Hulleman, 1993; Fujita *et al.* 2002 to more than 80%: Collins *et al.* 2006; Alahyane *et al.* 2007; Cotti *et al.* 2007) and the generation of reactive saccades depends mainly on a direct parieto-collicular pathway that does not rely on oculomotor frontal areas involvement (Gaymard *et al.* 1998; Rafal, 2006). In sum, data available so far do not favour the hypothesis that voluntary saccade adaptation involves the frontal cortex.

Another possibility is that the IPS (human homologue of monkey LIP), as a potential locus of the antisaccades vector inversion (see Introduction), could be directly influenced by voluntary saccade adaptation. Indeed, it has been implicated in the control of both eye and hand movements (Astafiev *et al.* 2003; Levy *et al.* 2007). Centers involved in voluntary saccade adaptation may also include structures located upstream of IPS, such as the parieto-occipital junction (POJ, human homologue of areas V6 and V6A in monkeys). Indeed, POJ (V6/V6A complex) has been shown to be involved in the localization of peripheral targets, particularly in the context of eye and hand movements (Galletti *et al.* 1999*a*,*b*; Prado *et al.* 2005).

Although our results do not allow us to distinguish between these different possible neural candidates (frontal or parietal oculomotor areas), it is the first study to provide testable predictions for future imaging studies in humans or studies at the single neuron level in monkeys: changes of activity in oculomotor cortical structures are in particular more likely to be observed when adapted saccades are of the voluntary type.

To conclude, the association of a classical saccadic adaptation paradigm with an antisaccade task allowed us to confirm that reactive saccade adaptation involves neural structures near the saccadic motor output and to demonstrate that voluntary saccade adaptation has a distributed influence on sensorimotor transformations, acting both upstream and downstream of the vector inversion required by the production of antisaccades.

References

Alahyane N, Devauchelle A-D, Salemme R & Pélisson D (2008). Spatial transfer of adaptation of scanning voluntary saccades in humans. *Neuroreport* **19**, 37–41.

Alahyane N, Koene A & Pelisson D (2004). Transfer of adaptation from visually guided saccades to averaging saccades elicited by double visual targets. *Eur J Neurosci* **20**, 827–836.

Alahyane N, Salemme R, Urquizar C, Cotti J, Guillaume A, Vercher JL & Pelisson D (2007). Oculomotor plasticity: Are mechanisms of adaptation for reactive and voluntary saccades separate? *Brain Res* **1135**, 107–121.

Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC & Corbetta M (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *J Neurosci* **23**, 4689–4699.

Awater H, Burr D, Lappe M, Morrone MC & Goldberg ME (2005). Effect of saccadic adaptation on localization of visual targets. *J Neurophysiol* **93**, 3605–3614.

Bahcall DO & Kowler E (1999). Illusory shifts in visual direction accompany adaptation of saccadic eye movements. *Nature* **400**, 864–866.

Barash S (2003). Paradoxical activities: insight into the relationship of parietal and prefrontal cortices. *Trends Neurosci* **26**, 582–589.

Bock O & Schneider S (2002). Sensorimotor adaptation in young and elderly humans. *Neurosci Biobehav Rev* **26**, 761–767.

Bruno A & Morrone MC (2007). Influence of saccadic adaptation on spatial localization: comparison of verbal and pointing reports. *J Vis* **7**, 16.1–16.13.

Collewijn H, Erkelens CJ & Steinman RM (1988). Binocular co-ordination of human vertical saccadic eye movements. *J Physiol* **404**, 183–197.

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

Collins T, Dore-Mazars K & Lappe M (2007). Motor space structures perceptual space: evidence from human saccadic adaptation. *Brain Res* **1172**, 32–39.

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

Condy C, Wattiez N, Rivaud-Péchoux S, Tremblay L & Gaymard B (2007). Antisaccade deficit after inactivation of the principal sulcus in monkeys. *Cereb Cortex* **17**, 221–229.

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

Deubel H (1987). Adaptivity of gain and direction in oblique saccades. In *Eye Movements: From Physiology to Cognition*, ed. O'Regan J & Levy-Schoen A, pp. 181–191. North Holland, Amsterdam.

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

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

Erkelens CJ & Hulleman J (1993). Selective adaptation of internally triggered saccades made to visual targets. *Exp Brain Res* **93**, 157–164.

Everling S & Munoz DP (2000). Neuronal correlates for preparatory set associated with pro-saccades and antisaccades in the primate frontal eye field. *J Neurosci* **20**, 387–400.

Frens MA & Van Opstal AJ (1994). Transfer of short-term adaptation in human saccadic eye-movements. *Exp Brain Res* **100**, 293–306.

Frens MA & Van Opstal AJ (1997). Monkey superior colliculus activity during short-term saccadic adaptation. *Brain Res Bull* **43**, 473–483.

Fujita M, Amagai A, Minakawa F & Aoki M (2002). Selective and delay adaptation of human saccades. *Cogn Brain Res* **13**, 41–52.

Funahashi S, Chafee MV & Goldman-Rakic PS (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed antisaccade task. *Nature* **365**, 753–756.

Galletti C, Fattori P, Gamberini M & Kutz DF (1999*a*). The cortical visual area V6: brain location and visual topography. *Eur J Neurosci* **11**, 3922–3936.

Galletti C, Fattori P, Kutz DF & Gamberini M (1999*b*). Brain location and visual topography of cortical area V6A in the macaque monkey. *Eur J Neurosci* **11**, 575–582.

Gauthier GM, Blouin J, Bourdin C & Vercher JL (2007). Adaptive control: a review of the ability to acquire and maintain high sensorimotor performance. *Comput Biol Med* **37**, 989–1000.

Gaymard B, Ploner CJ, Rivaud S, Vermersch AI & Pierrot-Deseilligny C (1998). Cortical control of saccades. *Exp Brain Res* **123**, 159–163.

Georg K & Lappe M (2009). Effects of saccadic adaptation on visual localization before and during saccades. *Exp Brain Res* **192**, 9–23.

Golla H, Tziridis K, Haarmeier T, Catz N, Barash S & Thier P (2008). Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. *Eur J Neurosci* **27**, 132–144.

Guitton D, Buchtel HA & Douglas RM (1985). Frontal-lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res* **58**, 455–472.

Hallett PE (1978). Primary and secondary saccades to goals defined by instructions. *Vision Res* **18**, 1279–1296.

Hernandez TD, Levitan CA, Banks MS & Schor CM (2008). How does saccade adaptation affect visual perception? *J Vis* **8**, 1–16.

Hopp JJ & Fuchs AF (2002). Investigating the site of human saccadic adaptation with express and targeting saccades. *Exp Brain Res* **144**, 538–548.

Hopp JJ & Fuchs AE (2004). The characteristics and neuronal substrate of saccadic eye movement plasticity. *Prog Neurobiol* **72**, 27–53.

Hopp JJ & Fuchs AF (2006). Amplitude adaptation occurs where a saccade is represented as a vector and not as its components. *Vision Res* **46**, 3121–3128.

Kojima Y, Iwamoto Y & Yoshida K (2004). Memory of learning facilitates saccadic adaptation in the monkey. *J Neurosci* **24**, 7531–7539.

Kröller J, De Graaf JB, Prablanc C & Pelisson D (1999). Effects of short-term adaptation of saccadic gaze amplitude on hand-pointing movements. *Exp Brain Res* **124**, 351–362.

Levy I, Schluppeck D, Heeger DJ & Glimcher PW (2007). Specificity of human cortical areas for reaches and saccades. *J Neurosci* **27**, 4687–4696.

McLaughlin SC (1967). Parametric adjustment in saccadic eye movements. *Percept Psychophys* **2**, 359–361.

Medendorp WP, Goltz HC & Vilis T (2005). Remapping the remembered target location for antisaccades in human posterior parietal cortex. *J Neurophysiol* **94**, 734–740.

Miller JM, Anstis T & Templeton WB (1981). Saccadic plasticity – parametric adaptive-control by retinal feedback. *J Exp Psychol Hum Percept Perform* **7**, 356–366.

Moidell BG & Bedell HE (1988). Changes in oculocentric visual direction induced by the recalibration of saccades. *Vision Res* **28**, 329–336.

Moon SY, Barton JJS, Mikulski S, Polli FE, Cain MS, Vangel M, Hamalainen MS & Manoach DS (2007). Where left becomes right: a magnetoencephalographic study of sensorimotor transformation for antisaccades. *Neuroimage* **36**, 1313–1323.

Munoz DP & Everling S (2004). Look away: The antisaccade task and the voluntary control of eye movement. *Nat Rev Neurosci* **5**, 218–228.

Noto CT, Watanabe S & Fuchs AF (1999). Characteristics of simian adaptation fields produced by behavioral changes in saccade size and direction. *J Neurophysiol* **81**, 2798–2813.

Nyffeler T, Rivaud-Pechoux S, Pierrot-Deseilligny C, Diallo R & Gaymard B (2007). Visual vector inversion in the posterior parietal cortex. *Neuroreport* **18**, 917–920.

Pierrot-Deseilligny C, Rivaud S, Gaymard B & Agid Y (1991). Cortical control of memory-guided saccades in man. *Exp Brain Res* **83**, 607–617.

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H & Perenin MT (2005). Two cortical systems for reaching in central and peripheral vision. *Neuron* **48**, 849–858.

Rafal RD (2006). Oculomotor functions of the parietal lobe: Effects of chronic lesions in humans. *Cortex* **42**, 730–739.

Raymond JL (1998). Learning in the oculomotor system: from molecules to behavior. *Curr Opin Neurobiol* **8**, 770–776.

Schlag-Rey M, Amador N, Sanchez H & Schlag J (1997). Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature* **390**, 398–401.

Scudder CA, Batourina EY & Tunder GS (1998). Comparison of two methods of producing adaptation of saccade size and implications for the site of plasticity. *J Neurophysiol* **79**, 704–715.

Semmlow JL, Gauthier GM & Vercher JL (1989). Mechanisms of short-term saccadic adaptation. *J Exp Psychol Hum Percept Perform* **15**, 249–258.

Smit AC, Van Gisbergen JA & Cools AR (1987). A parametric analysis of human saccades in different experimental paradigms. *Vision Res* **27**, 1745–1762.

Straube A, Fuchs AF, Usher S & Robinson FR (1997). Characteristics of saccadic gain adaptation in rhesus macaques. *J Neurophysiol* **77**, 874–895.

Takeichi N, Kaneko CRS & Fuchs AF (2007). Activity changes in monkey superior colliculus during saccade adaptation. *J Neurophysiol* **97**, 4096–4107.

Thura D, Hadj-Bouziane F, Meunier M & Boussaoud D (2008). Hand position modulates saccadic activity in the frontal eye field. *Behav Brain Res* **186**, 148–153.

Walker R & McSorley E (2006). The parallel programming of voluntary and reflexive saccades. *Vision Res* **46**, 2082–2093.

Wolpert DM, Ghahramani Z & Flanagan JR (2001). Perspectives and problems in motor learning. *Trends Cogn Sci* **5**, 487–494.

Zhang MS & Barash S (2000). Neuronal switching of sensorimotor transformations for antisaccades. *Nature* **408**, 971–975.

Zhang MS & Barash S (2004). Persistent LIP activity in memory antisaccades: Working memory for a sensorimotor transformation. *J Neurophysiol* **91**, 1424–1441.

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