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Functional activation of the cerebral cortex related to sensorimotor  
adaptation of reactive and voluntary saccades.

**Abbreviated title:** Cerebral cortex and saccadic adaptation

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## **Abstract**

Potentially dangerous events in the environment evoke automatic ocular responses, called reactive saccades. Adaptation processes, which maintain saccade accuracy against various events (e.g. growth, aging, neuro-muscular lesions), are to date mostly relayed to cerebellar activity. Here we demonstrate that adaptation of reactive saccades also involves cerebral cortical areas. Moreover, we provide the first identification of the neural substrates of adaptation of voluntary saccades, representing the complement to reactive saccades for the active exploration of our environment. A fMRI approach was designed to isolate adaptation from saccade production: an adaptation condition in which the visual target stepped backward 50 ms after saccade termination was compared to a control condition where the same target backstep occurred 500 ms after saccade termination. Subjects were tested for reactive and voluntary saccades in separate sessions. Multi-voxel pattern analyses of fMRI data from previously-defined regions of interests (ROIs) significantly discriminated between adaptation and control conditions for several ROIs. Some of these areas were revealed for adaptation of both saccade categories (cerebellum, frontal cortex), whereas others were specifically related to reactive saccades (temporo-parietal junction, hMT+/V5) or to voluntary saccades (medial and posterior areas of intra-parietal sulcus). These findings critically extend our knowledge on brain motor plasticity by showing that saccadic adaptation relies on an hitherto unknown contribution of the cerebral cortex.

## **Highlights:**

- Saccadic adaptation elicits fMRI activation in the cerebellum and cerebral cortex
- The neural substrates of adaptation are specific of the saccade type
- Cortical areas TPJ and hMT+/V5 are activated for reactive saccades
- Cortical parietal areas are activated for voluntary saccades

**Keywords:** fMRI, multi-voxel pattern classification, reactive saccades, saccadic adaptation, voluntary saccades.

## **1. Introduction**

Interacting with the environment is one of the most critical abilities of animals to survive. To maintain over the long-term efficient action performance despite modifications related to aging, growth, or eventually to lesions, the brain has to ensure optimal communication between sensory and motor systems. Sensorimotor adaptation processes are particularly critical for saccadic eye movements subtending our visual perception because saccades are too brief to allow for on-line trajectory correction by sensory feedback. Saccadic adaptation is also a well-established model to study brain plasticity, thanks to double-step target paradigms (modified from McLaughlin, 1967) in which a saccadic error is repeatedly produced by shifting the position of a visual target during the saccade (for reviews Hopp and Fuchs, 2004; Iwamoto and Kaku, 2010; Pélisson et al., 2010; Schubert and Zee 2010).

The neural substrates of adaptation of saccades elicited by sudden presentation of a visual target (reactive saccades, RS) are still only partly understood, mostly amounting to an involvement of the cerebellum. Evidence for this cerebellar involvement comes from monkey studies (for reviews Robinson et al., 2002; Hopp and Fuchs, 2004; Iwamoto and Kaku, 2010) and from human studies using positron emission tomography (PET) (Desmurget et al., 1998), transcranial magnetic stimulation (TMS) studies (Jenkinson and Miall, 2010; Panouillères et al., in press) or behavioural tests in cerebellar-damaged patients (Straube et al., 2001; Alahyane et al., 2008; Golla et al., 2008). In contrast, the role of the cerebral cortex in RS adaptation has only been addressed recently by Blurton et al. (2012) who reported an fMRI activation in the supplementary eye fields and in the temporal and insular cortices.

Getting a complete picture of saccadic adaptation also requires taking into consideration the different saccade categories. In everyday life, reactive saccades are outnumbered by saccades generated endogenously while scanning a stable environment. Despite this, the neural bases of adaptation of such scanning saccades, as well as of other types of voluntary saccades (VS), have never been directly investigated. In addition, a growing body of behavioural data argues against any extrapolation of our understanding of adaptation mechanisms from reactive saccades to voluntary saccades (for review Pélisson et al., 2010). In particular, the moderate transfer of reactive saccades adaptation to voluntary saccades suggests separate plasticity mechanisms (Deubel, 1995, 1999;

Fujita et al 2002; Collins and Doré-Mazars, 2006; Alahyane et al., 2007; Hopp and Fuchs, 2010; Zimmermann and Lappe 2009). The pattern of adaptation transfer to arm pointing movements and to anti-saccades (Kröller et al., 1999; Cotti et al., 2007; 2009; Hernandez et al., 2008), and to visual perception (Zimmermann and Lappe, 2009; Garaas and Pomplun, 2011), further indicate that adaptation of voluntary saccades recruits sensorimotor circuits located upstream those supporting reactive saccades adaptation, possibly involving occipito-parietal areas (Pélisson et al., 2010).

In summary, the literature provides consistent supports for a contribution of the cerebellum in saccadic adaptation. In contrast, the possible role of extra-cerebellar structures, although suggested by growing behavioural evidence, still lacks direct experimental demonstration. In addition, the hypothesis dating back to Deubel (1995) and suggesting different neural substrates for the adaptive control of different saccade categories, also lacks direct evidence. Answers to these questions are mandatory in order to ultimately understand the neural underpinnings of the two components of saccadic adaptation, i.e. the processing of error signals and the plastic changes of oculomotor commands. Thus, the present study aimed at identifying the brain substrates of adaptation for both reactive and voluntary saccades, using an fMRI study designed to differentiate adaptation from saccade production processes. Our rationale builds upon the fact that the amount of adaptation induced in the double-step target paradigm strongly decreases as the moment of target step is delayed relative to saccade termination (Bahcall and Kowler, 2000; Fujita et al., 2002). Thanks to multivoxel pattern analysis of fMRI data, we found that, beside the expected activity in the cerebellum, saccadic adaptation involves also the cerebral cortex, with specific cortical areas for each saccade category.

## **2. Materials and Methods**

### **2.1 Subjects**

Six subjects (3 males and 3 females) with normal or corrected to normal vision volunteered for this study (mean age  $\pm$  SD: 26 $\pm$ 3). Subjects gave informed written consent and were paid for their participation. The Comity for Person Protection (CPP, Lyon, France) approved all procedures.

## **2.2 Experimental set up and stimuli**

Experiments were performed at the CERMEP (Centre d'Etude et de Recherche Multimodal Et Pluridisciplinaire en imagerie du vivant, Bron, France) using a 1.5-Tesla Siemens Sonatra MRI scanner. A panel of light-emitting diodes (LEDs, 3mm diameter) located behind the magnet bore was seen by subjects through a tilted mirror secured onto the head coil. Eye movements were recorded with an infra-red eye tracker system (ISCAN) at a 240 Hz frequency. The camera of the eye tracker was located behind the magnet below the LED panel and monitored the subjects' left eye image through the same mirror. After calibration, by having the subjects look at 9 points of an array covering the LED panel, horizontal and vertical eye position was computed on-line during all functional scanning sessions. A real-time interface controlled by an in-house software allowed triggering of the MR sequence, continuous monitoring of eye movements, on-line detection of the onset and offset of primary saccades (as determined when the eye velocity exceeded and then decreased below a 80 deg/s threshold), changes of the targets (LEDs) illumination and storage of eye movements and target events for off-line analyses.

## **2.3 General design**

Each subject performed a reactive saccades (RS) task, a voluntary saccades (VS) task (scanning saccades), and a saccade localizer task. RS and VS were tested in two different sessions separated by at least two weeks to prevent any cross-over effect between sessions (according to the known duration of adaptation retention, Alahyane and Pélisson, 2005), and the saccade localizer task was evenly split over the two sessions (2 runs each).

In RS and VS tasks, subjects performed saccades directed to a visual target in the left hemifield. Thus, only leftward saccades were adapted and, because adaptation does not transfer to saccades made in the opposite direction (Miller et al., 1981; Deubel et al., 1986; Albano, 1996; Frens and vanOpstal, 1994), this allowed disclosing the laterality of neural substrates relative to the adapted saccade. In addition, to elicit brain activation specifically related to saccadic adaptation, we used a 2 (target delay) x 2 (target step) factorial design. Indeed, according to the literature (Bahcall and Kowler, 2000; Fujita et al., 2002) and to a pilot experiment testing RS adaptation in our 6 subjects, adaptation processes should be efficiently elicited with a short delay of stepped target presentation relative to saccade offset but not with a long delay. Thus, we manipulated this target delay factor and set it at 50

or 500 ms in separate blocks of trials (Figure 1a). We used 50 ms as the shortest delay to insure that the processing of the stepped target was unaffected by the saccadic suppression phenomenon, like with the 500 ms delay. In addition, to avoid that the repetition of these backstep target trials progressively saturates subjects' adaptation capabilities during a scanning session, an equal number of blocks with a stationary target (single-step) was randomly interleaved with double-step blocks (target step factor). Importantly, comparison between single-step blocks with a 50 ms or a 500 ms post-saccadic target delay also allowed us to test any direct effect of the target delay factor on brain activity.

For each subject, we first used the general linear model (GLM) approach to perform a whole-brain analysis of the RS and VS scans, contrasting DS50 versus DS500 and SS50 versus SS500 blocks. Second, a whole-brain GLM analysis of the Saccade Localizer scan identified regions of interest (ROI) related to saccade generation and visual processing (see 2.5). For each ROI, the fMRI data collected in RS and VS scans were then separately analysed with a multivariate pattern analysis (MVPA). MVPA is a sensitive method based on decoding spatio-temporal patterns of activated voxels (see Norman et al. (2006) for a review). This method consisted, separately for RS and VS scans, in training each ROI to discriminate trials blocks with adaptation (stepped target reappearing 50 ms after saccade termination) versus trials blocks without adaptation (stepped target delay of 500ms). This training was performed on the data of five of the 6 fMRI runs, and the classification performance (=prediction accuracy) was computed on the remaining run (see 2.6.3). The same procedure was reiterated, each time leaving a new run out, and the mean prediction accuracy averaged over 5 repetitions. These mean values were then compared with a traditional GLM univariate analysis and with a shuffle analysis (where protocols are randomly assigned to the activation pattern). A statistically larger MVPA prediction accuracy than in the univariate and the shuffle analyses was taken as a conservative criterion for considering a significant ROI involvement in the saccadic adaptation process. This whole procedure was also applied to assess ROI involvement in saccadic de-adaptation by contrasting in the stationary target (single-step) condition between blocks of trials with a 50ms or a 500ms post-saccadic target delay. This general procedure is detailed in the following paragraphs.

## **2.4 Saccade tasks**

Each RS and VS task comprised four protocols, presented in different blocks of trials: double-step with

short delay (DS50), double-step with long delay (DS500), single-step with short delay (SS50) and single-step with long delay (SS500). The reduction of saccade amplitude related to adaptation is expected to be larger in DS50 (“adaptation protocol”) than in DS500 (“reference protocol”), while other factors remain constant (position and total duration of fixation point and of targets T1/T2, subjects awareness of T2 onset and saccade responses). Thus the comparison of fMRI responses between these two protocols will provide metabolic changes specifically related to saccadic adaptation. Similarly, comparison of fMRI responses between the two single-step protocols should provide metabolic changes specifically related to saccadic de-adaptation. These two types of quantitative comparison were performed within, but not between, the RS and VS scans.

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Insert Figure 1 about here

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*2.4.1 RS task.* Subjects initially looked at a fixation point located at +9° (right hemifield) and saccaded in reaction to the sudden presentation of a visual target in the left hemifield (Fig. 1b). The target could appear randomly at two eccentricities (16° and 22°) such that the requested saccade amplitude could not be predicted. Two factors were manipulated: the target was turned off at saccade onset and reappeared after a delay of 50 or 500 ms after saccade completion (delay factor) and, in both cases, could re-appear at the same location (Single-Step) or at a location shifted (Double-Step) by 25 % in a direction opposite to the saccade (target step factor). The duration of the second target presentation (500 ms) was the same in all four trials types.

*2.4.2 VS task.* Subjects performed saccades elicited intentionally while scanning a set of three targets (Fig. 1c). In each trial, they first performed a downward saccade to the right-most lower target located at +9° (right hemifield), followed by a horizontal scanning voluntary saccade toward the lateral target situated at 16° or 22° in the left visual field. During the voluntary saccade, all targets were turned off at saccade onset and the two lower targets reappeared after a delay of 50 or 500 ms after saccade completion (delay factor) either at the same location or at a location shifted by 25 % in a direction opposite to the saccade (target step factor).



*2.4.3 Saccades localizer task.* Subjects initially looked straight ahead (0°) and saccaded in response to targets presented at different eccentricities in both hemifields. Four different protocols were designed in order to stimulate several visuo-saccadic processes (visual processing and memory, saccade planning and execution, corrective saccades generation) and elicit the largest set of ROIs. In the pro-saccade protocol, subjects had to shift their eyes from central fixation to a peripheral target located randomly at 4°, 10°, 16° or 20° in the left or right hemifield, as soon as the target replaced the fixation point (single-step target). In the memorized pro-saccade protocol, subjects were asked to keep fixating at the center while a target was flashed for 200 ms at 4°, 10°, 16° or 20° in the left or right hemifield. They then had to shift their eyes towards the memorized target location as soon as the fixation target disappeared (duration of memory delay varying randomly from 700 to 1000 ms). The target reappeared 300 ms after initiation of primary saccade to allow corrective saccades. In the anti-saccade and in the memorized anti-saccade protocols, the sequence of events was the same as in the pro-saccade and memorized pro-saccade protocols, respectively, but subjects were instructed not to move their eyes toward the target but rather toward its mirror position in the opposite field. Target did not reappear in the memorized anti-saccade protocol.

## **2.5 fMRI procedure**

### *2.5.1 fMRI Data Acquisition*

Functional and anatomical images were acquired using a 1.5-Tesla MRI scanner. T2\*-weighted functional (EPI) data were acquired from 29 axial slices [whole head coverage, repetition time: 2500ms (Reactive saccades scan) or 3000ms (Voluntary saccades and Saccades localizer scans), echo time: 50 ms, flip-angle: 80 °, 3 x 3 x 3 mm resolution]. EPI and T1-weighted anatomical (1 x 1 x 1 mm) data were collected with an eight-channel SENSE head coil.

*2.5.2 RS scan.* Subjects were instructed to perform saccades according to the four protocols of the block design defined above. A total of 576 trials were performed in 6 runs. Each run consisted in two repetitions of each of the four protocols (DS50 block, DS500 block, SS50 block and SS500 block) and in three blocks of fixation at the beginning, middle and end of the run. Each block of saccades was composed of 12 trials. This number of trials was chosen as the best compromise to yield i) a decent level of saccadic adaptation, ii) a reduced habituation of fMRI signals, an effect which occurs when identical trials are frequently repeated within blocks, and iii) an increase of BOLD response

strength related to a large number of repetition of each trial block (12). Each trial lasted 1500ms, and was separated from the next by an inter-trial period of central fixation (jitter duration from 700ms to 1300ms). Target eccentricities and jitters of fixation duration were randomized. Each block order was also randomized across runs and participants.

*2.5.3 VS scan.* The block design was the same as in the RS scan, except that each trial lasted 2200ms and the jitter of inter-trial period of central fixation was from 500ms to 1100ms.

*2.5.4 Saccades localizer scans.* Subjects performed 4 runs corresponding to the four saccades protocols. Each run was composed of five repetitions of saccade blocks (8 trials each), alternating with 6 fixation blocks (lasting 24 s each). In all 4 protocols, the fixation target duration was varied randomly between saccade trials, in order to prevent subjects from predicting when the peripheral target would appear and to decouple their saccadic response with respect to the MRI scanning sequence. Protocols order was also randomized across runs and participants.

## **2.6 fMRI Data Analysis**

All data were processed using Brain Voyager QX (Brain Innovations, Maastricht, The Netherlands). Slice-scan time correction, head movement correction, temporal high-pass filtering (3 cycles) and linear trend removal were first applied to the functional data. No spatial smoothing was applied [except in the group data analysis (Gaussian filter; full-width at half maximum, 6 mm)] to identify areas activated with saccades generation (Saccades localizer scans) or with saccadic adaptation process (RS and VS scans). 3D cortex was reconstructed and inflated from the anatomical data. Functional images were aligned to anatomical data and the complete data transformed into Talairach space.

*2.6.1 RS and VS scans.* For each scan, we first used a classical whole-brain general linear model (GLM) approach to compare fMRI data between the 50 ms and 500 ms blocks of the single-step and double-step protocols (SS50 versus SS500 and DS50 versus DS500). To this aim, smoothed volume time-course data (Gaussian kernel of 6 mm FWHM) was z-transformed and modelled with four regressors of interest (four protocols –DS50, DS500, SS50 and SS500– and fixation baseline) convolved with a canonical hemodynamic response function. A *t*-test shifted for the hemodynamic delay (4 sec) and corrected for multiple comparisons (*Bonferroni correction*) was used for GLM analyses of all scans, including Saccades localizer scans.

*2.6.2 Saccades localizer scans.* For each subject, regions of interest (ROIs) were identified by

contrasting all saccades blocks to all fixation blocks of the localizer scans, using a whole-brain GLM analysis similar to that described for RS and VS scans.

*2.6.3 Multi-voxel pattern analysis (MVPA).* MVPA tested, for each previously identified ROI, whether patterns of BOLD signal can discriminate between saccade protocols differing only in the post-saccadic delay of the visual target (50ms versus 500ms). Linear Support Vector Machine (SVM) classifiers and associated cross-validation procedures were used as in previous studies (Li et al., 2007; Gerardin et al., 2010). In particular, for each ROI identified in the Saccades localizer scans, we selected the 100 most active voxels according to their mean response level in the contrast between saccade localizer blocks and fixation blocks. This choice was validated by checking that, for all ROIs, the growth of prediction accuracy with pattern size had already saturated for this value (see examples in insets of Figures 5 and 6), a necessary condition for comparing MVPA results between ROIs and between subjects: indeed, as in Li et al. (2007), increasing the number of voxels improved prediction accuracy across brain areas and reached an asymptote at a maximum of 100 voxels, allowing us to use the same number of voxels for comparison of pattern classification across areas. In total, 28 ROIs (14 in each hemisphere) fulfilled this size requirement in all subjects and were selected for MVPA. To minimize baseline differences across runs, each voxel time course was separately z-score normalized for each run. Then within each run, we averaged together the two data vectors (100 voxels BOLD values each) collected in each of the 4 protocols (DS50, DS500, SS50 and SS500).

Data vectors were then selected according to the comparison of interest (DS50 versus DS500, or SS50 versus SS500) and split into a training sample composed of the data of five runs and a test sample (the remaining run). A six-fold cross-validation was executed leaving one run out (test sample). For each subject, accuracy rates (number of correctly assigned test patterns/total number of assignments) were averaged across the cross-validation runs. The reliability of the MVPA results was assessed by comparing them to two additional analyses (univariate analysis and shuffle analysis). First, univariate analysis of the mean signals across all voxels of each ROI failed to reveal any significant classification accuracy. This showed that DS or SS protocols classifications in the MVPA could not be extracted from the average ROI signal. Second, when the same classifiers were shuffled (i.e. run with randomly assigned category labels to the activation patterns), their classification accuracies showed no significant difference with chance, indicating that the MVPA DS and SS

classifications did not provide spurious results related to random patterns in the data (see statistical data in Table 2 for selected areas).

## **2.7 Eye Data Analysis**

Horizontal and vertical eye positions were filtered by a finite impulse response filter FIR (50 Hz cut-off frequency) and differentiated using a two-point central difference derivative algorithm to get eye velocity. All oculomotor parameters were then extracted from the horizontal component of primary saccades.

An automatic detection of primary saccades was based on a velocity threshold procedure (30°/sec). Each trial was displayed and the detection was manually corrected if necessary. The position and time of saccade onset and termination were extracted for subsequent calculations and statistical analyses of saccade parameters (Statistica v.8.0, StatSoft). Saccade horizontal amplitude was computed as the difference of horizontal eye position between saccade onset and termination. Saccade gain was computed as the ratio between saccade amplitude and target eccentricity (distance relative to initial eye position). The time-course of saccade gain changes within each block was quantified as the slope of the linear relationship between gain and trial number (n=12 trials). Then, for each of the four protocols (DS50, DS500, SS50 and SS500), the slopes were averaged over the 6 subjects and plotted as a function of the 12 blocks repetitions. These relationships were submitted to a regression analysis to ensure that the saccade gain variations were stable over the duration of the experiment.

## **3. Results**

### **3.1 Behavioural analysis of saccadic adaptation**

To ensure our experimental design was efficient in inducing adaptation of both RS and VS during scanning sessions, we compared saccade size between protocols (DS50, DS500, SS50, SS500). We first computed the relationship between primary saccade gain and trial number within each block and plotted this relationship after pooling across blocks repetitions. As shown in Figure 2a, saccade gain progressively decreased in the DS50 protocol for both RS and VS, yielding in both cases a statistically significant correlation ( $p < 0.05$ ). The slope of this relationship was then computed (% per trial) for each

protocol (DS50, DS500, SS50, SS500) and the mean slopes averaged over subjects were plotted as a function of blocks repetition (Fig. 2b). Applying a regression analysis to this parameter revealed no significant effect of blocks repetition ( $p > 0.05$ ) (except for the 50 ms Single-Step protocol in the RS session:  $r = 0.13$ ,  $p < 0.01$ ), showing a stable adaptation process during the whole session, for both RS and VS tasks (Fig. 2b). In addition, mean slopes computed over the 12 blocks repetitions (Mean in Fig. 2b) significantly differed from 0 ( $t$ -tests,  $p < 0.01$ ) in all protocols except SS500 in both RS and VS sessions, thus showing a significant decrease of saccade gain in DS50 and DS500 protocols and a significant increase in SS50 protocols. Finally, unpaired  $t$ -tests comparing slopes between DS50 and DS500 reveal in each subject a significantly more negative slope during DS50 than during DS500, for both RS (minimum  $t(22)$  value =  $-2.11$ ,  $p < 0.05$ ) and VS (minimum  $t(22)$  value =  $-2.10$ ,  $p < 0.05$ ) sessions. In sum, saccade gain significantly decreased in the DS50 protocol, and significantly more so than in the DS500 protocol. This indicates stronger adaptation in the DS50 protocol than in the DS500 protocol. Similarly, saccade gain significantly increased in the SS50 protocol, and significantly more so than in the SS500 protocol, revealing a stronger de-adaptation in the former as compared to the latter protocol. Thus, for both reactive saccades and voluntary saccades, significant gain modifications were observed during the adaptation protocol relative to the reference protocol, indicating that the two components of saccadic adaptation -error information processing and plastic oculomotor changes- were readily engaged during MR scanning.

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Insert Figure 2 about here

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Then, to further evaluate the behavioural responses elicited during MR scanning, we performed additional analyses of oculomotor responses. We first measured the number of corrective saccades produced by each subject in the different protocols and found no significant difference between DS50 and DS500 in RS scan (mean number per trial =  $1.16 \pm 0.18$  and  $1.18 \pm 0.19$ , respectively, unpaired  $t$ -tests,  $p > 0.05$ ) and in VS scan (mean number per trial =  $1.21 \pm 0.22$  and  $1.23 \pm 0.21$ , respectively,  $p > 0.05$ ). We also analyzed two parameters strongly linked to fatigue (saccade latency and peak eye velocity) and found no systematic change over the course of the study, as shown by plots of peak

velocity and saccade latency as a function of blocks repetitions (Figure 3). Indeed, a regression analysis revealed no significant change of latency or peak velocity over blocks repetitions, for both RS ( $r = -0.03$  and  $-0.03$ ,  $p > 0.05$ ) and VS tasks ( $r = -0.04$  and  $-0.04$ ,  $p > 0.05$ ).

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Insert Figure 3 about here

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### **3.2 Saccadic adaptation control experiment**

We next tested whether the rate of saccade adaptation recorded in our study is similar to that reported in the literature (e.g. Alahyane et al., 2007; Panouillères et al. 2009; Zimmermann and Lappe; 2010). To this aim, we performed an additional behavioural experiment in 6 new subjects recruited for each saccade category (Reactive or Voluntary Saccades). We deliberately chose experimental conditions similar to the three studies mentioned above: seated subjects looked at targets presented on a computer screen, and adaptation of a single saccade vector ( $8^\circ$ ) was elicited by an intra-saccadic step of the target of 25% of its initial eccentricity. Linear regression of the saccade gain decrease was computed over the first 12 adaptation trials. The mean regression slopes (%/trial) obtained in this control experiment (RS=  $-0.6 \pm 0.5$ ; VS=  $-0.5 \pm 0.9$ ) did not differ from those computed in the present fMRI study (RS=  $-1.1 \pm 0.5$ ; VS=  $-0.7 \pm 0.6$ , unpaired  $t$ -tests  $t(10)=1.7$  and  $0.3$ , respectively,  $p > 0.1$ ). Thus, adaptation of RS and of VS elicited in our fMRI study reached a similar rate as in control conditions classically used in the literature.

### **3.3 Metabolic activation related to saccade generation**

We report in this section on brain areas involved in saccades generation and/or saccade target visual processing, as identified in the *Saccades localizer scans*. By contrasting saccades blocks against fixation blocks in a whole brain GLM analysis, we disclosed for each subject a set of significantly activated regions in both hemispheres (Fixed effect analysis,  $p < 0.05$ , Bonferroni corrected). Areas located in the cerebellum (posterior vermis and hemispheric lobules VIIb/VIIIa and VI/Crus I), the basal ganglia (putamen and caudate nuclei), the parietal cortex (ventral-, posterior-, medial- and anterior-IPS, IPL), the temporo-parietal junction (TPJ) and the frontal cortex (medial Superior Frontal Gyrus, Precentral sulcus, inferior Precentral sulcus and DLPFC) are all known to be associated with

saccades (Connolly et al., 2002; Ettinger et al., 2008; Konen and Kastner, 2008; Petit et al., 2009; Schraa-Tam et al., 2009; Kagan et al., 2010). The other identified areas are the following visual regions: primary visual cortex (V1), lateral occipital sulcus (LOS) and middle-temporal cortex (hMT+/V5). Results of the group analysis are displayed in Figure 4 and Table 1. These regions were then used as regions of interest in the MVPA analyses reported in the following paragraphs, except the cerebellar vermis, putamen, caudate nuclei, cortical areas IPL and APFC as in these ROIs the requested minimum number of activated voxels (100) was obtained in less than half of the subjects. Altogether, 28 ROIs (14 in each hemisphere) were selected for subsequent MVPA analyses (4 in the cerebellum and 24 in the cerebral cortex, see underlined names in Table 1 legend).

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Insert Figure 4 and Table 1 about here

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### **3.4 Metabolic activation related to saccadic adaptation processes**

We report in this section on brain areas involved in saccadic adaptation and/or de-adaptation, as identified in the RS and VS scans. We first checked whether a classical whole-brain GLM analysis could reveal significant BOLD activation related to saccadic adaptation. To this aim, we contrasted DS50 versus DS500 blocks, separately for the RS and VS scans. No significant activation could be revealed in any brain regions, for both RS and VS sessions ( $p < 0.05$ , Bonferroni corrected). Similarly, contrasting SS50 versus SS500 blocks revealed no significant activation related to de-adaptation in any brain regions ( $p < 0.05$ , Bonferroni corrected).

We then submitted to multi-voxel pattern analysis (MVPA) each ROI identified in the saccades localizer task, separately for RS and VS scans. We assumed that if a ROI is involved in saccadic adaptation, the classification of DS50 versus DS500 should show a significantly higher accuracy than chance. In addition, if the ROI is also involved in de-adaptation, accuracy should also be higher than chance for the SS50 versus SS500 classification.

### 3.4.1 Reactive saccades

Linear Support Vector Machine (SVM) classifiers were trained for each ROI to discriminate whether patterns of fMRI activity across voxels relate to adaptation (Double-step protocols, DS) and/or to de-adaptation (Single-step protocols, SS) of reactive saccades. Thus, two different classifiers were used for the DS protocols (DS50 versus DS500) and the SS protocols (SS50 versus SS500).

Classification accuracy was above chance (0.5) for at least one of the two classifiers (DS or SS) in several ROIs. However, the performance of the classifiers was not uniform according to protocols and ROIs. Indeed, a repeated measures ANOVA testing the protocols factor (two levels: DS and SS) and the ROIs factor (14 levels) showed a significant interaction between these two factors ( $F(13,299)=8.9, p<0.01$ ).

DS protocol classification accuracies depended on the hemisphere in cerebellar ROIs and in cerebral cortex ROIs (dorsal visual and temporal areas) (Figure 5). Indeed, a repeated measures ANOVA testing the laterality factor (two levels: ipsi or contralateral relative to the tested saccade direction) and the ROI factor (14 levels) showed no significant effect of either factor, but a significant interaction ( $F(13,143)=4.2, p<0.05$ ). Post-hoc analyses revealed significantly higher accuracies in the ipsilateral cerebellar hemisphere (lobules VIIb-VIIIa:  $t(140)=2.77, p<0.01$ ) and in the contralateral cerebral hemisphere (area hMT+/V5,  $t(140)=-2.90, p<0.001$ , and area TPJ,  $t(140)=-4.20, p<0.001$ ), but no hemispheric difference for the region in the inferior Precentral sulcus (iPrCS) ( $t(140)=1.03, p=0.36$ ). All these areas, including iPrCS, also showed a significantly higher discrimination level than in the shuffling condition, which indicated that the significant discrimination levels of MVPA could not be accounted for by spurious effects due to statistical regularities (Table 2 (a)). Low classification accuracies without significant laterality difference were found in all remaining ROIs.

In the SS protocol, no significant effect of the laterality factor on classification accuracies was found ( $F(13,143)=1.44, p=0.15$ ). In addition, accuracies were generally low (around chance level) and showed no statistical difference with shuffling condition, except in the left cerebellar area VIIb-VIIIa where this difference just reached significance ( $t(5)=2.60, p<0.05$ ; and Table 2 (a)).

In sum, ipsilateral cerebellar area VIIb/VIIIa, contralateral cortical areas hMT+/V5 and TPJ, and bilateral cortical area iPrCS showed significant classification accuracies for the DS50 versus DS500 classifier testing the adaptation process. In contrast, only the ipsilateral VIIb/VIIIa area significantly discriminated between SS50 and SS500 (de-adaptation process).



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Insert Figure 5 and Table 2 about here

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### 3.4.2 Voluntary saccades

Similar to reactive saccades, a two-way repeated measures ANOVA disclosed a significant interaction between ROIs and protocols ( $F(13,299)=5.08$ ,  $p<0.02$ ), indicating again that the performance of the classifiers was not uniform according to protocols (DS vs SS) and to ROIs.

DS classification accuracies varied according to hemispheres (Figure 6), as shown by the significant interaction between the laterality factor and the ROI factor of the repeated measures ANOVA ( $F(13,143)=6.74$ ,  $p<0.05$ ). These accuracies were significantly biased in favour of the ipsilateral cerebellar hemisphere (VIIb-VIIIa:  $t(140)=2.90$ ,  $p<0.005$ ), the contralateral posterior area of the intra-parietal sulcus (pIPS:  $t(140)=-3.26$ ,  $p<0.005$ ), the contralateral medial area of the intra-parietal sulcus (mIPS:  $t(140)=-2.04$ ,  $p<0.05$ ), and the contralateral region of the inferior Precentral sulcus (iPrCS:  $t(140)=-1.98$ ,  $p<0.05$ ). Furthermore, these three cortical (pIPS, mIPS and iPrCS) and cerebellar areas showed a significantly higher accuracy of DS classification than in the shuffling condition (Table 2 (b)). Low classification accuracies without significant hemispherical difference were found for all other ROIs.

In the SS protocol, accuracies were low and showed no general difference between hemispheres ( $F(13,143)=1.47$ ,  $p=0.13$ ). Also, only the contralateral DLPFC area showed a significant statistical difference with shuffling condition ( $t(5)=3.1$ ,  $p<0.05$ , and Table 2 (b)).

In sum, ipsilateral cerebellar area VIIb/VIIIa and contralateral cortical areas pIPS, mIPS and iPrCS showed significant classification accuracies for the DS50 versus DS500 classifier that tested the adaptation process. However, only contralateral cortical area DLPFC significantly discriminated between SS50 and SS500 (de-adaptation process).

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Insert Figure 6 about here

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## **4. Discussion**

### **4.1 Summary of the results**

Behavioral analyses in the double-step protocols revealed that 1) the gain of primary saccades (RS and VS) significantly decreased during DS50 blocks, 2) these changes were consistent over the whole scanning session and reached the same magnitude as saccadic adaptation disclosed in our control experiment using conditions classically reported in the literature; in addition 3) decreases of saccade gain in the DS50 blocks were significantly larger than in the DS500 blocks whereas 4) the number of corrective saccades was the same during DS50 and DS500 blocks. Finally, analyses of the single-step protocols revealed that 5) the gain of primary saccades (RS and VS) consistently increased during SS50 blocks and 6) these changes were significantly larger than in the SS500 blocks. Taken together, these data indicate that adaptation of reactive saccades (RS) and voluntary saccades (VS) was induced in DS50 blocks and reached a similar rate as in previous studies, whereas de-adaptation was elicited in SS50 blocks. Furthermore, the significant differences of primary saccades gain changes between the 50 ms and the 500 ms target delays, without difference of corrective saccades frequency, validate our fMRI rationale using the post-saccadic target delay to isolate adaptation processes. Analyses of fMRI data based on a GLM approach did not reveal significant activation. This could be explained by the fact that our design deliberately emphasized the specificity of metabolic activation relative to adaptation processes (at the expense of sensitivity), by introducing a very subtle difference between conditions used in our GLM contrasts, i.e. a mere 450 ms change of post-saccadic target delay. In contrast, the more sensitive MVPA approach allowed us i) to identify two different sets of ROIs, respectively for RS and VS, for which DS50 and DS500 could be statistically discriminated, ii) to distinguish between these ROIs those involved in both saccade categories (cerebellum, frontal cortex) from those specifically related to RS (temporo-parietal junction, hMT+/V5) or to VS (medial and posterior areas of intra-parietal sulcus), and iii) to identify only two ROIs (cerebellar lobule VIIb/VIIIa for RS, and DLPFC for VS) for which SS50 and SS500 could be discriminated, with the notable failure to disclose any of the three tested visual ROIs (V1, LOS, hMT+/V5). Taken together these MVPA

results indicate that, in the two sets of ROIs reported above (except cerebellar lobule VIIb/VIIIa for RS), different patterns of fMRI activation took place when a target jump occurred at a short or long post-saccadic delay, but without comparable delay-related difference when the target remained stationary. This last observation rules out the possibility that these ROIs contributed solely to visual and/or memory processes related to the visual target delay factor, a conclusion reinforced by the lack of any MVPA discrimination for occipital visual areas (V1, LOS). Furthermore, a contribution of these ROIs in corrective saccades generation is also refuted by our analysis showing identical probability of corrective saccades with both target delays. Therefore, the reported pattern of MVPA results perfectly matches that predicted from an involvement of these brain areas in saccadic adaptation processes,

#### **4.2 Saccadic adaptation components**

Before discussing these findings further, it is necessary to ask which components of saccadic adaptation are specifically involved in our study. During the target double-step paradigm classically used to elicit adaptation (McLaughlin 1967), a consistent visual error is introduced, and yields a modification of the primary saccade gain over successive trials. Error signals are largest at the beginning of the adaptation session and thereafter decrease as, due to adaptive modifications, the primary saccade lands progressively closer to the displaced target. Thus, both error signals processing and enduring changes of oculomotor commands take place during an adaptation session. Although conceptually distinct, these error processing and plastic changes components are rarely experimentally dissociated (except by some studies which specifically focus on error processing: Bahcall and Kowler, 1999; Noto and Robinson, 2001; Catz et al., 2005; Soetedjo and Fuchs, 2006; Kojima et al. 2007, Panouillères et al., 2011; Wong and Shelhamer, 2011). The same is also true in our study. Indeed, on the one hand, the error processing component, which peaks at the start of a target double-step session, should be favoured by our short adaptation blocks. On the other hand, we found that such short blocks nonetheless induced consistent saccade gain changes, and that the level of adaptation was similar to that in our control experiment where conditions classically reported in the literature were reproduced. Furthermore, it has been suggested that saccadic adaptation is supported by two distinct processes with different time-course and retention, a fast process that forgets quickly and a slower process that retains longer (Ethier et al., 2008; Chen-Harris et al., 2008). Due to the restricted number of adaptation trials, we believe that the fast adaptation process largely

predominated over the slow process in our study. In sum, these different considerations strongly support our proposal that brain ROIs disclosed by MVPA in our main contrast (DS50 versus DS500) are involved in saccadic adaptation mechanisms. These mechanisms most likely involve both error signals processing and fast plastic oculomotor changes, and further studies are required to tease apart these two sub-components. Therefore, unless otherwise specified, “saccadic adaptation” in the rest of this paper will indistinctively refer to these two sub-components.

### **4.3 Cerebral cortex involvement**

The involvement of cerebral cortex areas in saccadic adaptation processes is a major original finding of our study. So far, electrophysiological recordings in monkey, clinical studies in patients, and TMS studies –as well as a PET study- in healthy subjects have all provided evidence that the substrates of saccadic adaptation (error signals processing and plastic changes components) are confined to the cerebellum and/or brainstem (see *Introduction*). The only hint of an involvement of the cerebral cortex was a report in two patients suggesting a contribution of the cerebello-thalamo-cortical pathway to reactive saccades adaptation (Gaymard et al., 2001). Most recently, an fMRI study of reactive saccade adaptation has reported metabolic activation in only two brain areas, the frontal (SEF) and temporo-insular cortices (Blurton et al., 2012). Based on behavioural evidence, some models do include a contribution of the cerebral cortex to saccadic adaptation, but only for voluntary saccades (Gancarz and Grossberg, 1999; Deubel, 1999; Pélisson et al., 2010). A predominant contribution of cerebellar/brainstem centers in visuo-motor adaptation is also documented for slow ocular movements (smooth pursuit: Chou and Lisberger, 2004, vestibulo-ocular-reflex: Anzai et al., 2010, vergence: Takagi et al., 2001), whereas for upper-limb reaching movements, parieto-frontal areas of the cerebral cortex are also recruited (visual rotation: Diedrichsen et al., 2005; wedge prisms: Clower et al., 1996; Luauté et al., 2009). Thus, the cerebral cortex involvement in saccadic adaptation demonstrated here is a feature shared by adaptation of limb reaching movements, but not by adaptation of slow ocular movements. Although surprising at first sight, this observation fits with the fact that accurate goal-directed movements, including saccades and limb reaches but not slow ocular movements, require visuo-attentional and spatial planning processes (i.e. target selection, localization, memorization and spatial remapping) that depend on extended parieto-frontal networks (Goodale and Westwood, 2004;

Andersen and Cui, 2009). A possible link with visuo-attentional processes is further supported in the following paragraph.

#### **4.4 Specificity of cortical areas relative to saccade categories**

The second main finding is the demonstration of two overlapping but different adaptation substrates specifically associated with the saccade category: cerebellum, middle-temporal, temporo-parietal and frontal areas for reactive saccades; the same cerebellar and frontal areas but also parietal areas for voluntary saccades. We first focus on the differences between these two groups of areas. Specifically, in posterior areas, we disclose an involvement of mIPS and pIPS areas only for VS and of hMT+/V5 and TPJ areas only for RS. This dissociation provides strong evidence for the hypothesis of different adaptation processes acting for the two saccade categories (Deubel, 1995, 1999; Collins and Doré-Mazars, 2006; Alahyane et al., 2007; Pélisson et al., 2010). Moreover, this dissociation closely matches the dorsal/ventral specialization of parieto-frontal streams relative to covert shifts of visual attention (Corbetta and Shulman 2002). According to these authors, endogeneous (intentional) shifts of attention depend on a dorsal system involving the superior parietal lobule and intraparietal sulcus of the contralateral hemisphere, whereas exogeneous (stimulus-driven) attention shifts mainly involve a ventral system comprising inferior parietal lobule and TPJ, with a strong right-hemisphere dominance. Thus, in our study, the selective involvement of intra-parietal sulcus (pIPS and mIPS) in adaptation of voluntary (intentional) saccades and of TPJ in adaptation of reactive (stimulus-driven) saccades nicely fits this proposed intra-parietal subdivision of attention control. This anatomical overlap predicts some functional links between saccadic adaptation and attention control, a hypothesis requiring future studies. Thus, we can tentatively propose that the role of the cerebral cortex could rely on attention modulated processing of peri-saccadic visual inputs, thus contributing predominantly to the error signals processing component of saccadic adaptation.

The fMRI literature on saccades generation also suggests a similar dorsal/ventral dissociation of saccade categories. IPS oculomotor areas are involved in both saccade categories (Connolly et al., 2002; Ettinger et al., 2008; Konen and Kastner, 2008), but more so for voluntary saccades than for reactive saccades (Mort et al., 2003). TPJ and hMT+/V5 both show metabolic activation for visually guided saccades (Schraa-Tam et al., 2009; van Broekhoven et al., 2009; Petit et al., 2009) and hMT+/V5 activation actually dominates for reactive saccades relative to voluntary saccades (Schraa-

Tam et al., 2009). Note that the hMT+/V5 activation we disclosed for RS unlikely results from motion signals related to target jumps, because the two simultaneously jumping targets of VS scans did not induce any activation. Therefore, similarly to TPJ, hMT+/V5 appears to be specifically involved for adaptation of RS, but not of VS. Note finally that the dorsal/ventral dissociation discussed here does not seem to fit a previously proposed specialization of parietal and frontal cortices for reactive and voluntary saccades, respectively. However, this latter specialization is supported mostly by the specific consequence of dysfunctions of these cortical areas on saccade latency (Pierrot-Deseilligny et al., 2004; Rafal, 2006; Müri and Nyffeler 2008), and would thus relate more to saccade initiation than to sensorimotor transformation. This last observation could explain why it is unrelated to the dorsal/ventral parietal specialization demonstrated here.

It is worth noting that the specific involvement of parietal areas in adaptation of voluntary saccades is also directly in line with behavioural evidence of a partial sharing of the underlying substrates with those of hand movement production and of anti-saccades programming. Indeed, adaptation of voluntary saccades but not of reactive saccades, transfers to hand pointing movements (Krölller et al., 1999; Cotti et al., 2007; Hernandez et al., 2008), and to anti-saccades elicited by a target presented in the adapted field (Cotti et al., 2009). These findings have led us to propose that voluntary saccades adaptation involves occipito-parietal areas (Pélisson et al., 2010). The present study thus validates this hypothesis and further extends it by revealing a role of TPJ specifically for adaptation of reactive saccades.

#### **4.5 Common areas for the two saccade categories**

Despite being dissociable, neural substrates involved in adaptation of reactive saccades and of voluntary saccades show two sites of overlap: the cerebellar hemisphere ipsilaterally and the inferior pre-central sulcus bilaterally. Concerning the cerebellum, an implication in RS adaptation has already been demonstrated by several studies in human and non-human primates, with strong emphasis placed on cerebellar vermis (Desmurget et al., 1998, 2000; Straube et al., 2001; Alahyane et al., 2008; Golla et al., 2008; Jenkinson and Miall, 2010; Iwamoto and Kaku, 2010; Pélisson et al., 2010; Panouillères et al., in press). The two functional imaging studies published so far have either failed to reveal any cerebellar involvement (Blurton et al. 2012) or highlighted a small zone in the posterior vermis during RS adaptation (Desmurget et al., 1998; 2000). However, as suggested recently, the

control condition used by these last authors (randomized target jumps) could have elicited some plastic saccadic changes (Srimal et al., 2008) or saccadic error processing (van Broekhoven et al., 2009), thereby underestimating the contrast of metabolic activation between the adaptation and control conditions. Note further that this study combined saccade adaptive shortening with saccade adaptive lengthening which, as we now know (Golla et al., 2008; Hernandez et al., 2008; Panouillères et al., 2009, Schnier et al. 2011), rely on different mechanisms. Focusing on adaptive shortening, we found an involvement of lobules VIIb-VIIIa of the ipsilateral cerebellar hemisphere for both reactive and voluntary saccades. Balanced activation for the generation of both saccade categories has also been reported in lateral cerebellum (Schraa-Tam et al., 2009). Another fMRI study has attributed activation in the lateral cerebellum to saccadic errors processing (van Broekhoven et al., 2009). Our findings are also consistent with deficits of RS adaptation observed in patients with lesions involving the cerebellar hemisphere (Straube et al., 2001; Alahyane et al., 2008; Golla et al., 2008). In addition, and for the first time, the present study demonstrates that the lateral cerebellum is involved in adaptation of VS. Finally, concerning the frontal cortex, we found that a region of the inferior pre-central sulcus is involved in the adaptation of both categories of saccade. Located in the ventral pre-motor cortex involved in upper-limb control and notably, in its adaptive component (Kurata and Hoshi, 1999), this inferior area of pre-central sulcus has been involved in oculomotor control as well (Fuji et al., 1998; Nagel et al., 2006) and furthermore, is very close to the lateral FEF identified by previous fMRI studies (see Müri (2006) for a comprehensive review). Noteworthy, the role of this lateral FEF area in saccades generation [memory-guided saccades (Brown et al., 2004), antisaccades (Ettinger et al., 2008) or reflexive saccades (McDowell et al., 2008)], as well as its precise anatomical location, is far less understood than that of the medial FEF. The proximity to the inferior pre-central sulcus area disclosed in the present study suggests that the lateral FEF could be involved in saccadic plasticity. An involvement of lateral FEF and/or iPrCS in saccadic adaptation is consistent with their anatomical connections with the hemispheric cerebellar areas disclosed here (Doron et al., 2010) and merits further investigation.

#### **4.6 Conclusion**

The present study reveals for the first time the extent of the cerebellar and cerebral cortex areas involved in adaptation of reactive saccades and of voluntary saccades, and confirms the hypothesis

that these saccade categories recruit different plasticity mechanisms. The study also indicates that plasticity of motor responses as simple as saccades involves various sensorimotor stages and that, at the level of the cerebral cortex, two partially overlapping sets of areas are deemed to subserve differential mechanisms of saccadic adaptation, in agreement with the dual system recently proposed for attentional control.

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## Tables

**Table 1:**

<b>Region Of Interest</b>						
<i>Cerebellum</i>	<b>TAL X</b>		<b>TAL Y</b>		<b>TAL Z</b>	
Vermis	1		-67		-38	
	<b>Left hemisphere</b>			<b>Right hemisphere</b>		
	<b>TAL X</b>	<b>TAL Y</b>	<b>TAL Z</b>	<b>TAL X</b>	<b>TAL Y</b>	<b>TAL Z</b>
<i>Cerebellum</i>						
VIIb - VIIIa	-25	-62	-40	23	-65	-37
VI – Crus I	-30	-42	-33	31	-48	-26
<i>Basal ganglia</i>						
Putamen	-23	-1	9	22	3	10
Caudate	-9	-1	11	9	-1	13
<i>Visual areas</i>						
V1	-6	-84	5	10	-80	5
LOS	-36	-78	7	38	-71	12
hMT+/V5	-44	-66	5	45	-62	6
<i>Temporo-Parietal Junction</i>						
TPJ	-53	-41	19	55	-38	23
<i>Parietal areas</i>						
vIPS	-22	-73	28	20	-73	27
pIPS	-13	-61	48	13	-63	49
mIPS	-27	-54	47	31	-55	48
aIPS	-38	-44	44	40	-41	45
IPL	-47	-38	39	50	-38	42
<i>Frontal areas</i>						
mSFG	-7	-5	58	6	-3	54
PrCS	-28	-2	52	31	-5	53
iPrCS	-45	2	34	47	3	33
APFC	-27	45	11	31	47	8
DLPFC	-35	28	30	35	31	32

Table 2:

(a)

Reactive Saccades (RS)

DS Protocols

Areas	Left Hemi.		Right Hemi.	
	t(5)	p	t(5)	p
VIIb-VIIIa	<b>-4.23</b>	<b>&lt;0.01</b>	1.33	0.17
hMT+/V5	0.12	0.86	-2.12	<b>&lt;0.05</b>
TPJ	-1.24	0.35	-4.05	<b>&lt;0.01</b>
pIPS	1.14	0.46	1.51	0.09
mIPS	0.85	0.40	0.22	0.88
iPrCS	-2.02	<b>&lt;0.05</b>	-3.95	<b>&lt;0.01</b>
DLPFC	0.23	0.73	0.04	0.97

SS Protocols

Areas	Left Hemi.		Right Hemi.	
	t(5)	p	t(5)	p
VIIb-VIIIa	<b>2.60</b>	<b>&lt;0.05</b>	-1.05	0.20
hMT+/V5	0.88	0.36	0.14	0.90
TPJ	0.33	0.82	-0.21	0.83
pIPS	0.89	0.42	1.02	0.33
mIPS	0.02	0.98	0.28	0.79
iPrCS	-1.55	0.10	0.97	0.22
DLPFC	1.01	0.54	1.20	0.36

(b)

Voluntary Saccades (VS)

DS Protocols

Areas	Left Hemi.		Right Hemi.	
	t(5)	p	t(5)	p
VIIb-VIIIa	-2.77	<b>&lt;0.05</b>	1.40	0.55
hMT+/V5	1.61	0.08	1.11	0.25
TPJ	0.44	0.70	1.45	0.10
pIPS	-1.79	0.42	-3.55	<b>&lt;0.01</b>
mIPS	-0.94	0.38	-2.08	<b>&lt;0.05</b>
iPrCS	1.03	0.18	-2.20	<b>&lt;0.05</b>
DLPFC	0.11	0.82	0.10	0.91

SS Protocols

Areas	Left Hemi.		Right Hemi.	
	t(5)	p	t(5)	p
VIIb-VIIIa	1.88	0.06	1.87	0.08
hMT+/V5	1.14	0.22	1.08	0.37
TPJ	0.67	0.52	1.05	0.39
pIPS	-0.44	0.70	-0.50	0.67
mIPS	0.01	0.99	0.20	0.78
iPrCS	1.15	0.16	0.56	0.62
DLPFC	0.12	0.85	<b>3.10</b>	<b>&lt;0.05</b>

## Table Legends

### **Table 1: Tables of Talairach coordinates for all ROIs showing significantly stronger activation for saccades versus fixation (Saccade Localizer, group analysis, N=6).**

Underlined areas are the 14 ROIs from left and right hemispheres (28 selected in total) tested with MVPA.

Cerebellar vermis; VIIb-VIIIa, lobule VIIb-VIIIa; VI-Crus I, lobule VI-Crus I; putamen; caudate; V1, primary visual cortex; LOS, Lateral Occipital Sulcus; hMT+/V5, motion-sensitive area; vIPS, ventral intraparietal sulcus; pIPS, posterior intraparietal sulcus; mIPS, medial intraparietal sulcus; aIPS, anterior intraparietal sulcus; IPL, inferior parietal lobule; TPJ, temporoparietal junction; mSFG, medial Superior Frontal Gyrus; PrCS, Precentral Sulcus; iPrCS, inferior Precentral Sulcus; APFC, anterior prefrontal cortex; DLPFC, dorsolateral prefrontal cortex.

### **Table 2: Classifiers performance compared with shuffling (RS and VS scans)**

One-tailed paired *t* tests were performed on individual ROIs to test statistical differences between classifiers performance and corresponding shuffling condition for RS (a) and VS (b). The table shows *t* values and associated P values.

## Figure Legends

**Figure 1: Oculomotor procedure.** (a) Double-step (DS) protocols. This panel illustrates the timing of visual stimulation events (target T1 offset and target T2 onset) relative to a schematized eye position trace during the 50 ms Double-step protocol (DS50) and the 500ms Double-step protocol (DS500). (b) DS50 or DS500 protocols for reactive saccades. Subjects were instructed to first look at a +9° fixation point (time 0) and then to shift their eyes as soon as the fixation point was replaced by a peripheral target (time 1) presented to the left randomly at -13° or -7° (corresponding respectively to a 22° or 16° target retinal eccentricity). The target was then shifted to the right from -13° to -7° or from -7° to -3° 50ms or 500ms after the end of primary saccade (time 2). (c) DS50 or DS500 protocols for voluntary saccades. Subjects were instructed to look at a +9° fixation point (time 0) and then to shift their eyes



downward as soon as a horizontal pair of targets was presented 5° below fixation (time 1) (the first target just below fixation point and the second presented randomly at -13° or -7° to the left, corresponding respectively to a 22° or 16° target separation). After looking at the target situated below the fixation point, subjects performed a self-initiated saccade toward the lateral target. Both targets were shifted to the right by 6° or 4° (for the 22° or 16° target separations, respectively), either 50ms or 500ms after the end of subjects' primary saccade (time 2). In both (b) and (c), the MR scan was triggered simultaneously with target onset (time1).

**Figure 2: Saccadic adaptation induced in the DS50 ms protocol.**

Comparison of Reactive Saccade task (left column) and of Voluntary Saccade task (right column). (a) Saccadic gain (saccade amplitude / initial target eccentricity) as a function of trial number for the 50ms Double-Step protocol. Data from one subject (S1), pooled for all 12 repetitions of the DS50 blocks. The slope of the relationships between saccadic gain and trial number (RS:  $\text{Gain}=0.84-0.0102 \times \text{Trial}$ ; VS:  $\text{Gain}=0.94-0.0121 \times \text{Trial}$ ) differs significantly from 0 in both cases ( $t$ -tests ( $df=11$ ),  $p<0.001$ ). (b) Mean slope of gain change (% per trial,  $\pm SD$ ) as a function of blocks repetition computed separately for the 50 ms Double-Step protocol, 500 ms Double-Step protocol, 50 ms Single-Step protocol and 500 ms Single-Step protocol; Mean: data averaged over the 12 blocks repetitions and the 6 subjects ( $N=72$ ). All mean slopes are significantly different from 0 ( $t$ -test ( $df=5$ ),  $p<0.01$ ) except for SS500 in both RS and VS sessions. Small stars represent significant mean differences between protocols (ANOVA post hoc tests,  $p<0.001$ ).

**Figure 3: Eye peak velocity and latency for all protocols.**

Comparison of Reactive Saccade task (left column) and of Voluntary Saccade task (right column): (a) mean eye peak velocity (deg/sec,  $\pm SD$ ) plotted as a function of blocks repetitions separately for the 50 ms Double-Step protocol (RS:  $273 \pm 11$ ; VS:  $289 \pm 12$ ), 500 ms Double-Step protocol (RS:  $276 \pm 10$ ; VS:  $288 \pm 12$ ), 50 ms Single-Step protocol (RS:  $276 \pm 12$ ; VS:  $286 \pm 13$ ) and 500 ms Single-Step protocol (RS:  $274 \pm 11$ ; VS:  $288 \pm 11$ ). (b) mean eye latency (ms,  $\pm SD$ ) plotted as a function of blocks repetitions separately for the 50 ms Double-Step protocol (RS:  $185 \pm 10$ ; VS:  $211 \pm 11$ ), 500 ms Double-Step protocol (RS:  $186 \pm 11$ ; VS:  $212 \pm 11$ ), 50 ms Single-Step protocol (RS:  $185 \pm 12$ ; VS:  $209 \pm 13$ ) and 500 ms Single-Step protocol (RS:  $184 \pm 12$ ; VS:  $210 \pm 13$ ).

#### **Figure 4: Metabolic activation related to saccade generation**

Group GLM map across subjects (N = 6) representing areas that were significantly activated in the saccades versus fixation contrast ( $p(\text{Bonferroni corrected}) < 0.001$ ) of the saccade localizer scans. (a) Activated cerebellar areas are shown superimposed on an individual three-dimensional anatomy (L/R = Left/Right hemisphere). (b) Activated areas of cerebral cortex are superimposed on an individual inflated cortical surface of the left and right hemispheres. The sulci are coded in darker gray than the gyri. See abbreviations in Table 1.

#### **Figure 5: Adaptation and de-adaptation classifiers for reactive saccades**

Multi-voxel Pattern Analysis (MVPA) for the classification of *adaptation* (50ms vs. 500ms Double-step protocols, dark line) and *de-adaptation* (50ms vs. 500ms Single-step protocols, dashed grey line) from fMRI data of the Reactive Saccade scan. Mean classification accuracy (pattern size = 100 voxels per area) is shown for each ROI and for each hemisphere. Error bars indicate SEM across subjects (N = 6). Small stars indicate significant mean differences of accuracy of each 100<sup>th</sup> voxel (arrow in the inset) versus shuffling (see Table 2a). The dashed line indicates the classification chance level (50%). Inset: classification accuracy in one subject (S1) as a function of voxel number for five representative areas. See abbreviations in Table 1.

#### **Figure 6: Adaptation and de-adaptation classifiers for voluntary saccades**

Multi-voxel Pattern Analysis (MVPA) for the classification of *adaptation* (50ms vs. 500ms Double-step protocols, dark line) and *de-adaptation* (50ms vs. 500ms Single-step protocols, dashed grey line) from fMRI data of the Voluntary Saccade scan. Mean classification accuracy (pattern size = 100 voxels per area) is shown for each ROI and for each hemisphere. Error bars indicate SEM across subjects (N = 6). Small stars indicate significant mean differences of accuracy of each 100<sup>th</sup> voxel (arrow in the inset) versus shuffling (see Table 2b). The dashed line indicates the classification chance level (50%). Inset: classification accuracy in one subject (S1) as a function of voxel number for five representative areas. See abbreviations in Table 1.