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Effects of structural and functional cerebellar lesions on sensorimotor adaptation of saccades

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Abstract The cerebellum is critically involved in the adaptation mechanisms that maintain the accuracy of goal-directed acts such as saccadic eye movements. Two categories of saccades, each relying on different adaptation mechanisms, are defined: reactive (externally triggered) saccades and voluntary (internally triggered) saccades. The contribution of the medio-posterior part of the cerebellum to reactive saccades adaptation has been clearly demonstrated, but the evidence that other parts of the cerebellum are also involved is limited. Moreover, the cerebellar substrates of voluntary saccades adaptation have only been marginally investigated. Here, we addressed these two questions by investigating the adaptive capabilities of patients with cerebellar or pre-cerebellar stroke. We recruited three groups of patients presenting focal lesions located, respectively,

in the supero-anterior cerebellum, the infero-posterior cerebellum and the lateral medulla (leading to a Wallenberg syndrome including motor dysfunctions similar to those resulting from lesion of the medio-posterior cerebellum). Adaptations of reactive saccades and of voluntary saccades were tested during separate sessions in all patients and in a group of healthy participants. The functional lesion of the medio-posterior cerebellum in Wallenberg syndrome strongly impaired the adaptation of both reactive and voluntary saccades. In contrast, patients with lesion in the supero-anterior part of the cerebellum presented a specific adaptation deficit of voluntary saccades. Finally, patients with an infero-posterior cerebellar lesion showed mild adaptation deficits. We conclude that the medio-posterior cerebellum is critical for the adaptation of both saccade categories, whereas the supero-anterior cerebellum is specifically involved in the adaptation of voluntary saccades.

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Introduction

The cerebellum is a key structure in the control and sensorimotor adaptation mechanisms of saccadic eye movements (Glickstein et al. 2011). Saccades triggered by exogenous cues, like the sudden appearance of a new object, belong to the category of reactive saccades. But to explore our visual environment, we most frequently generate scanning saccades which are triggered according to internal goals and which belong to the voluntary saccades category. The different properties of these two types of saccades are linked to anatomic-functional specificities of the oculomotor areas of the cerebral cortex (Johnston and Everling 2008; Muri and Nyffeler 2008). At the level of the cerebellum instead, evidence for such specialisation is scarce (Schraa-Tam et al. 2009) and contradicted by recent monkey data showing undifferentiated neuronal activities in the medio-posterior cerebellum for the generation of these two saccade types (Kojima et al. 2010). Regarding the adaptation mechanisms maintaining saccade accuracy (so-called saccadic adaptation), several behavioural studies have highlighted that they differ for reactive and voluntary saccades, but they did not test the neural substrates underlying this difference (Alahyane et al. 2007; Collins and Dore-Mazars 2006; Cotti et al. 2007; Cotti et al. 2009; Deubel 1995; Erkelens and Hulleman 1993; Fujita et al. 2002; Zimmermann and Lappe 2009).

Concerning adaptation mechanisms that allow decreasing the amplitude (adaptive shortening) of reactive saccades, a major contribution of the medio-posterior cerebellum has been demonstrated (oculomotor vermis composed of lobules VI–VII and caudal part of the fastigial nucleus: Hopp and Fuchs 2004; Iwamoto and Kaku 2010; Pelisson et al. 2010; Prsa and Thier 2011; Tian et al. 2009). This has initially been based on lesion studies in animals (Barash et al. 1999; Optican and Robinson 1980; Takagi et al. 1998) and then in human patients with cerebellar lesions affecting the vermis (Golla et al. 2008) as well as in patients with a neurodegenerative disease primarily affecting the Purkinje cells, particularly in the vermis (Xu-Wilson et al. 2009). Although induced by a lesion outside the cerebellum, in the lateral medulla, Wallenberg syndrome is a good model of dysfunction of the medio-posterior cerebellum in humans. Indeed, by interrupting olivo-cerebellar fibres travelling in the inferior cerebellar peduncle, the lesion yields functional deficits such as saccadic lateropulsion that are similar to those resulting from damage of the fastigial nucleus (Helmchen et al. 1994; Straube et al. 1994; Tilikete et al. 2006). Unfortunately, previous studies concerning the adaptive

capabilities of Wallenberg patients provided contradictory results (Choi et al. 2008; Waespe and Baumgartner 1992). Despite this controversy, the role of the medio-posterior cerebellum in reactive saccades adaptation has been confirmed by other approaches (Desmurget et al. 1998; Jenkinson and Miall 2010). To our knowledge, no previous studies tested the involvement of the medio-posterior cerebellum in voluntary saccades adaptation. Moreover, very little is known regarding the involvement of the cerebellar hemispheres in either reactive saccades or voluntary saccades adaptation. A recent transcranial magnetic stimulation (TMS) study disclosed a contribution of the hemispheric lobule Crus I in the adaptation of reactive saccades (Panouilleres et al. 2012a). A role of the cerebellar hemisphere was also suggested by deficits of adaptation of reactive saccades (Alahyane et al. 2008b; Choi et al. 2008; Golla et al. 2008; Straube et al. 2001) or of voluntary saccades (Alahyane et al. 2008b) in patients with lesions involving both the medial and lateral parts of the cerebellum. A recent study, using functional neuroimaging, investigated the brain areas underlying adaptation of both categories of saccades (Gerardin et al. 2012). Besides the newly demonstrated involvement of the cerebral cortex, the authors reported that hemispheric lobules VIIb–VIIIa of the cerebellum are involved in the adaptation of both saccade types.

The aim of the present study was to investigate the cerebellar substrates of saccadic adaptation in human. We focused on the adaptive shortening mechanisms because, although the most studied behaviourally, their neural bases remain largely unknown. We searched for adaptation deficits resulting from stroke lesions in cerebellar and Wallenberg patients and looked for possible dissociations between reactive and voluntary saccades according to the affected territories.

Methods

Standard protocol approval, registrations and patients consent

Experimental procedures were approved by the national French committees on human experimentation (CPPRB Lyon B, agreement 2003-036B and DGS agreement 2003/0506). A written informed consent was obtained from all patients and all healthy subjects.

Subjects

From 2005, we prospectively included 18 patients with isolated focal cerebellar or medullary stroke. Four patients were excluded because of difficulty in understanding and/or in performing the oculomotor tasks. The clinical features

Table 1 Clinical data of the 14 patients

Patients	Sex	Age	Delay	Initial clinical manifestations	BARS (at time of examination)						Type of stroke	Territory	Side
					I	II	III	IV	V	Total			
P1	M	58	9 d	Static cerebellar ataxia, right Horner sign, left spino-thalamic deficit, right saccadic lateropulsion, left-beating head-shaking nystagmus	1	0	0	0	1	2	Isch	IPICA	Right
P2	M	51	5 m	Vertigo and right-beating nystagmus	0	0	0	0	0	0	Isch	l&mPICA	Right
P3	M	41	25 m	Vertigo and right-beating nystagmus	0	0	0	0	1	1	Isch	mPICA	Left
P4	M	63	27 d	Vertigo, right Horner sign, left spino-thalamic deficit	0	0	2	0	1	3	Isch	mPICA	Right
P5	M	61	4 m	Vertigo, left-beating nystagmus, right kinetic cerebellar syndrome, dysarthria, left spino-thalamic deficit	3	2	0	0	1	6	Isch	mPICA	Right
P6	M	40	10 d	Right kinetic cerebellar syndrome, right-beating nystagmus, right-sided tinnitus	2	2	2	0	1	7	Isch	ISCA	Right
P7	M	39	1.5 m	Dysarthria	0	0	0	2	0	2	Isch	ISCA	Right
P8	M	56	2 m	Ataxia, nausea, right kinetic cerebellar syndrome, dysarthria	1	1	1	1	0	4	Isch	ISCA and AICA	Right
P9	M	50	1 m	Ataxia, right kinetic cerebellar syndrome	3	2	2	0	0	7	Hem	“mSCA”	Right
P10	F	38	18 m	Paraesthesia, vertigo, ataxia, left spino-thalamic deficit, right kinetic cerebellar syndrome, torsional nystagmus	3	2	0	0	1	6	Isch	Medulla	Right
P11	M	49	2 m	Ataxia, hiccup, right spino-thalamic deficit, left kinetic cerebellar syndrome, left Horner sign, left skew deviation, torsional nystagmus	2	0	0	0	1	3	Isch	Medulla	Left
P12	F	38	2 m	Left axial lateropulsion, swallowing and phonation deficit, left peri-ocular pain, right spino-thalamic deficit, left hemifacial sensory deficit, right-beating nystagmus	1	0	0	0	1	2	Isch	Medulla	Left
P13	M	58	9 m	Vertigo, left-beating nystagmus, left Horner sign, left central facial palsy, right spino-thalamic deficit, swallowing and phonation deficit, left skew deviation	2	2	0	1	1	6	Isch	Medulla	Left
P14	F	36	28 m	Vertigo, right-beating nystagmus, right hemiparesia, left spino-thalamic deficit, right Horner sign, right saccadic lateropulsion, right skew deviation	3	0	0	0	2	5	Isch	Medulla	Right

M male, *F* female, *d* day, *m* month, *PICA* postero-inferior cerebellar artery, *SCA* superior cerebellar artery, *l* lateral branch, *m* medial branch. We used the thirty-point brief ataxia rating scale (BARS) (Schmahmann et al. 2009) to assess ataxia or cerebellar signs at time of examination. This test translates the classical symptomatology of ataxia into 5 semi-quantitative scores (I, postural and stance disturbances; II, inferior limb movements disturbances; III, superior limb movements disturbances; IV, speech disorders; V, oculomotor disorders)

of the 14 remaining patients are summarised in Table 1. MRI showed a stroke at the level of the postero-inferior cerebellar artery (PICA) territory in 5 patients (P1–P5, PICA group), of the superior cerebellar artery (SCA) and/or of the antero-inferior cerebellar artery (AICA) in 4 patients (P6–P9, SCA–AICA group) and in the medulla (Wallenberg) in 5 patients (P10–P14, Wallenberg group). The vermis of SCA–AICA and PICA patients was completely spared in four patients and only partly affected in the five remaining patients. Data of patients P5 and P6 have been reported elsewhere (Alahyane et al. 2008b), as well

as the data of 6 healthy adults (age 22–48 years old), with no history of neurological disease, who served as controls (Alahyane et al. 2007).

Experimental set-up and design

Participants sat in front of a computer screen (vertical refresh rate: 140 Hz—visual angle: 30° × 40°) located at 57 cm, their head being restrained with chin and cheekbone rests. Presentation of stimuli was controlled by a VSG system (Visual Stimuli Generation—CRS Cambridge, UK),

and subjects were instructed to carefully follow visual targets (black circles of 6 mm diameter on a grey background). Eye movements were binocularly recorded at 250 Hz with a helmet-mounted infrared eye tracker (Eye-link 2, SR-Research, Canada).

The paradigm used in the present study is identical to the one reported in previous articles (Alahyane et al. 2007; Alahyane et al. 2008b). Details of the protocol are described in supplementary material. Reactive saccades and scanning voluntary saccades were tested in two separate sessions, with a counterbalanced order between subjects. Each session was composed of 3 phases: pre-adaptation (24 saccades), adaptation (240 saccades), post-adaptation (24 saccades). During the adaptation phase, we used the double-step target paradigm to adaptively shorten saccade amplitude (McLaughlin 1967): at the beginning of each primary horizontal saccade (when eye velocity reached a 70–110°/sec threshold), the visual stimulus (one target for the reactive saccade protocol and the set of four targets and fixation point for the voluntary saccade protocol) was displaced in the direction opposite to the saccade (Fig. 1, top panels, adaptation). This intra-saccadic visual perturbation produced an error between the eyes landing position and the target location which, when repeated over trials, led to a progressive decrease in saccade amplitude. Rightward and leftward saccades were simultaneously adapted by presenting the target at $\pm 8^\circ$ pseudo-randomly in the same sessions. The intra-saccadic visual perturbation corresponded to 25 % of initial target eccentricity for the first three adaptation blocks (3 \times 48 saccades: a25, b25, c25) and to 40 % for the last two blocks (2 \times 48 saccades: d40, e40), respectively. Paradigms based on a similar increase in the size of intra-saccadic target jump were successfully used in the past (Alahyane and Pelisson 2005; Alahyane et al. 2007; Alahyane et al. 2008b; Panouilleres et al. 2011; Panouilleres et al. 2012b; Panouilleres et al. 2013; Wong and Shelhamer 2011; Zimmermann and Lappe 2009). We decided to use this strategy of increasing the size of the intra-saccadic target step in our patients in order to maximise the amount of saccadic adaptation. Finally, short breaks were interleaved between blocks of trials to avoid the development of excessive fatigue in the participants. However, because there were only four breaks during the adaptation phase and because their duration was not constant between subjects (from 30 s to 2–3 min), we did not attempt to study the forgetting of adaptation which might occur during breaks (Ethier et al. 2008; Xu-Wilson et al. 2009).

In the pre-adaptation and post-adaptation phases, subjects performed one block of 24 saccades (12 in each direction) directed towards targets presented at $\pm 8^\circ$ relative to the centre of the screen (Fig. 1, bottom panels, pre- and post-adaptation). Instead of an intra-saccadic step, the visual stimulus disappeared at the beginning of the primary

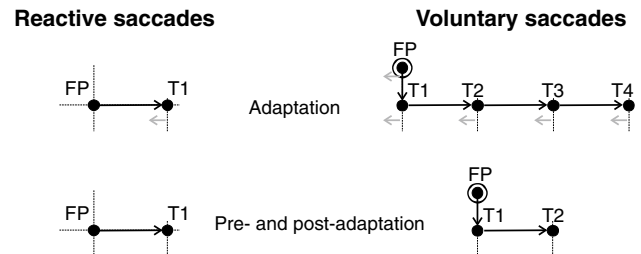


Fig. 1 Protocols for the adaptation (*top row*) and for the pre- and post-adaptation phases (*bottom row*). Reactive saccades were triggered by the sudden appearance of a target (T1) at 8° (in this example, *on the right*), simultaneously with the disappearance of the fixation point (FP). During an adaptation trial, the initiation of the reactive saccade (*black arrow*) was responsible for the intra-saccadic jump (*short grey arrow*) of the target. During pre- and post-adaptation trials, T1 disappeared at saccade onset. In the adaptation trials for the voluntary saccade, the visual stimulus consisted in the fixation point (FP) and 4 targets, all presented simultaneously. At the disappearance of the *circle* surrounding the FP, subjects were required to explore the different targets in the following order: T1, T2, T3 and T4. For each *horizontal saccade* (*black horizontal arrow*), the entire set of targets and FP jumped intra-saccadically (*short grey arrow*). For the pre- and post-adaptation trials of the voluntary saccade experiment, only three targets were presented. When the *circle* surrounding the FP disappeared, participants were required to make first a *vertical saccade* towards T1 and then a *horizontal saccade* towards T2. During the *horizontal voluntary saccade*, all targets disappeared

saccade (velocity threshold 70–110°/sec) to suppress any visual feedback. These pre-adaptation and post-adaptation blocks were aimed at evaluating the saccadic baseline parameters and the after-effects of adaptation, respectively. Pre-adaptation, adaptation and post-adaptation trials are detailed in the supplementary material.

Data analysis

The beginning and end of primary saccades were detected offline with a custom program developed in Matlab v.7.1 (Mathworks, MA., U.S.A.), using a 50°/sec velocity threshold. For every phase, saccadic gain was calculated as the ratio between saccadic amplitude and initial target eccentricity. Saccades contaminated by a blink and/or associated with an incorrect or absent intra-saccadic visual perturbation, and saccades with gain outside the [mean of 12 saccades ± 3 standard deviation] range were excluded (in total, 3 % of reactive and 3 % of voluntary saccades in healthy subjects, while 6 and 8 %, respectively, in patients). The change of gain of each saccade (n) in the pre-adaptation, adaptation and post-adaptation phases was calculated relative to the pre-adaptation phase as follows:

$$\text{Gain change of saccade } n = \frac{\text{Gain of saccade } n - \text{Mean gain pre}}{\text{Mean gain pre}}$$

For each subject, a mean gain change was determined for each of the 5 blocks (a25, b25, c25, d40 and e40) of the adaptation phase and for the post-adaptation block (“adaptation after-effect”). Moreover, for each pre-adaptation trial, the duration, latency and peak velocity were computed for all horizontal saccades (i.e., first movement in the reactive saccade task and second movement in the voluntary saccade task). In the case of the voluntary saccade sessions, the termination of the vertical saccade was detected to allow computation of the latency of the horizontal saccade, defined as the duration of the fixation period separating the two saccades. Saccadic gain variability was measured for each subject as the standard deviation of the mean gain in pre-adaptation.

Statistical analyses were performed with the R software (R Development Core Team 2012) using nonparametric tests, as detailed in the supplementary material. Briefly, different statistical tests were used for the pre-adaptation/post-adaptation phases (Kruskal–Wallis tests) and for the adaptation phase (nonparametric ANOVA). For each of these three phases, the analysis (Kruskal–Wallis or nonparametric ANOVA) allowed to compare patient performances relative to controls, separately for the two saccade types and for the three patients’ groups. Significance was set at $p < 0.05$.

Results

Saccadic baseline

The baseline parameters of reactive and voluntary saccades measured in the pre-adaptation phase are presented in Table 2. Each baseline parameter was submitted to Kruskal–Wallis tests (see supplementary material),

separately for reactive and voluntary saccades and for the three groups of patients, to assess differences between ipsilesional saccades, contralesional saccades and control saccades (right and left saccades were pooled together for controls). Kruskal–Wallis tests were followed by Dunnett tests, to directly compare controls with patients. For both categories of saccades, the latency did not differ among groups (Kruskal–Wallis tests < 3.3 , $p > 0.19$). But, as expected [see e.g. (Alahyane et al. 2007)], the latency was longer for voluntary saccades than for reactive saccades. Compared to controls, the gain of ipsilesional reactive saccades was significantly higher for both SCA–AICA patients (Kruskal–Wallis test = 7.7, $p < 0.05$; Dunnett test, $p < 0.001$) and Wallenberg patients (Kruskal–Wallis test = 4.8, $p = 0.09$; Dunnett tests, $p < 0.05$). Regarding contralesional reactive saccades, a higher peak velocity was found in SCA–AICA and Wallenberg patients than in healthy subjects (Kruskal–Wallis tests = 4.8, $p = 0.09$ and 6.5, $p < 0.05$, respectively; Dunnett tests, $p < 0.001$). Further, ipsilesional voluntary saccades lasted longer in Wallenberg patients than in controls (Kruskal–Wallis test = 5.5, $p = 0.06$; Dunnett test, $p < 0.001$), and this could be linked to the nonsignificant trend of larger saccade gain (Wallenberg: 1.14 ± 0.35 versus controls: 0.94 ± 0.05). PICA patients were more hypometric than controls for contralesional voluntary saccades (Kruskal–Wallis test = 5.5, $p = 0.06$; Dunnett test, $p < 0.001$) and Wallenberg patients produced contralesional voluntary saccades with higher peak velocity than controls (Kruskal–Wallis test = 5.1, $p = 0.08$; Dunnett tests, $p < 0.001$). We also compared the intra-subject variability of gain, measured as the standard deviation of the mean, in the pre-adaptation phase between the three groups of patients and the controls, separately for the voluntary and the reactive saccades, but did not find any

Table 2 Baseline parameters of reactive and voluntary saccades

	Controls	PICA patients		SCA–AICA patients		Wallenberg	
		Ipsi	Contra	Ipsi	Contra	Ipsi	Contra
Reactive saccades							
Latency (ms)	247 ± 79	238 ± 54	257 ± 59	192 ± 34	208 ± 59	261 ± 65	254 ± 81
Gain	0.88 ± 0.02	0.83 ± 0.06	0.82 ± 0.08	0.96 ± 0.01***	0.94 ± 0.08	1.03 ± 0.17*	0.89 ± 0.08
Duration (ms)	41 ± 4.3	43 ± 6.3	43 ± 7	39 ± 7.6	40 ± 7.2	54 ± 15.9	47 ± 16.6
Peak vel. (°/s)	243 ± 19	246 ± 73	246 ± 70	310 ± 67	306 ± 52***	268 ± 29	279 ± 17***
Voluntary saccades							
Latency (ms)	438 ± 157	523 ± 132	504 ± 185	570 ± 120	560 ± 154	486 ± 114	513 ± 199
Gain	0.94 ± 0.05	0.89 ± 0.04	0.86 ± 0.05***	0.91 ± 0.09	0.94 ± 0.04	1.14 ± 0.35	0.89 ± 0.06
Duration (ms)	42 ± 4.2	46 ± 11.0	49 ± 16.9	43 ± 7.1	43 ± 6.7	63 ± 22.5***	50 ± 16.6
Peak vel. (°/s)	249 ± 17	268 ± 60	249 ± 67	290 ± 94	278 ± 88	269 ± 70	293 ± 25***

Mean values with standard errors of saccade latency, gain, duration and velocity peak (peak vel.)

Significant differences between patients and controls: * $p < 0.05$, *** $p < 0.001$ (Dunnett tests)

difference between groups (Kruskal–Wallis tests < 3.4 , $p > 0.18$).

Adaptation time-course

To estimate the time-course of adaptation induced by the double-step target paradigm, the change in gain for each adaptation trial was computed relative to the mean pre-adaptation gain. The time-course of adaptive changes induced by the double-step target paradigm is shown in Fig. 2 in one representative subject of each group (control, PICA, SCA–AICA and Wallenberg patients), for reactive saccades (Fig. 2a) and for voluntary saccades (Fig. 2b). Each symbol corresponds to a single saccade. The x -axes represent the course of the experimental sessions, and the y -axes represent the gain changes calculated relative to the mean gain in pre-adaptation. Saccades in the two directions were plotted separately (all patients represented in this figure had right-sided lesion). As exemplified by the control participant (top row), the intra-saccadic target steps used

during the adaptation phase led to a progressive decrease of gain. For this participant, the gain remained reduced in the post-adaptation phase by about 25 % relative to pre-adaptation for the reactive saccades and by about 11 % for voluntary saccades. A similar adaptation can be observed for the PICA patient (second row). For the SCA–AICA patient (third row), the adaptive changes of the ipsilesional (rightward) voluntary saccades measured at the end of the adaptation phase and in the post-adaptation phase were smaller as compared to the control subject. Finally, for the Wallenberg patient (last row), only small gain changes were observed for the ipsilesional (rightward) reactive and voluntary saccades, during the adaptation phase and hence during the post-adaptation phase as well.

The time-course of adaptation was then studied separately for each group of patients. The change in gain was averaged among participants of each group and plotted as a function of the adaptation block, separately for voluntary and reactive saccades (Fig. 3). A general progressive decrease of gain occurred in all subjects groups, but to

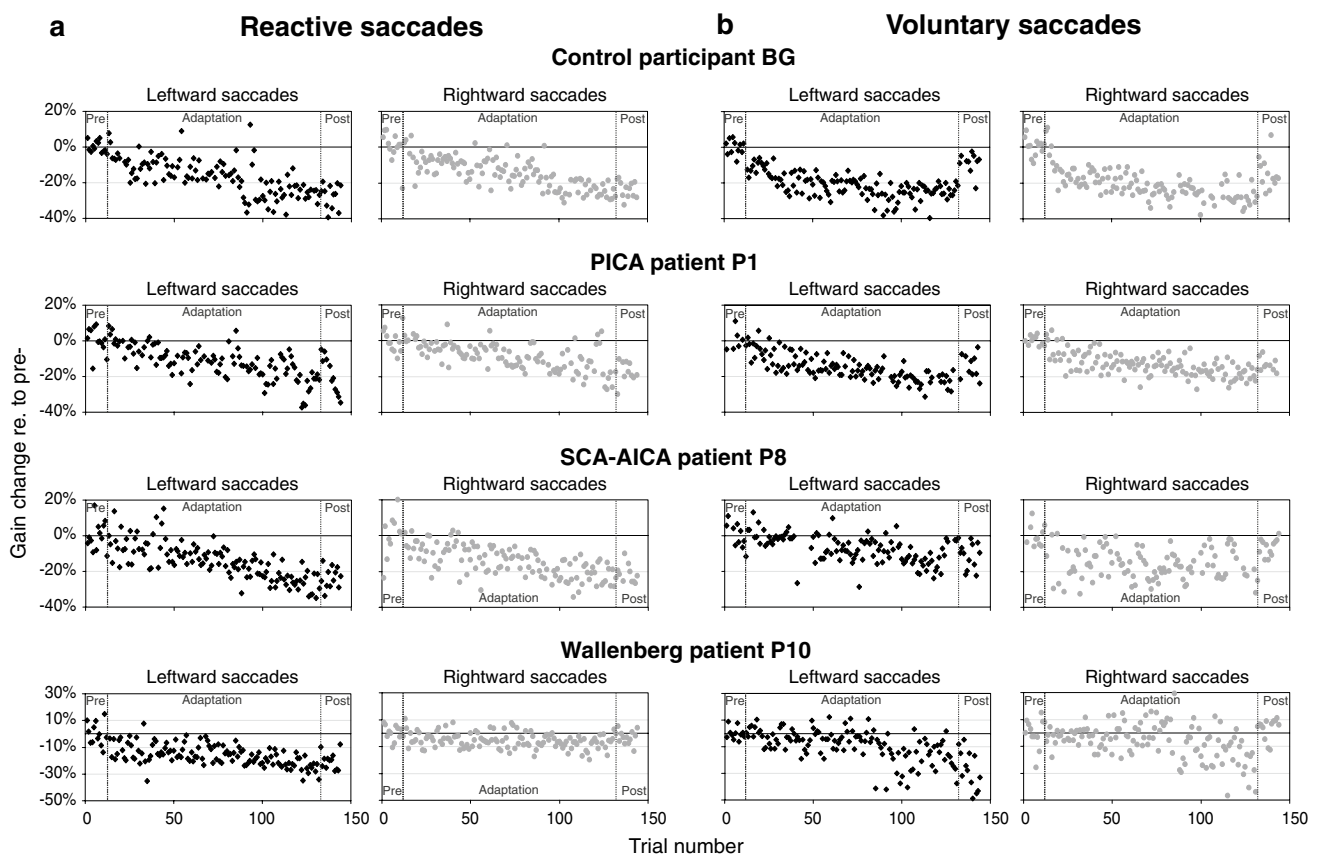


Fig. 2 Gain changes of representative subjects of each group for the reactive saccade and the voluntary saccade experiments. The scatter plots represent the trial-by-trial gain changes, relative to mean pre-adaptation gain, of the reactive saccades (**a**) and of the voluntary saccades (**b**). Leftward saccades (*black diamonds*) and rightward sac-

cades (*grey discs*) are plotted separately. *Vertical dotted lines* indicate the separation between the different phases: pre-adaptation (Pre), adaptation and post-adaptation (Post). PICA patient P1 and SCA–AICA patient P8 had right lesions of the cerebellum. Wallenberg patient P10 had a right lesion of the lateral medulla

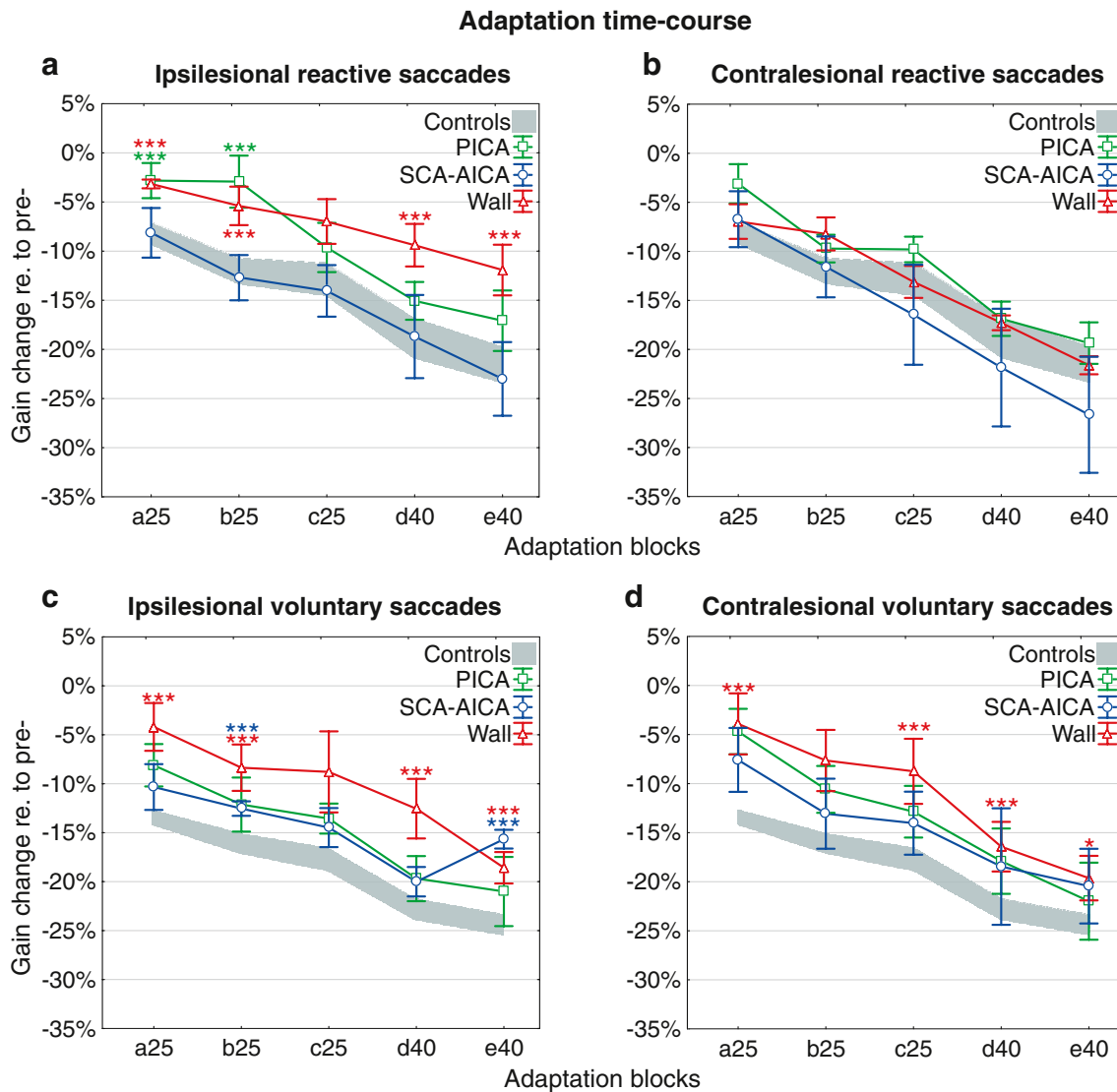


Fig. 3 Development of the adaptation for the different groups of patients and for the controls. Gain changes relative to the mean gain in pre-adaptation are plotted as a function of adaptation blocks: a25, b25, c25 (perturbation of visual stimulus of 25 % of initial target eccentricity) and c40, d40 (perturbation of 40 %). These plots were built separately for reactive (a, b) and voluntary (c, d) saccades produced in the ipsilesional (a, c) and contralesional (b, d) directions. The grey-shaded areas represent mean values ± 1 standard error of the

mean (SEM) of gain changes measured for the control group (data of *rightward* and *leftward* saccades were averaged). The *green, blue and red lines and symbols* correspond to gain changes, respectively, for the PICA, SCA–AICA and Wallenberg patients (*error bars* show SEMs). *Asterisks (same colour code)* indicate significant differences of gain changes for a particular adaptation block between PICA, SCA–AICA or Wallenberg patients and the control group: * $p < 0.05$, *** $p < 0.001$ (Dunnett tests)

different extents depending on the cerebellar lesion. Non-parametric ANOVAs (see supplementary material) were performed on the gain changes, separately for reactive and voluntary saccades and for the three groups of patients, with the “group” factor (patient ipsilesional \times patient contralesional \times controls) and the repeated measures “adaptation blocks” factor (a25 \times b25 \times c25 \times d40 \times e40). Significant ANOVAs were followed by post hoc Dunnett tests. The observation of a general progressive gain decrease during the adaption phase was confirmed by the main effect of

the “adaptation blocks” factor in all six ANOVAs (nonparametric ANOVA, $p < 0.001$). However, differences between controls and patients were also revealed with these non-parametric ANOVAs. For the PICA patients, a main effect of the group factor on gain changes was found for reactive saccades ($p < 0.05$), without any interaction with the adaptation blocks ($p = 0.34$). This main effect was related to the fact that, as compared to control subjects, a smaller decrease in gain for ipsilesional saccades during the first two adaptation blocks could be observed (Fig. 3a—Dunnett

tests, $p < 0.001$). No difference between PICA patients and controls was detected for the adaptive changes of voluntary saccades (Fig. 3c, d—nonparametric ANOVA, group factor and group \times adaptation blocks interaction, $p > 0.6$). In the case of SCA–AICA patients, gain changes for reactive saccades were similar to the ones of the control participants (Fig. 3a, b—nonparametric ANOVA, group factor and group \times adaptation blocks interaction, $p > 0.13$). However, a significant interaction between the group factor and the block factor was revealed for the voluntary saccades ($p < 0.05$). Indeed, ipsilesional voluntary saccades were less shortened for the patients in the third adaptation block and in the last adaptation block than for the control subjects (Dunnett tests, $p < 0.001$). Surprisingly, the difference between controls and SCA–AICA patients in the last adaptation block was due to a quick drop of adaptation for the patients (Fig. 3c). This drop was specific to the ipsilesional, but not to the contralesional saccades. Note, however, that, although present in all 4 patients of this group, the mean effect is mainly driven by patient P6 who showed a much larger drop of adaptation between the fourth and last adaptation blocks (about 10 %) than the other three patients (only 2–3 %, data not shown). Finally, Wallenberg patients showed strong deficits in adaptation time-course for both reactive and voluntary saccades (nonparametric ANOVA, group effect, $p < 0.001$ and $p < 0.01$, respectively). Indeed, gain changes of ipsilesional reactive saccades were smaller for Wallenberg patients than for controls for most of the adaptation phase, except the third block (Fig. 3a—Dunnett tests, $p < 0.001$). Similarly, the adaptive changes for both directions of voluntary saccades were strongly impaired for the patients compared to controls (see Fig. 3c, d, Dunnett tests, $p < 0.05$).

To summarise, for PICA patients, the decrease in ipsilesional reactive saccade gain was smaller than in healthy subjects only at the beginning of the adaptation phase. For SCA–AICA patients, a reduced gain change relative to controls was observed for ipsilesional voluntary saccades, at the very end of the adaptation phase, but this effect was mainly driven by one patient. Finally, Wallenberg patients showed a poor decrease in gain for ipsilesional reactive saccades and for both voluntary saccades directions for most of the adaptation phase.

Adaptation after-effect

The change in saccade gain in the post-adaptation phase when the visual perturbation was stopped provided a measure of adaptation after-effect. It is therefore considered to specifically assess the amount of adaptation, independently of any cognitive or strategic factors (Bastian 2008). As shown in Fig. 4, after-effects differed among groups. Kruskal–Wallis tests (see supplementary material) were

performed separately for reactive and voluntary saccades and for the three groups of patients, to compare after-effects between controls and the ipsilesional and contralesional saccades of the patients. PICA patients had similar after-effects than controls for both saccade types (Fig. 4a, b—Kruskal–Wallis test < 1.8 , $p > 0.40$). The after-effects of reactive saccades were also similar for SCA–AICA patients and controls (Fig. 4b—Kruskal–Wallis test = 0.38, $p = 0.83$). However, the after-effect of ipsilesional voluntary saccades was significantly smaller for SCA–AICA patients compared to control subjects (Kruskal–Wallis test = 5.1, $p = 0.08$; Dunnett tests, $p < 0.001$). Because the reduced gain change at the end of the adaptation phase was mainly driven by one SCA–AICA patient (see previous section), we looked at the after-effect separately in each patient. The after-effects of the patients ranged from -4 to -12 % (mean -8.1 ± 3.1 %), whereas the after-effects of the 6 control participants ranged from -10 to -20 % (mean -15.4 ± 3.9 %). Thus, a reduced after-effect for ipsilesional voluntary saccades appears consistent for all SCA–AICA patients. Concerning Wallenberg patients, a strong reduction of after-effect was observed for both ipsilesional and contralesional reactive saccades (Fig. 4a—Kruskal–Wallis test = 8.8, $p < 0.05$; Dunnett tests, $p < 0.001$ and $p < 0.05$, respectively) and for ipsilesional voluntary saccades (Fig. 4b—Kruskal–Wallis test = 4.5, $p = 0.10$; Dunnett tests, $p < 0.05$).

Thus, the adaptation after-effect was significantly and consistently reduced, relative to controls, in SCA–AICA patients for ipsilesional voluntary saccades, in Wallenberg patients for reactive saccades bidirectionally and again in Wallenberg patients for ipsilesional voluntary saccades.

Discussion

The main aim of this study was to investigate the role of different cerebellar territories in saccadic adaptation. Before discussing this aspect, we compare the baseline saccade parameters between the different subjects groups.

Saccade metrics and cerebellar lesions

One of the typical features of Wallenberg syndrome is the saccadic lateropulsion, characterised by ipsilesional saccades hypermetria, contralesional saccades hypometria and ipsilesional deviation of vertical saccades (Helmchen et al. 1994; Straube et al. 1994; Tilikete et al. 2006). As indicated in “Introduction”, saccadic lateropulsion could reflect a dysfunction of the fastigial nucleus, resulting from damage of the afferent pathway from the inferior olive. In our Wallenberg patients, the ipsilesional hypermetria tendency is consistent with saccadic lateropulsion, and with a damage

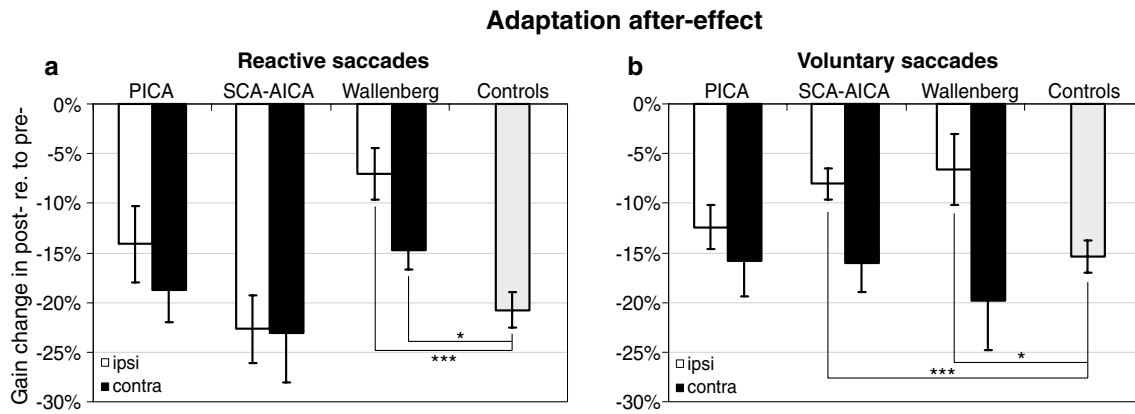


Fig. 4 Adaptation after-effects for reactive saccades (**a**) and for voluntary saccades (**b**). After-effects were calculated as gain changes in post-adaptation relative to the mean gain measured in pre-adaptation. Mean values are plotted separately for the ipsilesional saccades (white bars) and for the contralateral saccades (black bars)

of the three groups of patients and as the average of the *rightward and leftward saccades* of the control group (grey bars). Error bars show SEMs. Asterisks indicate significant differences of after-effects between PICA, SCA-AICA or Wallenberg patients and the control group: * $p < 0.05$, *** $p < 0.001$ (Dunnett tests)

of this pathway, despite the lack of contralesional hypometria. The absence of hypometria might reflect an incomplete clinical picture and/or insufficient evaluation (target eccentricity too small). The fact that the hypermetria tendency was observed for both reactive and voluntary saccades further suggests that the olivo-cerebellar pathway could be implicated in the control of these two saccade categories. This hypothesis is consistent with data in monkeys, which showed that the oculomotor vermis contributes similarly to the production of reactive and scanning voluntary saccades (Kojima et al. 2010). This hypothesis is also supported by recent fMRI data in humans (Schraa-Tam et al. 2009).

Our PICA and SCA-AICA patients showed hypometric contralesional voluntary saccades and hypermetric ipsilesional reactive saccades, respectively. As mentioned in “Methods”, the lesion predominantly affected the cerebellar hemispheres in both groups of patients. This suggests that the control of saccade metrics is also implemented in cerebellar territories other than the vermis. Some studies have reached this conclusion for reactive saccades (Dietrich et al. 2000; Hayakawa et al. 2002; Panouilleres et al. 2012a; Schraa-Tam et al. 2009). Two fMRI studies also suggested that nonvermal cerebellar regions, lobules VI and Crus I, could play a role in the control of reactive and voluntary saccades (Hayakawa et al. 2002; Schraa-Tam et al. 2009). These hemispheric lobules are located above the horizontal fissure, in the vascular domain of the SCA (Schmahmann et al. 2000; Tatu et al. 1996). In complement with these findings, our results suggest that the supero-anterior cerebellum is implicated in the control of reactive saccades metrics and that the infero-posterior cerebellum (vascular domain of the PICA) would play a more important role in the control of voluntary saccade metrics.

Adaptation of reactive saccades and cerebellar lesions

A crucial contribution of the cerebellum to reactive saccades adaptation has been repeatedly demonstrated (reviewed in Hopp and Fuchs 2004; Pelisson et al. 2010; Prsa and Thier 2011; Tian et al. 2009). Lesions studies in monkeys showed the involvement of medio-posterior cerebellum, composed of vermal lobules VI–VII and of the caudal part of the fastigial nucleus, in saccadic plasticity (Barash et al. 1999; Iwamoto and Kaku 2010; Optican and Robinson 1980; Takagi et al. 1998). Similarly, lesion studies in human patients consistently point to the key role of the cerebellum in reactive saccade adaptation (Alahyane et al. 2008a; Choi et al. 2008; Golla et al. 2008; Straube et al. 2001; Waespe and Baumgartner 1992). Golla et al. (2008) specifically reported that only the patients with lesion including the vermis showed impaired adaptation. Moreover, Xu-Wilson et al. (2009) showed that patients with spinocerebellar ataxia type 6 (SCA6), a neurodegenerative disease mainly affecting the Purkinje cells and especially the vermis, presented strong deficits of saccadic adaptation. In comparison, the effects of lateral medullary infarctions on saccadic adaptation are still discussed, as decreased capabilities of adaptation in Wallenberg patients were reported in one study (Waespe and Baumgartner 1992), but not in the other (Choi et al. 2008). Our own results disclosed a strong deficit of saccadic adaptation in Wallenberg patients. Note that contrary to the present study and to Waespe and Baumgartner’s (1992), patients in Choi et al.’s study did not present clear signs of saccadic lateropulsion. This last observation suggests that the olivo-cerebellar saccadic pathway was partly spared in their Wallenberg patients, which could account for their normal saccadic adaptation capabilities.

Medio-posterior cerebellum and error signal for saccadic adaptation

We found that Wallenberg patients presented strong impairment of ipsilesional saccades adaptation and characterised by slow development and weak after-effect of adaptive changes. The slowing of adaptation time-course seems to suggest that the olivo-cerebellar pathway is involved in the transmission of a signal necessary for the establishment of adaptive changes. Recent studies in monkeys proposed that an error signal leading to saccadic adaptation is produced at the level of the deep layers of the superior colliculus (Kaku et al. 2009; Soetedjo et al. 2009). Kaku et al. (2009) further proposed that this signal would be conveyed to the oculomotor vermis via the inferior olivary nucleus. Our data in Wallenberg patients are compatible with this hypothesis, and because adaptation of both reactive and voluntary saccades was impaired in these patients, our study supports the hypothesis that this collicular-olivo-cerebellar pathway can be implicated in conveying adaptive error signals for both saccade categories. Alternatively, our results are also compatible with the popular forward model hypothesis (Wolpert et al. 1998). According to this hypothesis, the cerebellum uses an efference copy of motor commands to compute a prediction of visual feedback and ultimately an error signal required for sensorimotor adaptation. Saccadic adaptation deficits in our Wallenberg patients could then result from an alteration of error signal related to an impaired cerebellar forward model. We therefore conclude that the medio-posterior cerebellum plays a critical role in the adaptation of the two saccade types, either in modifying the oculomotor commands by processing an error signal transmitted through the olivo-cerebellar pathway or in computing this error signal necessary for adaptation.

Hemispheric cerebellar structures involved in saccadic adaptation

Postero-inferior cerebellar artery patients presented essentially an abnormally slow decrease in ipsilesional reactive saccades gain at the beginning of the adaptation phase. However, gain changes that occurred later during the adaptation phase and the after-effects measured in post-adaptation matched those of controls. These partial deficits suggest that the territories vascularised by PICA are not really critical for saccadic adaptation. On the contrary, SCA–AICA patients presented, for ipsilesional voluntary saccades, a consistently smaller gain decrease than controls in post-adaptation, and a less consistent, albeit significant, difference with controls in the last adaptation block. This suggests that the damaged cerebellar structures are involved in late acquisition and/or maintenance of voluntary saccades adaptation. A recent study on the adaptation of the upper

limb to visuomotor rotation concluded that SCA patients show impairment of both error reduction and after-effect of adaptation, whereas PICA patients were mainly impaired during the error reduction phase (Werner et al. 2010). Thus, for both the voluntary movements of the upper limb and of the eyes, the superior part of the cerebellum could be crucial for the after-effect of sensorimotor adaptation.

In conclusion, this study shows for the first time that the modulation of the medio-posterior cerebellum by the olivo-cerebellar pathway contributes to the development of adaptation of both reactive and voluntary saccades. Our results also highlight that the supero-anterior part of the cerebellar hemispheres is specifically involved in the adaptation of voluntary saccades.

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