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Review

Sensorimotor adaptation of saccadic eye movements

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ABSTRACT

Sensory-motor adaptation mechanisms play a pivotal role in maintaining the performance of goal-directed movements. The saccadic system, used to explore the visual environment through fast and accurate shifts of the eyes (saccades), is a valuable model for studying adaptation mechanisms. Significant progresses have been recently made in identifying the properties and neural substrates of saccadic adaptation elicited by the double-step target paradigm. Behavioural data collected in healthy and brain-damaged subjects, and neurophysiological data from non human primates, will be reviewed in an attempt to build a coherent picture of saccadic adaptation mechanisms. Emphasis will further be put on the contextual factors of saccadic adaptation, and on the link between adaptive changes of oculomotor commands and visual perception. It will be shown that saccadic adaptation relies on multiple mechanisms according to experimental contexts, time-scales, saccade categories, and direction of adaptive changes of saccade amplitude (shortening versus lengthening). Taking into account this complexity will be a key toward a comprehensive understanding of the physiopathology of saccadic adaptation and toward the development of possible rehabilitation procedures.

Contents

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1. Introduction

1.1. Definitions and role of adaptation

1.1.1. Saccades

Saccadic eye movements, allowing rapid changes of gaze direction, represent a major component of active visual perception. In primates, a saccade is generated 2 or 3 times per second on average, reflecting their outmost importance in normal visual perception. Goal-directed saccades have been subdivided into two main categories according to the experimental conditions in which they are triggered (Gaymard et al., 1998; Tusa et al., 1986). Reactive visually guided saccades (also known as reflexive or automatic or externally triggered) occur automatically in response to the sudden presentation of a new visual target. In laboratory, they are studied in the target step paradigm in which a punctual visual stimulus suddenly steps from an initial location (fixation point) to a randomly selected peripheral location. Latencies of reactive saccades are typically around 200 ms. But if a short temporal gap is introduced between the extinction of the fixation point and the appearance of the target (gap paradigm), express saccades can be elicited with latencies as short as 100 ms (Fischer and Weber, 1993). Conversely voluntary saccades (also known as intentional or internally triggered) are not initiated in response to the target sudden presentation, but rather on the basis of internal goals and motivations. Latencies of voluntary saccades are typically larger than 250 ms. Different sub-categories of voluntary saccades have been described such as: delayed saccades (looking at a permanently visible peripheral target only after a central go signal), memory-guided saccades (looking at the remembered location of a previously presented target), scanning saccades (looking sequentially between the elements of a stable visual scene), predictive saccades (looking between two regularly alternating targets), anti-saccades (looking toward a location opposite to a visual target). The neural substrates of the generation of these different saccade categories have been increasingly studied over recent years (Johnston and Everling, 2008; Leigh and Zee, 1999; McDowell et al., 2008; Munoz and Everling, 2004; Müri and Nyffeler, 2008; Pierrot-Deseilligny et al., 1995; Pierrot-Deseilligny et al., 2003). All this work has led to the commonly accepted view of a partial separation for reactive and for voluntary saccade generation, with a higher specificity to saccade categories in cortical areas than in sub-cortical areas (Fig. 1). Saccadic centers in the brainstem and cerebellum indeed belong to the common final network involved in all types of saccades. In the brainstem, the superior colliculus (SC) is a crucial visuo-motor integrating center which provides a link between, on the one hand, the various cortical eye fields and related basal ganglia loops and, on the other hand, the brainstem saccadic generator where the saccadic commands are ultimately generated. The cerebellum acts as a controller of this whole cortico-subcortical network and ensures optimal saccade performance by fine tuning the saccadic commands. Despite their frequent occurrence in our daily activities, voluntary saccades have been much less studied than reactive saccades, and this is especially the case for saccadic adaptation mechanisms

1.1.2. Adaptation

Any abnormality of saccades, either in their initiation or trajectory, increases the time necessary to bring the line of sight toward an object of interest in the visual field, and hence results in an impaired (and potentially unstable) visual perception (Leigh and Zee, 1999). But fortunately, all throughout the lifetime, saccades have quite stable performance, notably speed and accuracy (Munoz et al., 1998). The accuracy of a goal-directed saccade is defined by its gain, the ratio between the distance travelled by the eyes (saccade amplitude) and the distance of the target from the initial eye position (desired saccade amplitude). Under normal conditions, the saccadic response falls slightly short of the target and has a baseline gain near 0.9–0.95 (Becker, 1989). How does the central nervous system control this optimal gain of saccades? Accurate programming processes are essential because saccades are so fast that information from visual feedback cannot be used to correct midflight any error of trajectory (except under rare circumstances: Gaveau et al., 2003; Zee et al., 1976). Monkey studies have further shown that proprioceptive feedback information of eye position cannot be used either to compensate for errors of trajectory midflight (Guthrie et al., 1983; Lewis et al., 2001). Thus, the generation of adequate saccades, in spite of diseases and of numerous physiological changes related to development or aging, critically depends on a continuous recalibration of the oculomotor system by visuo-motor adaptation mechanisms. These

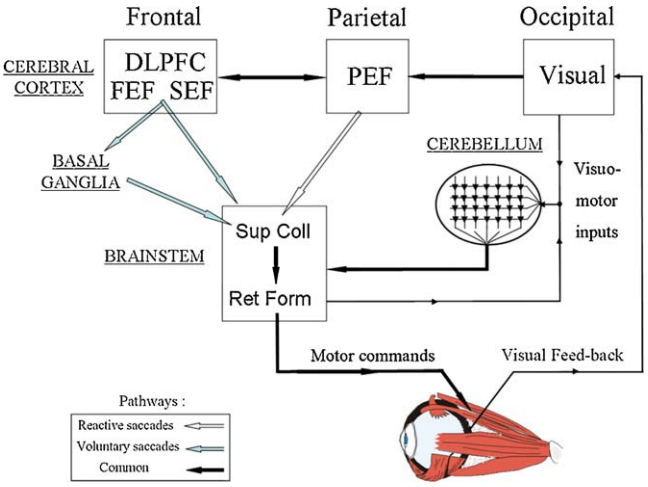

Fig. 1. Schematics of neural network involved in the generation of saccadic eye movements. Common pathways involved in the generation of all saccades are shown as black lines, whereas pathways contributing more to the reactive and the voluntary category are shown by white and grey lines, respectively. Posterior cortical areas (visual, parietal) show larger involvement for reactive saccades, and conversely frontal areas and basal ganglia are more recruited for voluntary saccades (McDowell et al., 2008; Munoz and Everling, 2004; Pierrot-Deseilligny et al., 1995; Pierrot-Deseilligny et al., 2003); both saccade categories similarly recruit brainstem and cerebellar common pathways (Leigh and Zee, 1999; Scudder et al., 2002). The cerebellum, shown as a bi-dimensional neuronal network, receives information from various sensori-motor levels ("visuo-motor inputs"), and projects back to these different levels (only brainstem projections are shown). FEF: frontal eye fields, SEF: supplementary eye fields, DLPFC: dorso-lateral prefrontal cortex, PEF: parietal eye fields, Sup Coll: superior colliculus, Ret Form: reticular formation.

adaptation mechanisms process errors in motor performance and iteratively update the relationship between a visual target location and the motor commands necessary to look at this target. Adaptation of saccadic eye movements (saccadic adaptation) has been initially demonstrated in patients suffering from monocular muscle weakness (Abel et al., 1978; Kommerell et al., 1976; Optican et al., 1985; Zee et al., 1976). Adaptation was induced by placing a patch to block vision in the patients' non-affected eye, thus forcing the central nervous system to monitor the visual consequences of hypometric saccades (i.e. too short) produced by the weak eye. This led to a progressive increase of the saccade amplitude until normometric responses of the affected eye was re-established after a few days. These observations have been confirmed by muscular lesion studies in the monkey (Optican and Robinson, 1980; Scudder et al., 1998).

In laboratory, saccadic adaptation has been studied mostly by the so-called double-step target paradigm initially reported by McLaughlin (1967). The principle is to simulate a spatial error in saccadic generation by systematically shifting the visual target during saccade execution. As schematized in Fig. 2A, a first step of the target from a central to a peripheral position of the visual field elicits a primary saccade in the course of which, taking advantage of the saccadic suppression phenomenon (Pelisson et al., 1986; Volkmann et al., 1968), the target is surreptitiously shifted (second step). During initial trials, the primary saccade is followed by corrective saccades to re-align the line of sight onto the shifted target. Repeating this intra-saccadic, second, target step over successive trials causes a progressive modification of the metrics (amplitude and/or direction) of the primary saccade (Fig. 2B) – allowing the eyes to land closer to the shifted target – and an associated reduction of the size and number of corrective saccades. Depending on the direction of second target step relative to the on-going saccade, different adaptive changes can be elicited: saccade amplitude is lengthened (gain increase) when the target is shifted in the saccade direction (forward step) or shortened (gain decrease) when the target is shifted in the opposite direction (backward step), and a change of saccade direction is elicited when the target is shifted orthogonally relative to the saccade direction. Because the changes of saccade amplitude or direction follow a quick time-course and reach significant levels after only some tens of min, they have been referred to as short term saccadic adaptation. Despite its fast time-course, short-term saccadic adaptation elicited by the double-step target paradigm has been recognized as a valuable model of the long-term adaptation described above in pathological conditions (Scudder et al., 1998). The changes observed during the adaptation phase are gradual, independent of any conscious detection of the perturbation, and demonstrate an after-effect (or retention) typical of plastic sensory-motor changes. This after-effect is measured by comparing before and after adaptation (pre-adaptation and post-adaptation, respectively) (Fig. 2B), the amplitude or direction of saccades directed toward a target which is switched off intra-saccadically. The after-effect, which reflects the true saccade adaptation resulting from plasticity mechanisms, is usually slightly smaller than the saccade change reached at the end of the adaptation phase. This difference thus suggests an involvement in the adaptation phase of strategic or intentional processes (Alahyane et al., 2007; Straube et al., 1997; Tian et al., 2009). However, this contribution is rather small and will not be specifically addressed in this paper. In sum, the double-step target paradigm is a non-invasive procedure which leads to a fast, unconscious and lasting change of saccade metrics, without requiring any specific instruction. Therefore, the double-step target paradigm has been applied widely to different subject populations, including laboratory animals, children with developemental disorders, and patients with cognitive deficits.

1.2. Scope of review

Our knowledge of short term saccadic adaptation mechanisms has grown quickly, particularly during the last two decades. In this review, we first describe this basic knowledge accumulated over the years. The studies which have already been detailed in the comprehensive review of Hopp and Fuchs (2004) will be summarized here and updated by recent data. When no further precision is provided, we deal with reactive saccades elicited by sudden presentation of a visual target, as adaptive mechanisms have been much thoroughly investigated for this saccade category. Again unless otherwise stated, most of the paper addresses the adaptive changes of saccade amplitude (with Section 4 focussing on the differences between amplitude shortening and lengthening), because adaptive changes of saccade direction have been only recently investigated (Chen-Harris et al., 2008; Xu-Wilson et al., 2009) and briefly reviewed (Tian et al., 2009). Sections 3–6 present more recent data, derived mostly from behavioural studies in human subjects and neurophysiological studies in the monkey, which often significantly refine or challenge our understanding of saccadic adaptation.

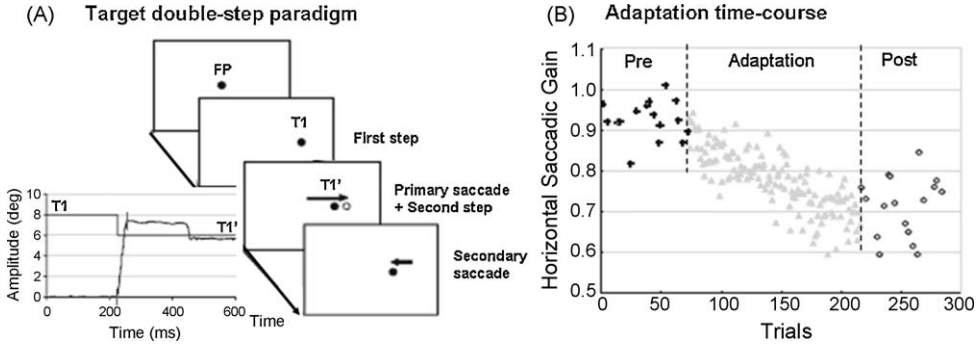

Fig. 2. Induction of adaptation of reactive saccades by the target double-step paradigm in a human subject (modified from Panouilleres et al., 2009c). (A) Time course of a typical "backward" double-step adaptation trial: presentation of fixation point, presentation of target (1st step), primary saccade (rightward arrow) and intra-saccadic target displacement (2nd step), secondary saccade (leftward arrow). The bottom-left panel shows a saccadic response recorded at the beginning of the adaptation session. (B) Individual example of adaptation time-course in a backward experiment. Each data point illustrates the gain of the primary saccadic response recorded before (pre '+'), during (adaptation '△') and after (post '◇') the adaptation phase. In pre- and post-adaptation trials the visual target was turned off during the saccadic response, whereas in adaptation trials the target jumped backward during the saccadic response by 25% or 40% of the first target step (i.e. 2° or 3.2°) respectively for the 1st and 2nd half of the adaptation session. Comparison between pre- and post-adaptation sessions allows computation of the net adaptation-related change of saccade gain (adaptation after-effect). Note the progressive decrease of the primary saccade gain during the adaptation session, and the retention of this gain change during the following post-adaptation session.

2. Basic properties

This section summarizes the basic functional properties of the short term saccadic adaptation. We will review the origin of the error signals which elicit saccadic adaptation, the effects of adaptation on saccade metrics (amplitude and/or direction), the effects on saccade dynamics (acceleration/deceleration and relationships between peak velocity, duration and amplitude) and finally the dependency of adaptation on contextual factors.

2.1. Error signals

Error signals could be derived from the retinal error, i.e. the visual estimate of the spatial separation between target position and saccade endpoint (=visual hypothesis) or from the motor commands of the corrective saccades generated toward the target (=motor hypothesis). Note that extra-ocular proprioception apparently does not contribute to error signals encoding, since its surgical removal has been shown not to interfere with saccadic adaptation in two deafferented monkeys (Lewis et al., 2001). Two studies were performed in the monkey to compare the visual and motor hypotheses and both concluded for the former hypothesis (Noto and Robinson, 2001; Wallman and Fuchs, 1998). Indeed, they showed that saccadic adaptation still occurs under conditions in which corrective saccades are minimized or eliminated. Another study confirmed this finding in humans (Bahcall and Kowler, 2000). This latter study further showed that adaptation also occurs when a large and empty circle is used as a double-step target, demonstrating that post-saccadic retinal error provided by a punctual target is not necessary. Thus, refining the error signals visual hypothesis, the authors proposed that error signals for adaptation result from a comparison between the post-saccadic retinal feedback and the predicted feedback, the latter corresponding to the target retinal error encoded before saccade initiation and remapped by extra-retinal signals of eye displacement (see similar conclusion in Ditterich et al., 2000b). This hypothesis of an elaborated processing of error signals is consistent with the hypometric tendency of primary saccades performed under normal conditions (gain near 0.9–0.95: Becker, 1989). Although its actual origin is still debated (e.g. Harris, 1995), this natural saccadic hypometria indeed suggests that saccadic adaptation does not nullify the post-saccadic retinal error but instead keeps it close to its baseline value (see also Henson, 1978). Thus, the error signals driving the adaptation mechanisms do not correspond to the post-saccadic retinal error per se but to a reconstructed internal information signalling departure from expected behaviour. Finally, a recent study published as an abstract (Gegenfurtner et al., 2008) went further by showing that saccadic adaptation can be elicited without any physical change of target position. In this experiment, the stationary saccade target was filled with a drifting sine-wave grating which changed its motion direction during the saccade, eliciting a visual illusion of target displacement. By showing that such perceived position error can trigger saccadic adaptation, this study provides additional evidence that error signals result from elaborated visual processing mechanisms (see also Bonnetblanc and Baraduc, 2007).

Another main issue concerns the temporal dynamics of the error signals. Studies in the monkey (Shafer et al., 2000) and in human subjects (Bahcall and Kowler, 2000; Fujita et al., 2002) showed that delaying the presentation of the shifted target relative to saccade end led to a progressive decrease of adaptation rate until reaching a non significant level for delays larger than about 600 ms. Moreover, in the no delay condition, reducing the duration of the presentation of the shifted target to less than about 100 ms led to a very steep decrease of the amount of adaptation (see also Panouilleres et al., 2009a). Combined together, these two relationships indicated that the shifted target must be visible within a critical time-window nearly immediately after primary saccade termination to induce maximal saccadic adaptation.

2.2. Effects on saccade metrics: adaptation field

Contrary to earlier suggestions (e.g. Deubel et al., 1986; McLaughlin, 1967), it is now known that saccadic adaptation does not result from a parametric change of the saccadic system gain. Instead, the generalization of adaptation of a saccade of a given vector (i.e., amplitude and direction) is spatially limited (Fig. 3A). A number of studies have measured the effect (or "transfer") of adaptation of a single reactive saccade to other reactive saccades with different spatial properties (amplitude, direction, initial eye position) (Albano, 1996; Deubel, 1987; Frens and van Opstal, 1994; Miller et al., 1981; Noto et al., 1999; Semmlow et al., 1989; Straube et al., 1997; Wallman and Fuchs, 1998). The general conclusions are: (1) adaptation fully transfers to saccades of the same amplitude and direction (i.e., same vector) as the adapted saccade, irrespective of initial position of the eyes; (2) conversely, the transfer to saccades which do not share the same vector as the adapted saccade varies negatively with this vector difference, and is null for a direction difference of 90° or more; (3) the set of saccades significantly affected by adaptation transfer defines a large but circumscribed region of oculocentric space centered on the adapted saccade; this region was initially called "activity region" by Semmlow et al. (1989) and then "adaptation field" by Frens and VanOpstal (1994); (4) the adaptation field is symmetrically shaped around the adapted saccade direction but is asymmetrical around the adapted saccade amplitude (Fig. 3B). This resembles the shape of movement fields of oculomotor neurons recorded at different levels of the saccadic system, such as the superior colliculus and the frontal eye fields (Noto et al., 1999). The spatial generalization and the adaptation field have been recently extended to voluntary saccades (Alahyane et al., 2007, 2008; Collins et al., 2007). Finally, the definition of adaptation field as a region of oculocentric space expressed in polar coordinates implies that motor commands modified by adaptation encode the saccade vector. This last point has been specifically addressed by testing the transfer of adaptation between saccades performed in different directions (Hopp and Fuchs, 2006; Watanabe et al., 2003). Both studies did suggest that adaptive changes in humans take place at a level where saccadic commands encode the vectorial eye displacement, rather than at a downstream level[2] where the horizontal and vertical eye displacement components are separately encoded (but see Kojima et al., 2005 for an opposite proposal in the monkey).

2.3. Effects on saccade dynamics

Another important question, which can help identify the neural substrate of adaptation mechanisms, is whether adaptation also affects the dynamical characteristics of saccades. Saccades are very fast and brief movements, and are characterized by a stereotypical relationship linking their peak velocity or duration to their amplitude. This main sequence relationship (Bahill et al., 1975; Scudder et al., 2002) reflects the operation of the saccadic pulse generator of the brainstem reticular formation (Scudder et al., 2002), but electrical micro-stimulation studies in awake animals also suggest some contribution of upstream structures like the

[2] In all the paper, the relative hierarchical levels of two functional processes are defined according to the sensory-to-motor flow of information. Thus process A is said to take place upstream from process B (i.e. at a higher level) if A is closer to the sensory end of the sensory-motor transformation, whereas A is said to take place downstream from process B (i.e. at a lower level) if closer to the motor end of sensory-motor transformation.

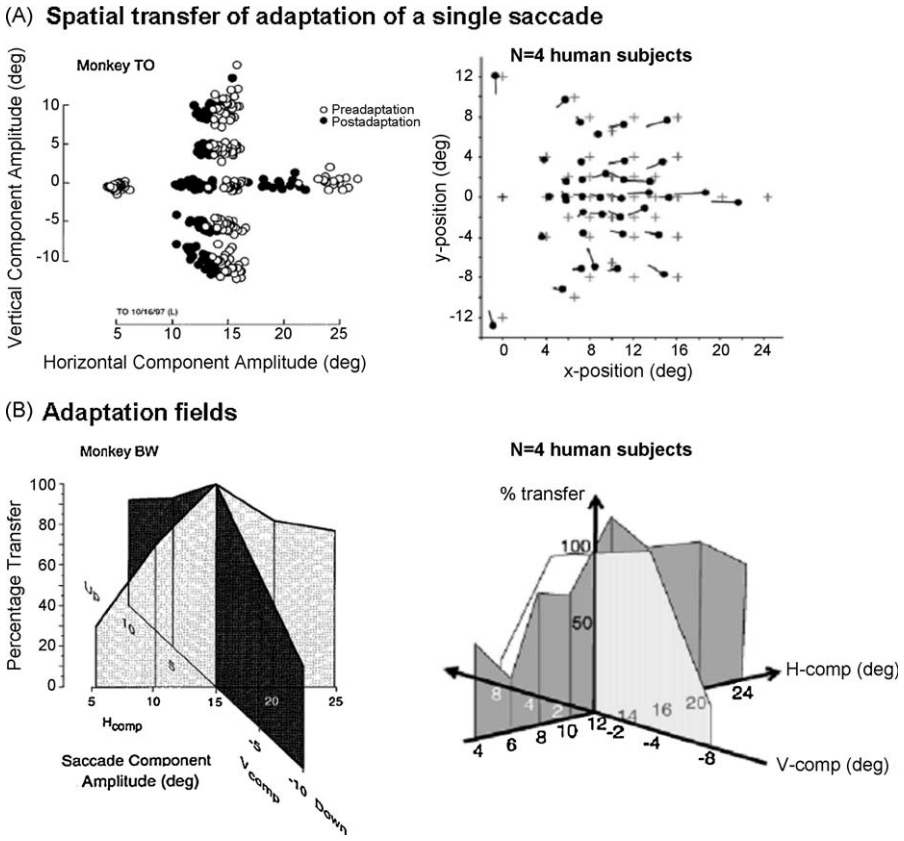

Fig. 3. Spatial extent of transfer of adaptation of a single horizontal saccade. (A) Saccade endpoints and visual targets used for adaptation induction and transfer tests. Left panel (modified from Noto et al., 1999): each circle corresponds to an individual saccade recorded before (○) or after adaptation (●) in a monkey; right panel (modified from Collins et al., 2007): each vector (—●) is the pre-adaptation (●) versus post-adaptation difference of mean saccade endpoints in 4 human subjects, target positions are shown by grey crosses (✚). In both studies, adaptation of a single horizontal rightward saccade (15° or 12° of amplitude in left and right panels, respectively) was induced by backward target steps (4.5° or 4°). (B) Adaptation fields. These plots, drawn from the same studies as in A, represent the amount of adaptation transfer as a function of the horizontal (H-comp) or vertical (V-comp) component of the tested saccade. By convention, the transfer of the adapted saccade (shown at the intersection of the two axes) is 100%. Note that in both species, saccades showing transfer define a wide area ("adaptation field") within which the amount of transfer progressively decreases as the saccade vector deviates from the adapted saccade vector.

superior colliculus (Guillaume and Pelisson, 2006; Stanford et al., 1996). Whether or not the main sequence relationship is modified by saccadic adaptation is still debated.

On the one hand, some studies failed to reveal any significant modification specifically related to adaptation (Alahyane et al., 2007; Alahyane and Pelisson, 2005; Frens and van Opstal, 1994). In particular, Alahyane and Pelisson (2005) evaluated the main sequences immediately before and after a double-step target session in which large adaptive reductions of saccade amplitude were achieved. Moreover, to control for potential effects of fatigue on saccade dynamics, they recorded for comparison an equivalent number of saccades generated in the same condition except that no intra-saccadic target step occurred. These authors found a very slight increase of saccade duration in post-adaptation relative to pre-adaptation, and a non significant decrease of saccade peak velocity. Since these small changes were statistically equivalent in the adaptation and control conditions, the authors concluded for a non-specific consequence of fatigue rather than an effect of adaptation per se. The exact same observations were made in another study comparing adaptation between reactive saccades and voluntary (scanning) saccades (Alahyane et al., 2007). It is worth noting that in these two studies, the saccades used to compare the dynamics before and after adaptation were performed under identical conditions (target switched off during the saccade).

On the other hand, other studies in the monkey (Frens and van Opstal, 1997; Straube et al., 1997) and in humans (Abrams et al., 1992; Straube and Deubel, 1995; Ethier et al., 2008a) reported some changes in saccade dynamics. Straube et al. (1997) observed a large variability between animals, with only the more adapted one exhibiting an increase of duration and a decrease of peak velocity. Similarly, Catz et al. (2008) showed that the decrease in saccade amplitude resulting from backward adaptation is selectively associated with a decrease of peak velocity, without saccade duration change, thus leading to a change of main sequence. However, due to the large number of adaptation trials and the lack of control condition in these studies, one cannot reject the possibility that saccade slowing resulted from fatigue. In humans, Straube and Deubel (1995) found that the peak acceleration/peak deceleration ratio decreased for adapted versus non-adapted (control) saccades of matched amplitude, without significant change of duration or peak velocity. However, the adapted and control saccades were performed under different stimulation conditions (target jumping backward or stationary). Finally, two recent studies circumvented this limitation. Collins et al. (2008a) compared saccades generated under the same conditions in a post-adaptation session and in a pre-adaptation session. They did not observe any effect of backward adaptation onto the peak velocity versus amplitude relationship. Nonetheless, they reported a significant reduction of the peak deceleration, of the duration of saccades and specifically of their deceleration phase (hence associated with an increase of the skewness ratio between the acceleration and deceleration durations). However, again in this last study, the absence of quantitative comparison to a control

condition prevented from testing the effect of fatigue (only selected saccadic trajectories of one subject were provided). Ethier et al. (2008a) compared for each subject, saccades measured at the end of a long adaptation session to matched amplitude saccades measured in a control session. They demonstrated that adaptation specifically reduced the peak acceleration, peak velocity, peak deceleration, and increased the duration of saccades, thus only partly confirming the Collins et al.'s (2008a) findings.

To conclude, the effect of adaptation on saccade dynamics is still disputed, largely because of the large variety of experimental protocols and of analysis methods. Complementary experiments, that notably exclude confounding factors, are thus necessary to put an end to the debate.

2.4. Effect of context

Sensory-motor adaptation mechanisms are usually distinguished from motor learning by a lower dependency on context, i.e. on the specific experimental conditions under which they are induced. However, experimental evidence accumulated over recent years has shown that saccadic adaptation depends on several contextual factors. The effects of context considered here are different from the effect of saccade vector reported in Section 2.2. Two types of approaches have been followed to study these contextual factors. In both cases, saccades of the same vector are compared between two contexts (A and B) which differ from each other only by a single factor (e.g. eye position, target size, target colour ...). The first approach consists of studying the transfer of adaptation from saccades generated in context A (e.g. initiated from a leftward orbital position) to saccades of the same vector generated in context B (e.g. initiated from a rightward orbital position). The rationale is that the larger the transfer, the lower the specificity or dependency of adaptation relative to the contextual factor of interest (horizontal eye position in example above). In this way, by demonstrating large transfers of adaptation, the two following factors have been shown not to act as contextual cues: the presence – or lack of – visual background (Deubel, 1995a; Ditterich et al., 2000b; Robinson et al., 2000), and the orbital eye position (Albano, 1996; Deubel, 1995a; Frens and van Opstal, 1994; Miller et al., 1981; Noto et al., 1999; Semmlow et al., 1989). The second approach consists in submitting, during the same adaptation session, saccades generated in two contexts A and B to two different adaptive demands (e.g. backward target step in A vs no step in B) or to two opposite demands (backward step in A vs forward step in B). A strong specificity of adaptation will be revealed if saccades associated with the two contexts can be adapted differently (i.e. selective saccade shortening in context A for the first situation above; simultaneous shortening of saccades in context A and lengthening of saccades in context B for the second situation). In this way, this second approach revealed several contextual cues: target visual property (flicker: Herman et al., 2009), target distance (Chaturvedi and Van Gisbergen, 1997), horizontal and vertical orbital eye position (Alahyane and Pelisson, 2004; Shelhamer and Clendaniel, 2002a), head orientation (Shelhamer and Clendaniel, 2002b) and, to some extent, gravity level (Shelhamer et al., 2002). Conversely, this approach failed to disclose a contextual effect of the colour and shape of the saccade target (Deubel, 1995a), but this negative finding has been recently challenged (Herman et al., 2009). Note that for eye position, the only contextual factor tested by both approaches, the conclusions seem contradictory. The conclusion of the first approach, that eye position is not a relevant contextual factor, agrees with many studies suggesting that saccadic adaptation is expressed in eye displacement – not eye position – coordinates (see Section 2.2 above). However, the opposite conclusion of the second approach, that eye position information is used by saccadic adaptation mechanisms, also makes sense if one considers the constraints prevailing when saccadic adaptation compensates for deficits of the peripheral neuromuscular apparatus. In such case, indeed, the requested adaptive changes of motor commands often depend on eye position (Scudder et al., 1998). This discrepancy between the two conclusions may be only apparent. Indeed, although saccadic adaptation "by default" transfers to other eye positions, this is not meant to demonstrate that eye position information cannot be used by adaptive mechanisms when necessary, e.g. when two different adaptive changes are simultaneously required. In other words, this second approach may be more sensitive to reveal contextual effects. This approach further suggests that eye position information is used as a contextual signal both during the adaptation and retention periods, allowing the saccadic system to switch state over successive responses between high or low gains. In summary, the influence of different contextual factors revealed by the second approach suggests that the adaptive mechanisms rely on some type of associative motor memory. This context-specificity is a challenge for future studies because it implies the recruitment of different adaptation modules for different contexts and it increases the complexity of the underlying brain network.

3. Sensory or motor level(s) of saccadic adaptation? Studies of transfer

This section details how adaptation of a given saccade affects non motor (perceptual) responses, shifts of visual attention, goal-directed motor responses of the head or limb, and saccades of other categories. Like other studies of adaptation transfer reviewed above, these studies usually provide critical information about the functional level (sensory or motor) where adaptive mechanisms take place. They also indirectly point to possible neural substrates (see introduction of Section 5.1).

3.1. To visual perception

As indicated above, the fact that saccadic adaptation transfers to other saccades with a similar vector and forms an eye-centered adaptation field indicates that adaptive mechanisms act on a vectorial representation of the desired eye movement. However, this does not tell us whether this representation is exclusively used for the programming of a saccade toward the target (motor plasticity hypothesis) of for the perceptual localization of the target (sensory plasticity hypothesis). Nonetheless, the question of a potential sensory component of saccadic adaptation has initially not received the interest it deserves. The first study of perceptual localization of a peripheral visual target (verbal report in an eye fixation condition) after saccadic adaptation has found a small mis-localization representing less than 20% of the amount of saccadic adaptation (Moidell and Bedell, 1988). However, this effect was statistically significant only when perceptual localization was compared between a backward adaptation condition and a forward adaptation condition. Further studies of adaptive shortening of reactive saccades confirmed the absence of significant target mis-localization measured under eye fixation condition (Awater et al., 2005; Collins et al., 2007; Georg and Lappe, 2009). In sum, backward adaptation of reactive saccades does not result in significant perceptual mis-localization of a target in an eye fixation condition.

In contrast, several studies have reported that reactive saccade adaptation leads to mis-localization of a flashed stimulus in a saccade task (Awater et al., 2005; Bahcall and Kowler, 1999; Bruno and Morrone, 2007; Collins et al., 2007, 2009; Georg and

Lappe, 2009; Zimmermann and Lappe, 2009). In this peri-saccadic localization task, subjects have to saccade toward a visual target and to report verbally on the location of a visual probe which is flashed shortly after the saccade target but before the saccade onset. Systematic errors in perceptual judgement of flash position were revealed when comparing the responses in post-adaptation to baseline responses collected before adaptation. However, no mis-localization occurred when the probe was flashed after saccade termination (Georg and Lappe, 2009). These mis-localizations could result from a dissociation between the actual saccadic displacement of the eye and the displacement estimated from extra-retinal information (Bahcall and Kowler, 1999). Accordingly, these extra-retinal signals no longer encode veridical eye displacement because they are encoded upstream from the level of saccadic adaptation. However, this perceptual remapping hypothesis has been challenged by several observations (see Georg and Lappe, 2009 for extensive discussion). First, visual objects (saccade target or screen border) available after saccade termination can be used as landmarks to localize the flashed stimulus (Deubel, 2004). Thus, the perceptual system does not need to rely on extra-retinal signals when such visual cues are available. Second, the mean size of mis-localizations observed when no post-saccadic visual cue is available is much smaller than the amount of adaptation (Bruno and Morrone, 2007; Georg and Lappe, 2009). Moreover, the spatial distribution of such localization errors is non-uniform and rather resembles that of adaptation fields (Collins et al., 2007). These two features indeed differ from the large and uniformly distributed mis-localization predicted by the perceptual remapping hypothesis. The resemblance between the spatial distribution of mis-localizations and the adaptation field led the authors to propose the following alternative hypothesis: when a probe used for a perceptual judgement is flashed while subjects prepare a saccade toward the 'adapted' target, the metrics of the saccade which would be necessary (though actually not initiated) to foveate the probe contribute to its spatial localization.

In conclusion, although commonly observed, the effect of saccadic adaptation on peri-saccadic localization and its origin (perceptual or motor) are still not clearly understood (Georg and Lappe, 2009). At the least, the repeated finding of a lack of localization errors measured under eye fixation condition suggests that saccadic adaptation does not affect the earliest visual processing stages devoted to both action and perception.

3.2. To pre-saccadic shift of visual attention

Studies described in this sub-section have mainly used saccadic adaptation as a tool to investigate visuo-spatial attention, and to better characterize the visual attention shift which is known to shortly precede the saccadic response (Deubel and Schneider, 1996; Hoffman and Subramaniam, 1995; Kowler et al., 1995). Reciprocally, they also provide interesting insight about the functional level of adaptation. The rationale of these studies was to measure, both before and after induction of saccadic adaptation, this pre-saccadic attention shift using the following double-task. Shortly after presentation of a visual saccade target, and during the subjects' latency period, a discrimination target was presented for a brief duration, at the same location as the saccade target or at a neighbouring location. Subjects had to saccade to the visual target and then to report verbally on the identity of the discrimination target. A first study reported that the location where best discrimination performance was achieved did not change following adaptation of reactive saccades, and remained anchored to the saccade target location (Ditterich et al., 2000a). This suggested that the pre-saccadic shift of visual attention is coupled to the visual target rather than to the actual saccadic response to it. In contrast, Collins and Dore-Mazars (2006) and Dore-Mazars and Collins (2005) showed that saccadic adaptation leads to a shift of the locus of best discrimination in order to remain anchored on the saccade landing position. Their initial paper focussed on voluntary saccades, but in their second paper they confirmed this finding for both voluntary and reactive saccades. A possible reason for the difference with the results obtained by Ditterich et al. (2000a) could be a lack of sensitivity in the latter study. Indeed, the post-adaptation phase of data collection started after only 50 adaptation trials, which may have been insufficient to elicit a significant change of saccade amplitude and of associated shift of attention. Another, non-exclusive, explanation is that the pre-saccadic shift of visual attention depends on the type of saccade target used in these studies, namely a punctual target (Ditterich et al., 2000a) or an extended visual simulus (Collins and Dore-Mazars, 2006; Dore-Mazars and Collins, 2005). As a result, the stronger need for a target selection mechanism would have favoured the coupling of visual attention shift with the target in the first study relative to the other two studies. In conclusion, although more experiments are required to definitively establish its consistency, the best evidence is for a coupling between pre-saccadic visual attention shift and saccade endpoint (not visual target). As implied by this hypothesis, the fact that the extra-retinal eye displacement signals involved in re-orienting visual attention are still veridical after saccadic adaptation suggests that this latter takes place upstream from the site(s) where such extra-retinal signals are encoded.

3.3. To subsequent saccade programming

The internal monitoring of eye displacement by extra-retinal signals is also crucial for the generation of more complex actions, such as sequences of movements. This has been particularly well demonstrated in the saccadic system by the double step task introduced by Hallett and Lightstone (1976). In this task, subjects have to generate a sequence of two saccades in response to a rapid presentation of two flashed targets. Since the two targets are turned off at the time of first saccade onset, the programming of the second saccade requires a vectorial combination between the retinal signal elicited by the second target and the extra-retinal signal of the first saccade. The fact that the second saccade is executed accurately demonstrates that an internal monitoring of eye displacement is used for the programming of the subsequent saccade. Using this task in the monkey, Tanaka (2003) investigated the locus of saccadic adaptation relative to extra-retinal signals used for internal eye displacement monitoring. The first saccade of the two saccade sequences that monkeys had to produce to flashed targets had the same vector as the adapted saccade. The main result of this study was that modifications of the first saccade amplitude through adaptation are fully compensated in the programming of the second saccade. A recent study performed in our laboratory has replicated this observation in human subjects, both in case of adaptation of reactive saccades (upper row in Fig. 4C) and of voluntary saccades (Panouilleres et al., 2009b). These findings suggest that extra-retinal signals used in the programming of the second saccade in this double-saccade task encode the actual (not desired) amplitude of the first saccade, and therefore that saccadic adaptation takes place upstream from the site(s) where these extra-retinal signals are encoded (see also Dore-Mazars et al., 2006). Note that this conclusion is similar to the conclusion proposed above for pre-saccadic visual attention. Whether this analogy is purely coincidental or reflects the existence of common extra-retinal feedback mechanisms for both subsequent saccade programming and pre-saccadic attention shifts remains to be established.

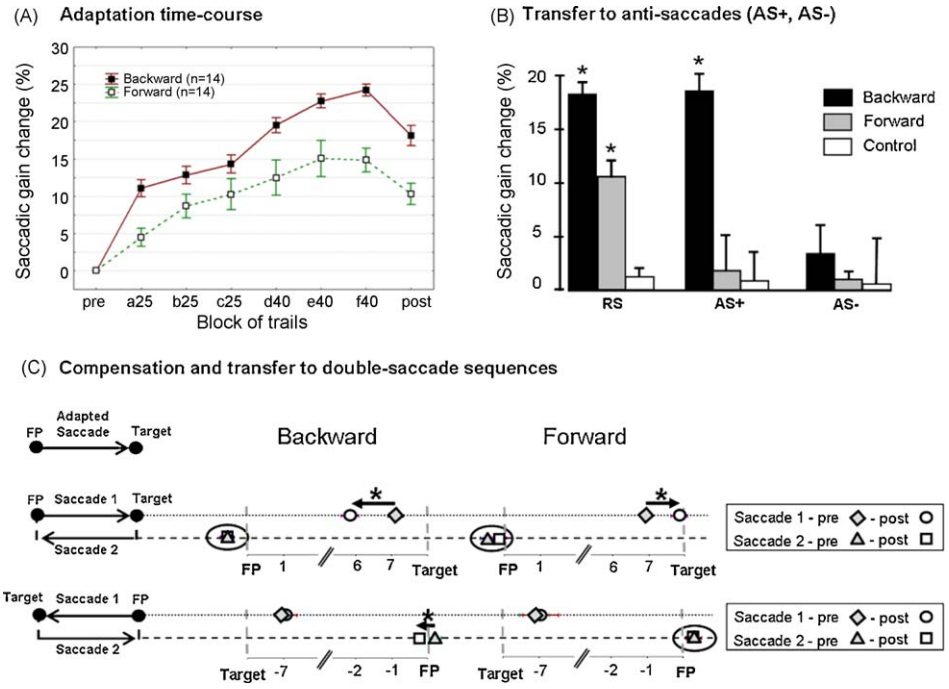

Fig. 4. Differences between forward and backward adaptation of reactive saccades (panels A and B modified from Panouilleres et al., 2009c). (A) Adaptation time-course. The mean saccade gain change relative to the pre-adaptation session (pre) is plotted for the 6 blocks of adaptation trials (numbers indicate percent size of intra-saccadic target jump: 25% in a25, b25 and c25; 40% in d40, e40 and f40) and for the test trials (pre and post). Each curve has been computed in a group of 14 subjects. For the forward condition, 19 subjects were tested but 5 were removed because they did not show any significant after-effect (post–pre gain difference), whereas no subject was removed for the backward condition. (B) Adaptation transfer to anti-saccades. Mean gain changes of adapted reactive saccades (RS), of anti-saccades generated in the adapted direction (AS+) and of anti-saccades generated in the non adapted direction (AS−) are plotted for 3 subjects groups: backward adaptation ($n = 14$), forward adaptation ($n = 14$) and control (no adaptation, $n = 17$). Note that backward adaptation fully transferred to AS+ but not to AS−, whereas in both forward adaptation and control groups no transfer to either type of anti-saccade was found. Note also the statistically larger amount of backward RS adaptation than forward RS adaptation. (C) Compensation and transfer to rapid sequences of two saccades (from Panouilleres et al., 2009b). As shown on the left, this study consisted in adapting one saccade (+8° rightward) and measuring the amplitude change of saccades performed in a two-saccade sequence. In this "refixation" task, subjects performed a first saccade ("saccade 1") in the adapted direction or in the opposite direction (first and second rows, respectively) and then a second saccade ("saccade 2") back toward the remembered location of the fixation point (FP extinguished during saccade 1). Plots in the middle and on the right indicate the mean endpoints of saccades 1 and 2 after backward adaptation or forward adaptation, respectively ($n = 6$ subjects each). As shown in the 1st row, in both adaptation conditions, the size of saccade 1 performed in the adapted direction was significantly modified (transfer shown by arrows in 1st line) and the size of saccade 2 was similarly modified (compensation) to keep the same endpoint (as shown by ellipses in 2nd line). Conversely, when saccade 1 was performed in the non adapted direction (2nd row), its size was logically unaffected but, unexpectedly, a significant transfer to saccade 2 was only observed in the backward condition (arrow) but not in the forward condition (ellipse).

3.4. To other body segments

Under natural conditions, and particularly for large target eccentricities (>15°), orienting gaze shifts involve movements of the eye, head and sometimes trunk (gaze is defined as the direction of the line of sight in space, and is the sum of eye-in-orbit, head-on-trunk and trunk-in-space positions). However, few studies have investigated the transfer of saccadic adaptation to head movements or have addressed the adaptation of gaze shifts in the head-unrestrained condition. Concerning the transfer of saccadic adaptation to head movements, Kroller et al. (1996) found in human subjects that adaptation of saccades performed in the head-restrained condition did not modify the amplitude of head movements generated subsequently in a target directed head movement task. Note that head movements contributing to gaze shifts in a goal-directed gaze shift task were not tested in this study. In contrast, a second study in the monkey was aimed at measuring the transfer of head-restrained saccadic adaptation to head movements in a post-adaptation gaze shifts task (Phillips et al., 1996). The results indicated that saccadic adaptation transfers to the head-unrestrained condition by modifying both the eye and the head movement components of goal-directed gaze shifts. In agreement with more extended investigations in monkeys and humans (Cecala and Freedman, 2008, 2009), this suggested that saccadic adaptation acts at a level where commands encoding the displacement of gaze in space are generated, namely upstream from the elaboration of commands encoding the displacement of the eye in the orbit and of head-related motor commands. The lack of adaptation transfer to target-directed head movements in Kroller et al.'s study (1996) suggests that these head movements recruit a sensory-motor pathway independent of that involved in combined eye-head gaze shifts.

In every-day life, saccadic eye movements almost obligatorily participate in goal-directed arm movement behaviour (Pelisson and Prablanc, 2009). Thus, saccadic adaptation could impact on arm movements. A couple of studies have tested whether saccadic adaptation does transfer to goal-directed arm movements. The first (McLaughlin et al., 1968) was published soon after the initial description of the double-step target paradigm (McLaughlin, 1967) and showed no change of hand pointing movements after a short adaptation phase of 11 double-step trials. Subsequent studies using longer adaptation periods confirmed this lack of transfer (see Fig. 5A, Cotti et al., 2007; Hernandez et al., 2008; Kroller et al., 1996) or found a small amount (30%) of transfer (de Graaf et al., 1995). In all these studies, reactive saccades were submitted to an adaptive decrease of amplitude (backward adaptation), and the lack of transfer was observed when hand pointing movements were performed without concomitant gaze shift. Some amplitude change of hand pointing was seen when subjects were allowed to move their gaze/eyes toward the target while pointing (Bekkering et al., 1995; Hernandez et al., 2008; Kroller et al., 1996; see also Bock et al., 2008 for transfer of saccade direction adaptation).

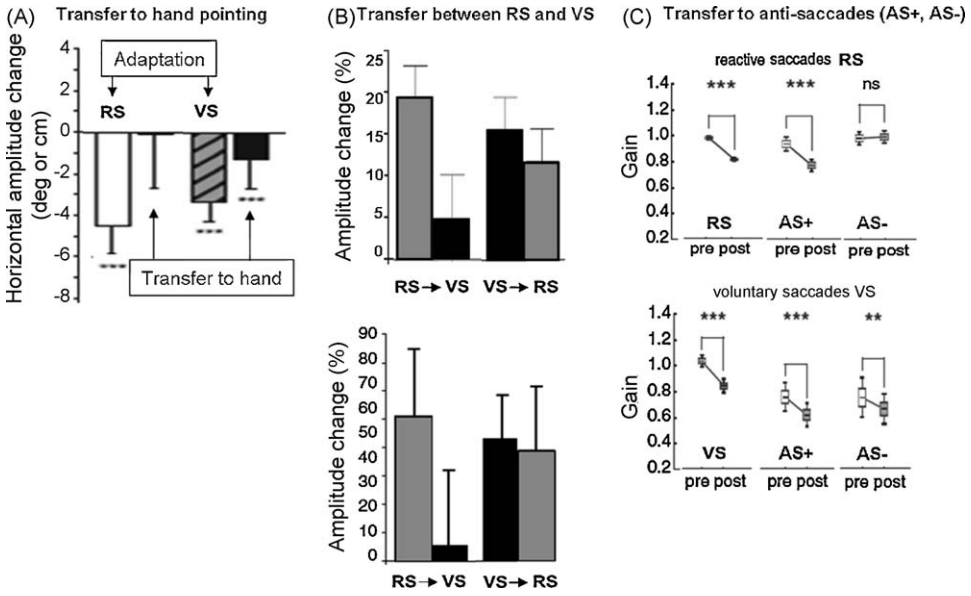

Fig. 5. Differences of backward adaptation between reactive saccades (RS) and voluntary saccades (VS). (A) Transfer to hand pointing (modified from Cotti et al., 2007). Adaptation of VS, but not RS, leads to a small but significant change of the amplitude of hand pointing movements generated without concomitant eye movement (eye fixation condition). (B) Transfer between RS and VS [modified from Alahyane et al., 2007 (top) and Collins and Dore-Mazars, 2006 (bottom)]. Very similar asymmetrical patterns of adaptation transfer between RS and VS were found in these two studies, characterised by a much larger transfer of VS to RS than of RS to VS. (C) Transfer to anti-saccades (modified from Cotti et al., 2009). Adaptation of RS fully transferred to anti-saccades generated in the adapted direction (AS+) but not to anti-saccades in the non-adapted direction (AS−). In contrast, adaptation of VS transferred to both AS+ and AS− anti-saccade types.

However, this effect likely resulted from eye-hand coupling mechanisms (see e.g. Van Donkelaar et al., 2000) rather than from real adaptation transfer. More interestingly, a larger transfer to hand pointing was observed when voluntary saccades rather than reactive saccades were submitted to adaptation (Cotti et al., 2007, see Fig. 5A). This observation provides further evidence for the existence of separate adaptation mechanisms for the two saccade categories (see next sub-section).

3.5. To other saccade categories

3.5.1. Evidence for separate mechanisms

Reactive saccades and voluntary saccades generation relies on partially separated neural substrates, with cortical areas generally demonstrating higher specificity to saccade categories than sub-cortical areas (see Section 1 and Fig. 1). Accordingly, it is theoretically possible that separate adaptation mechanisms are specifically involved in the calibration of different saccade categories by modifying the oculomotor commands at different neural loci. Alternatively, a common adaptation mechanism could act at a single locus of the final common pathway recruited for all saccade categories. Testing these two hypotheses has been a major motivation of the studies reviewed in this sub-section.

Deubel (1995b, 1999) performed the first comprehensive analysis of the transfer of adaptation between the reactive, memory-guided, delayed and scanning categories. The observed pattern of transfer led the author to distinguish between three categories of saccades: (1) reactive and express, (2) voluntary (delayed, overlap and scanning), and (3) memory-guided. On the one hand, small adaptation transfers were found between categories. This is the case for the transfers from scanning saccades to reactive saccades (37%, similar to the 24% transfer previously observed by Erkelens and Hulleman, 1993), and conversely from reactive saccades to scanning saccades (11%). Note also that adaptive changes of reactive saccades are completely reversed by a 15 min period of practice of reactive saccades toward stationary targets (de-adaptation), but not by an equivalent practice of voluntary saccades (Gaveau et al., 2005). Low transfer levels were also reported by Fujita et al. (2002), with a symmetrical pattern of reciprocal transfers (25%) between the two saccade categories. This study further demonstrated the possibility to simultaneously and concurrently adapt memory-guided saccade amplitude in one direction (e.g. increase) and reactive or voluntary saccade amplitude in the opposite direction (e.g. decrease). This last observation strengthens the conclusion of separate adaptation mechanisms between the memory-guided saccade category and the reactive and voluntary categories. On the other hand, high levels of adaptation transfer between saccades within each category have been tested and found in the following situations: between express saccades and reactive saccades (Deubel, 1999; Hopp and Fuchs, 2002), and from scanning saccades to saccades triggered in an overlap task (Deubel, 1999). Of particularly interest are the nearly complete and reciprocal transfers of adaptation between reactive and express saccades, suggesting a common level of adaptation.

Three more recent studies have focussed on the reactive and voluntary saccade categories and confirmed the hypothesis of separate adaptation mechanisms. They have moreover described a more complex, asymmetrical, pattern of transfer (Fig. 5B). Indeed they found a smaller transfer from reactive to scanning saccades (22% in Alahyane et al., 2007, 57% in Cotti et al., 2007, and 12% in Collins and Dore-Mazars, 2006) than the reciprocal adaptation transfer from voluntary to reactive saccades (79%, 75%, 91%, respectively). Based on these findings and on a quantitative comparison of adaptive properties of the two saccade categories, Alahyane et al. (2007) proposed a two-level scheme of saccade adaptation. At the level of the final common pathway, possibly in the brainstem, a single locus contributes to adaptation of both saccade categories. At another level, supposedly in the cerebellum, two partially overlapping loci are specific to each saccade category. Thus this proposed scheme combines the two hypotheses presented at the beginning of Section 3.5, i.e. assumes both a common adaptation locus in the final pathway and two separate loci specific to each saccade category.

The hypothesis of separate cerebellar loci has been more directly tested and corroborated in a recent case report (Alahyane

et al., 2008). In this study, adaptations of reactive and of voluntary saccades were tested in two patients with a vascular lesion affecting different cerebellar areas. The results revealed a double-dissociation pattern of deficits for ipsilesional saccades: adaptation was selectively impaired for the reactive category in the patient with a medio-posterior cerebellar lesion, whereas adaptation was selectively impaired for the voluntary category in the patient with a latero-anterior lesion. This is the first indication that adaptation of different saccade categories may rely on specific cerebellar territories. But, as suggested in several papers (Cotti et al., 2009; Deubel, 1999; Gancarz and Grossberg, 1999; MacAskill et al., 2002), other brain areas could also be specifically involved in adaptation of different saccade categories, such as the brainstem and the thalamo-cortical circuits. These areas may in turn receive category-specific adaptive signals respectively from the medio-posterior and latero-anterior zones of the cerebellum. Clearly, further lesion and neuroimaging studies are required to delineate the full network involved in adaptation of different saccade categories.

3.5.2. Assessment of the adaptation levels

These studies indicate that, at least in humans, separate mechanisms are involved for adaptive control of saccades launched through different initiation mechanisms. We now review other studies which have tested the functional level of saccadic adaptation by measuring its transfer to two other saccades categories, averaging saccades and anti-saccades, taking advantage of the key programming steps involved in these two saccade tasks (vector averaging and vector inversion, respectively).

The first study (Alahyane et al., 2004) tested the transfer of reactive saccades adaptation to averaging saccades, i.e. automatic responses aimed at the average position of two targets simultaneously presented at two close locations (Findlay, 1982). A mixed adaptation procedure was designed to simultaneously decrease the amplitude (backward target steps) of a horizontal reactive saccade and increase the amplitude (forward target steps) of two oblique reactive saccades of the same desired size. Then, both pre-adaptation and post-adaptation tests included horizontal averaging saccades which were elicited by presentation of a target pair. Specifically, targets of the adapted oblique saccades were the same as the target pair used to elicit the averaging saccade and the target of the adapted horizontal saccade defined the same vector as that of the averaging saccade. Two opposite predictions were made: the averaging saccade amplitude should increase if adaptation acts before vector averaging, thus increasing the amplitude of the two separate oblique vectors (upstream hypothesis) or decrease if adaptation acts after vector averaging, thus decreasing the amplitude of the single horizontal vector (downstream hypothesis). The results revealed that the mixed adaptation procedure yielded a statistically significant reduction of averaging saccade amplitude, clearly rejecting the upstream hypothesis. Thus, although slightly smaller than predicted by the downstream hypothesis (see for details Alahyane et al., 2004), this reduction suggested that adaptation of reactive saccade involves processing stages located at or downstream from the level of saccade averaging process.

The second study (Cotti et al., 2009) tested this time the transfer of saccadic adaptation to anti-saccades. In an anti-saccade task, subjects have to produce a saccade away from a visual target, i.e., in the opposite direction (Hallett, 1978; Munoz and Everling, 2004). One of the critical processing steps required by this task is the spatial "inversion" of the visual target vector into an oppositely directed saccade vector. The objective of Cotti et al.'s (2009) study was to assess the relative hierarchical levels of saccadic adaptation and of anti-saccade vector inversion. Backward adaptation was induced for a single saccade vector directed horizontally (also called "adapted direction", e.g. rightward), testing in different subject groups reactive saccades and voluntary saccades. Then, in each group, the test phase (pre- and post-adaptation) included two types of anti-saccade trials: "non-adapted direction anti-saccades" (AS- in Fig. 5C) were elicited by a visual target presented in the adapted direction (e.g. to the right) and thus directed in the opposite direction (e.g. leftward), and "adapted direction anti-saccades" (AS+ in Fig. 5C) were directed in the adapted direction (e.g. rightward) in response to a visual target presented in the non-adapted direction (e.g. to the left). Reactive saccade adaptation fully transferred to "adapted direction anti-saccades" but not to "non-adapted direction anti-saccades". On the contrary, the adaptation of voluntary saccades led to a large transfer (82% on average) of adaptation to both "adapted direction" and "non-adapted direction" anti-saccades. This striking difference of transfer patterns between reactive saccade adaptation and voluntary saccade adaptation confirms the hypothesis of separate adaptation mechanisms for the two saccade categories. For reactive saccades, the unbalanced pattern of transfer demonstrates that adaptation takes place at a level hierarchically lower than the level of vector inversion of anti-saccades. For voluntary saccades, the transfer to both types of anti-saccades suggests the recruitment of two different levels, situated respectively upstream and downstream from the vector inversion level of anti-saccades. Accordingly, Cotti et al. (2009) proposed a two-level hypothesis similar to Alahyane et al.'s (2007): a final common pathway (downstream) level recruited by adaptation of both saccade categories, and an additional (upstream) level involved in adaptation of voluntary saccades. For these authors, this upstream level could correspond to cortical areas of the parietal cortex (parietal eye fields: PEF) or of the temporo-occipital junction projecting to PEF. Note that, as measured in a visual target localization task similar to that used by Moidell and Bedell (1988), the subjective estimate of peripheral target location was not modified following adaptation of voluntary saccades (Cotti et al., unpublished observations). Thus, the upstream, cortical, site which would be specifically recruited for adaptation of voluntary saccades according to Cotti et al. (2009), does not contribute to the earliest visual processes required in target perceptual localization. Finally, another recent study has investigated the transfer of saccadic adaptation to anti-saccades (Collins et al., 2008b). Although this study differs from Cotti et al.'s (2009) by different aspects (see Discussion in Cotti et al., 2009; Panouilleres et al., 2009c), the full transfer of adaptation to "adapted direction anti-saccades" without any transfer to "non adapted direction anti-saccades" reported in this study are fully compatible with the reactive saccade adaptation condition of Cotti et al. (2009). As a final remark, the hypothesis of separate loci is however not supported by the high and symmetrical levels of transfer between saccade categories observed in the monkey (Fuchs et al., 1996), suggesting an intriguing difference of adaptation mechanisms between the two species.

4. Amplitude shortening versus lengthening (backward versus forward adaptation)

Studies reviewed so far have mostly addressed the adaptive shortening of saccade amplitude elicited by stepping the target backward during the saccade. Here, it will be shown that the properties of such backward adaptation may not extend to saccade lengthening (or forward) adaptation.

It has been frequently observed that forward adaptation takes longer to develop and reaches a lower level than backward adaptation, in both humans (Ethier et al., 2008a; Hernandez et al., 2008; Miller et al., 1981; Panouilleres et al., 2009c; Straube and Deubel, 1995) and monkeys (Cecala and Freedman, 2009; Straube

et al., 1997). The difficulty to elicit adaptive saccade lengthening is particularly illustrated by Panouilleres et al. (2009c) who reported that 5 out of 19 subjects tested in the forward condition did not demonstrate any significant adaptation after-effect, whereas all 14 subjects tested in the backward condition showed a significant adaptation after-effect. In addition, comparing the 2 groups of 14 significantly adapted subjects revealed that saccade amplitude changes reached after the same number of trials were twice smaller for forward than for backward adaptation (Fig. 4A). This lower efficacy of forward adaptation was recently confirmed for both reactive saccades and voluntary saccades (Panouilleres et al., unpublished observations).

We now review studies which more directly bear on the functional properties of forward adaptation. The earliest one (Semmlow et al., 1989) documented a different pattern of spatial generalization between backward and forward adaptation. The authors suggested that backward adaptation results from an overall reduction of saccade gain and that forward adaptation rather relies on a remapping of final eye position. Ethier et al. (2008a) proposed a similar remapping hypothesis for forward adaptation and additionally suggested that backward adaptation instead results from a change of the "internal model" involved in saccadic feedback control. Indeed, as compared to non-adapted saccades of matched amplitude, saccades recorded after backward adaptation revealed several changes of dynamical parameters (increase of duration, decrease of peak velocity, of peak acceleration and of peak deceleration) whereas saccades disclosed no statistical change of dynamics after forward condition (see also Zimmermann and Lappe, 2009). Finally, several recent studies have tested the transfer of forward adaptation to different saccade types or to hand pointing. First, Panouilleres et al. (2009c) studied the transfer of adaptation of a single reactive saccade to anti-saccades. The rationale of the study and the group of subjects tested in the backward condition were the same as in the Cotti et al.'s (2009) study described in Section 3.5. Recall that in this condition (see Fig. 4B), a transfer of adaptation was observed only for anti-saccades in the "adapted direction" (or AS+), but not to anti-saccades in the opposite direction (AS−). In marked contrast to this asymmetrical pattern of transfer, adaptation in the forward condition transferred neither to the "adapted direction" nor to the "non-adapted direction" anti-saccades. This difference suggests that forward adaptation does not rely on the same mechanisms as backward adaptation. A second study performed in our laboratory has provided additional evidence for this conclusion (Panouilleres et al., 2009b). As detailed in Section 3.3, the objective was to look for the transfer of adaptation of a rightward saccade to a sequence of two back-to-back saccades performed in rapid succession. When the second saccade of the sequence shared the same rightward vector as the adapted saccade (Fig. 4C lower row), a strong transfer was found after backward adaptation, but not after forward adaptation (Fig. 4C). This observation suggests that forward adaptation, as opposed to backward adaptation, may not involve the motor pathways common to all rightward saccades, in agreement with the remapping hypothesis. The third approach based on adaptation transfer involved hand pointing movements performed in eye fixed condition (Hernandez et al., 2008). Again, a dissociation was found between the two adaptation conditions: no significant transfer to hand pointing movements was found for backward adaptation but in contrast, a small but significant transfer was found in the case of forward adaptation. These authors thus proposed that adaptive shortening of reactive saccades can be fully accounted for by sensory-motor transformation changes, i.e. acting downstream from visual registration of the stimulus, whereas adaptive lengthening can be mainly accounted for by sensory-motor transformation changes and partly for by changes of the visual registration of the target. This proposal is qualitatively consistent with the target remapping hypothesis of Semmlow et al. (1989) and Ethier et al. (2008a), but these last two studies went further by proposing that forward adaptation can be fully, and not only partially, accounted for by target remapping.

Some studies of the neurophysiological substrates have also alluded to a strong difference between forward and backward adaptation. First, Catz et al. (2008) showed in the monkey that forward adaptation and backward adaptation were respectively associated with an increase of saccade duration and a decrease of peak velocity. Second, electrophysiological recordings reported by Catz et al. (2008) revealed that the firing of Purkinje cells in the cerebellar oculomotor vermis changed in an asymmetrical way for the two adaptation conditions. Whereas the simple spikes population burst remained synchronized with saccade offset after forward adaptation, such synchronization was broken after backward adaptation. Third, Golla et al. (2008) found on average a stronger deficit of forward adaptation than of backward adaptation in patients with cerebellar lesion, suggesting a functional dissociation between the two types of adaptation. An indirect indication of this dissociation can be found by comparing two previous studies of lesion of the cerebellar vermis in the monkey, which respectively revealed a permanent loss of forward adaptation (Barash et al., 1999) and only a temporary loss of backward adaptation (Takagi et al., 1998). Unfortunately, none of these two latter studies measured in the same animals the effectiveness of adaptation in the opposite direction (backward and forward, respectively).

In conclusion, both behavioural and neurophysiological studies clearly indicate that backward and forward adaptations rely on different mechanisms. Besides a postulated dissociation of cerebellar involvement, more detailed knowledge about the underlying neural substrates is awaiting further investigations.

5. Neural substrates

Saccadic adaptation mechanisms can be decomposed into two major processes. First, error encoding processes allow the detection of systematic alterations in saccade spatial parameters. Second, progressive and plastic changes of the oculomotor commands allow enduring changes of saccade metrics to reduce these saccade errors. Most neural data available today concern the plastic oculomotor changes, which will thus be discussed first here, the substrates of error encoding processes being addressed only very recently.

5.1. Plastic changes of saccadic commands

A number of behavioural studies reviewed in the previous sections have led to hypothesize on the neural substrate of saccadic adaptation. A coherent picture emerges as to the possible locus of backward adaptation of reactive saccades. On the one hand, it has been shown that saccadic adaptation: (1) does not modify visual perception as measured in target localization tasks performed under eye fixation condition; (2) does not, or only marginally, transfer to goal-directed head and arm movements; (3) transfers to anti-saccades executed in the adapted direction but not to anti-saccades elicited by a visual target in the adapted field; (4) transfers to averaging saccades and to express saccades; (5) is associated with changes of saccade dynamical parameters such as the ratio of peak acceleration versus peak deceleration. All these findings are consistent with adaptation of reactive saccades acting at a low level site of saccade circuitry, close to the final oculomotor output. More specifically, point #3 is consistent with a site of adaptation located downstream from the level where the vector inversion process involved in the anti-saccade task occurs. Since this process has been proposed to occur in the parietal cortex

(monkey lateral intraparietal area LIP: Zhang and Barash, 2000; human parietal eye fields PEF: Nyffeler et al., 2007; Van Der Werf et al., 2008) or in the frontal cortex (Moon et al., 2007), saccadic adaptation is likely to take place at a sub-cortical level. Moreover, point #4 is consistent with a locus of saccadic adaptation at the level of – or downstream from – the superior colliculus because this structure has been suggested to contribute to the programming of averaging saccades (Glimcher and Sparks, 1993; Moon et al., 2007; van Opstal and Van Gisbergen, 1990) and of express saccades (Schiller et al., 1987). Finally, point #5 suggests an involvement of the caudal fastigial nucleus of the cerebellum since this area has been suggested to control the size of saccades through specific modulations of their acceleration and deceleration phase (Fuchs et al., 1993; Kleine et al., 2003; Ohtsuka and Noda, 1991). On the other hand, it has been suggested that adaptation: (i) does not affect the main sequence relationship; (ii) affects oculomotor commands which encode the saccade vector rather than its horizontal and vertical components; (iii) affects motor commands driving saccadic movements of gaze (eye-in-space) rather than of its eye component, and (iv) affects extra-retinal signals involved respectively in re-orienting visual attention and in monitoring eye displacement for subsequent saccade programming. This second set of findings suggests that saccadic adaptation does not act at the very final motor stage (i.e. the oculomotor neurons). Together with points #1–5, points #i–iv are therefore consistent with adaptation of reactive saccades acting at a pre-oculomotor level. As will be seen in the following paragraphs, the neurophysiological data reviewed in this section are globally consistent with this hypothesis (Fig. 6).

As for many motor activities, a crucial contribution of the cerebellum to sensory-motor adaptation of saccades has been demonstrated. The first evidence dates back to the study of Optican and Robinson (1980) who surgically weakened the extraocular muscles of one eye in the monkey. Recall that exposure to viewing through the operated eye (the unoperated eye being patched) led over a few days to a progressive modification of the saccade size (i.e., adaptation), reducing the dysmetria of the operated eye. When a large lesion of the cerebellar vermis encroaching upon the fastigial nucleus was subsequently performed and the monkeys tested again, saccade adaptation was now virtually abolished. Other lesion studies confirmed the involvement of the cerebellum when short term saccadic adaptation was induced in the double-step paradigm. In the monkey, adaptation deficits were reported when focal lesions affected the medial deep – or fastigial – nucleus of the cerebellum (Goldberg et al., 1993) and the oculomotor vermal cortex – lobules VI and VII – (Barash et al., 1999; Takagi et al., 1998). These nuclear and cortical cerebellar zones, which play a major role also in on-line (non adaptive) control of saccade amplitude (see reviews in Pelisson et al., 2003; Robinson and Fuchs, 2001), will be referred to as the medio-posterior cerebellum. In humans, deficits of backward adaptation of reactive saccades were related to stroke or degenerative lesions affecting the cerebellum (Alahyane et al., 2008; Choi et al., 2008; Golla et al., 2008; Straube et al., 2001). Patients suffering from a Wallenberg syndrome consecutive to infarcts of the lateral medulla, which possibly interrupt an afferent cerebellar input from the inferior olive (see discussion in Tilikete et al., 2006), also showed adaptation deficits in one study (Waespe and Baumgartner, 1992) but not in another (Choi et al., 2008). In our own on-going study, we confirmed that adaptation deficits were found only in some Wallenberg syndrome patients (abstract by Pelisson et al., 2006). Finally an inactivation study in the monkey tried to narrow down the candidate cerebellar areas involved in saccadic adaptation (Robinson et al., 2002). In this study, saccadic eye movements were elicited after unilateral or bilateral inactivation of the oculomotor (caudal) part of the fastigial nucleus. In accordance with earlier investigations (Fuchs et al., 1993; Goffart and Pelisson, 1994, 1998), saccadic eye movements were strongly hypermetric after injection of muscimol in the ipsilateral nucleus. No sign of adaptation was observed during recording periods extending up to 1000 saccades, a number of saccades sufficient to elicit in normal monkey a strong adaptation of saccade amplitude in the double-step paradigm (e.g. Straube et al., 1997). Thus, inactivation of the caudal fastigial nucleus leads to inaccurate saccades without any sign of compensation through saccadic adaptation. However, after the effects of muscimol had dissipated over a 10 h period in darkness, the two bilaterally injected monkeys exhibited a reduction of saccadic gain relative to the baseline value recorded in the pre-inactivation period. The authors suggested that this delayed gain reduction resulted from saccadic adaptation processes triggered by the hypermetric saccadic errors experienced during the inactivation period. They concluded that saccadic adaptation could be elicited despite inactivation of the fastigial nucleus but could not be expressed until this cerebellar output pathway regained its function. Confirming that the cerebellum is involved in saccadic adaptation, this study further suggests that structures upstream from the fastigial nucleus – like vermal lobules VI and VII – are specifically involved and that the adapted signals are sent through the fastigial nucleus to cerebellar-recipient saccadic areas (see related hypothesis proposed by Kojima et al., 2004). This hypothesis is consistent with data published in an abstract showing that vermal inactivation blocks saccade adaptation (Robinson and Noto, 2005).

Another evidence for an involvement of the cerebellum in saccadic adaptation is provided by the only available neuro-imaging study of saccadic adaptation (Desmurget et al., 1998; Desmurget et al., 2000). Healthy human volunteers were scanned using Positron Emission Tomography (PET) while generating

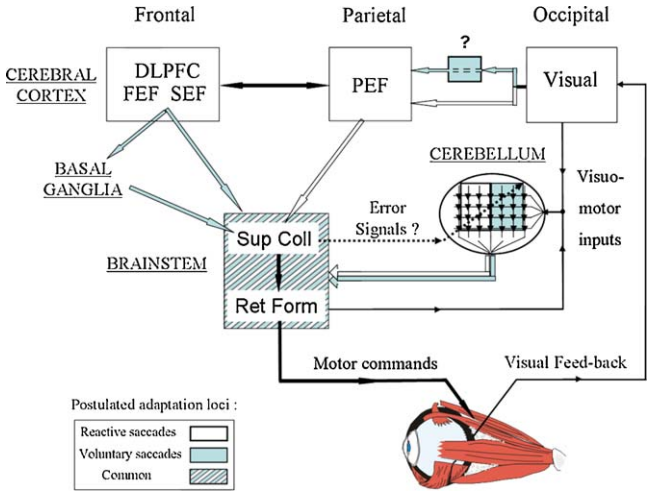

Fig. 6. Postulated neural loci of saccadic adaptation. These sites are indicated in the neural saccadic network schematised in Fig. 1. Neural loci more specifically involved in the adaptation of reactive and voluntary saccades are shown as white and grey boxes, respectively, and a common brainstem locus involved in the adaptation of both saccade categories is shown as a hatched area. Available data on reactive saccade adaptation (see Section 5) consistently imply low-level areas (brainstem and cerebellum), whereas fewer recent studies of voluntary saccades adaptation further suggest the contribution of the same brainstem site (hatched area) and of specific cerebellar (and possibly parietal) sites (grey boxes). Future studies will be necessary to delineate the whole extent of the network subtending plastic changes of reactive and voluntary saccades (the possible contribution of Nucleus Reticularis Tegmenti Pontis, thalamo-cortical pathways and basal ganglia have been omitted here) and to identify the neural substrates encoding the error signals eliciting adaptation (only the recently proposed contribution of the superior colliculus (Kaku et al., 2009) has been illustrated here). FEF: frontal eye fields, SEF: supplementary eye fields, DLPFC: dorso-lateral prefrontal cortex, PEF: parietal eye fields, Sup Coll: superior colliculus, Ret Form: reticular formation.

reactive saccades in a target double step paradigm. Continuous electro-oculographic recording of eye position allowed to shift the visual target during saccade execution either systematically over successive trials (adaptation condition) or randomly (control condition). Metabolic changes computed between the adaptation and control sessions revealed a selective activation of the cortical areas of the medio-posterior cerebellum. The lack of activation in any other cerebellar or extra-cerebellar areas could be due either to a surprisingly high specificity of the neural substrates of saccadic adaptation or to the low sensitivity of the PET approach. As will be detailed below, electrophysiological neuronal recordings in the monkey strongly favour the second explanation.

Fitzgibbon and Goldberg (1986) reported in an abstract that the activity of the superior colliculus (SC) saccade neurons toward a given visual target remained qualitatively unaffected by saccadic adaptation. More precisely, the tuning of neural activity relative to visual space remained unchanged. But because saccade size had changed, the tuning relative to motor space did change (i.e. the neurons' movement field shifted). This finding, which was confirmed in another unit recording study (Frens and van Opstal, 1997), suggests that the adaptation locus is situated downstream from the SC. In another paper (Fitzgibbon et al., 1986), the authors investigated the transfer of saccadic adaptation to saccades elicited by electrical micro-stimulation of the SC. Unexpectedly, no transfer of saccadic adaptation was found, suggesting that the adaptation locus is situated at the SC level or upstream. How can these two sets of contradictory observations be reconciled? In favour of the first (downstream) hypothesis, it can be proposed that electrically evoked saccades are not modified after adaptation of visually triggered saccades because these two saccades categories do not recruit the same SC-recipient network (see also Melis and Van Gisbergen, 1996). Indeed the effect of saccadic adaptation on electrically evoked saccades was later reported to vary with the intensity of SC micro-stimulation and the lack of adaptation transfer was confirmed only for saccades elicited with high current (Edelman and Goldberg, 2002). In contrast, this same study disclosed a full transfer of adaptation in the low current condition, which was further hypothesized to more closely mimic the natural conditions under which the visually elicited saccades were generated and exposed to adaptation training. Thus, the electrophysiological works in the SC converge on the idea that saccadic adaptation modifies circuits which are situated downstream from the SC. Because the cerebellum is situated downstream from the SC and in parallel with the final common pathway of the brainstem, it represents an ideal candidate as a substrate of adaptation. Then, a second series of electrophysiological investigations was performed in the monkey to verify this cerebellar involvement. Studies of caudal fastigial nucleus activity (Inaba et al., 2003; Scudder and McGee, 2003), and of complex-spike (Catz et al., 2005; Soetedjo and Fuchs, 2006) and simple-spike activities (Catz et al., 2008) in the oculomotor cerebellar cortex, all showed significant changes related to saccadic adaptation. In addition, burst neurons of the brainstem reticular formation, which receive oculomotor cerebellar signals through fastigial projections (Noda et al., 1990), have also been shown to change their activity during adaptation (Kojima et al., 2008). Similarly, neuronal activity changes related to saccadic adaptation have been described in the nucleus reticularis tegmenti pontis (NRTP) (Takeichi et al., 2005), specifically in areas which project to the medio-posterior cerebellum and also receive cerebellar feedback projection from the caudal fastigial nucleus. Note that in all these areas (cerebellar vermis, fastigial nucleus, brainstem reticular formation, NRTP), only a fraction of recorded neurons showed adaptation-related change. Analyses performed by P. Thier's team even demonstrated that an effect of adaptation on neural activity in the cerebellar cortex does not emerge at the level of individual Purkinje cells but only at the population level (Catz et al., 2005, 2008).

Taken together, the results of these lesion, neuroimaging and unit recording studies are consistent with a contribution to reactive saccades backward adaptation of an extended neural network comprising the cerebellum (medio-posterior cerebellar areas: vermal lobules VI/VII and caudal fastigial nucleus) and several brainstem areas connected to the cerebellum. However, a clear picture of the exact contribution of the different neuronal populations within this network is still lacking.

Another open question is whether effects of saccadic adaptation extend beyond this cerebellar network. The only published neuroimaging study did not find any activation apart from the medio-posterior cerebellum (Desmurget et al., 1998; Desmurget et al., 2000) but, as mentioned above, this negative result may be due to the low sensitivity of the PET approach. Further neuro-imaging studies using advanced scanning and analyses methods (such as functional magnetic resonance imaging) and accurate on-line monitoring of eye position, are clearly necessary to evaluate the whole adaptation network. A recent electrophysiological study revealed that adaptation-related changes take place also at the level of the superior colliculus (Takeichi et al., 2007), challenging the initial observations of Fitzgibbon and Goldberg (1986) and Frens and van Opstal (1997). However, modifications of the spatial tuning of individual neurons activity were seen both when expressed in visual and motor coordinates. This does not allow to unambiguously conclude on the level (upstream or downstream) of adaptation related to the recorded SC neurons. At the least, this study suggests that the SC receives some information related to saccadic adaptation. A study in human patients suggested that the cerebellar-recipient part of the thalamus is necessary for saccadic adaptation (Gaymard et al., 2001). Indeed, two patients with a lesion involving the ventrolateral thalamic nucleus (VL) and demonstrating a cerebellar syndrome showed a deficit of adaptation of contralesional reactive saccades as compared to healthy subjects and to two other patients with a thalamic lesion but without cerebellar syndrome. In summary (Fig. 6), as far as reactive saccades are concerned, the critical neural network so far includes the medio-posterior cerebellum and its recipient oculomotor structures of the brainstem (reticular formation, NRTP, SC) and thalamus. An extension of this network to the cerebral cortical level can be expected from the study of Gaymard et al. (2001) but has not yet been directly investigated. If one now considers other saccade categories, an involvement of the basal ganglia in adaptation of memory-guided saccades was suggested in a study of Parkinsonian patients (MacAskill et al., 2002). Moreover, the functional implications of studies reviewed in Section 3 also designate some areas of the parietal or temporo-occipital cortex as further candidates contributing to adaptation of voluntary saccades (Fig. 6). Finally, little is known about the neural substrates of the adaptive lengthening of saccade amplitude (but see the cerebellar hypothesis proposed by Catz et al., 2008 and Golla et al., 2008) and of adaptation of saccade direction.

5.2. Error encoding

A prominent feature of the Marr's (1969) theory of the cerebellar role in learning is the postulated role of the climbing fibers system in conveying movement error information. Two different laboratories have tested this hypothesis for saccadic adaptation by recording in the monkey the activity of Purkinje cells complex spikes (Catz et al., 2005; Soetedjo and Fuchs, 2006) but did not achieve a consensus. Indeed, Catz et al. (2005) proposed that the climbing fibers system does not encode error signals driving saccadic adaptation but instead helps stabilize the ensuing plastic changes. Effectively, their population-based analysis of

Purkinje cells complex spikes showed activity changes which were not coupled with the transient changes of saccade error during the adaptation phase. In contrast, Soetedjo and Fuchs (2006) suggested that the variation of complex spikes discharge observed during the adaptation phase could encode the direction (saccade amplitude lengthening versus shortening) but not the amount of saccade error.

A recent study provided exciting new insight into the neural bases of the error signals inducing adaptation (Kojima et al., 2007). This monkey study is indeed the first to suggest that saccadic adaptation can be elicited by an intra-cerebral electrical micro-stimulation, without any external error signal. To this aim, the authors applied a brief intra-cerebral micro-stimulation immediately after the termination of each saccade directed to a stationary target. Micro-stimulation was targeted to the medial part of the mesencephalic tegmentum, with stimulation intensities below the threshold to elicit a saccade. During the course of a few hundreds of such saccade-stimulation pairing trials, the saccade amplitude gradually increased or decreased (depending on the site of stimulation), in a manner very similar to that observed in a classical double-step target paradigm. This amplitude change transferred to other saccades not paired with stimulation if their vector (amplitude and direction) was close to the "adapted saccade" vector, but not if orthogonal or opposite to it. Also, the stimulation was most effective when applied during the first 150–300 ms following saccade termination, but not if applied 1000 ms later. These features (time-course, spatial transfer and effective timing) of the stimulation-induced changes of saccade amplitude are consistent with the proposal of a recruitment of saccadic adaptation processes. In other sessions, monkeys performed a random series of two oppositely directed saccades (e.g. rightward and leftward) and the micro-stimulation of a single site was applied on every trial. In these double-saccades pairing sessions, the endpoints of both saccades were modified in a very similar way, depending on the stimulated site (e.g. saccades endpoints shifted rightwards after a stimulation of the right side). This observation and the effective timing of micro-stimulation together strongly suggest that the experimentally induced activity mimicked a saccadic error signal. A last interesting observation is that the progressive modification of the endpoint of saccades paired with micro-stimulation was accompanied by an increase in the frequency and size of corrective saccades toward the visual target. In other words, micro-stimulation triggered an adaptation-like change of primary saccade but had no effect on the generation of accurate corrective saccades. Thus, micro-stimulation appeared to generate a visual error signal for saccadic adaptation, at a locus downstream from the pathway that provides the error signals for corrective saccades. Note in this respect that the effective stimulated loci are located in a region of the mesencephalic tegmentum that contains cerebellar-projecting fibers originating in the SC and parvocellular red nucleus.

The involvement of the SC was recently demonstrated by the same team (Kaku et al., 2009). Using the same micro-stimulation-saccade pairing approach and targeting the intermediate layers of the SC, the authors elicited the same adaptive-like changes of saccade endpoint as in the Kojima et al.'s study (2007). Again, the effect could be observed with stimulation intensities below the threshold needed to elicit a saccade, and did not prevent the generation of a subsequent corrective saccade. Thus, "... an overt motor signal, tightly coupled to saccade execution, does not serve as a saccade learning signal. However, these findings do not necessarily indicate that the learning signal is purely visual" (Kaku et al., 2009, p. 5273). Moreover, effective stimulation sites were most likely located in the rostral part of the SC, as suggested by the small ($<6^\circ$) size of saccades evoked by supra-threshold stimulation.

To conclude, these two studies provide a most valuable tool to dissect in animals the neural network involved in saccadic error encoding and adaptation, and strongly suggest that an error signal is encoded by the SC and transmitted to the cerebellum to elicit saccadic adaptation.

6. Major open issues for future studies

In this last part, we identify what we think will be the most challenging and promising issues for the near future. This non exhaustive list illustrates the complexity of getting a comprehensive understanding of saccadic adaptation, but hopefully also proposes new paths to reach this goal by moving the spotlight to some insufficiently studied issues.

6.1. Multiple adaptation states

Does the short term saccadic adaptation studied by the double-step target paradigm result from those adaptive processes involved when pathological conditions impair the sensory-motor saccadic pathways? Short term saccadic adaptation is much faster (tens of minutes) than adaptation to a peripheral muscle weakness (hours or days). However, in the second situation, subjects perform voluntary saccades in natural settings such that the number of different saccade vectors exposed to learning is commensurably higher than the few saccades vectors used in the double-step paradigm. It is conceivable that the speed of adaptation is inversely proportional to the variety of saccades to adapt. Indeed by comparing the two methods in the monkey, Scudder et al. (1998) found very similar time-courses of gain change when the two types of adaptation are induced with the same number of stimuli (and hence of exposed saccade vectors). Based on this influential study, short term saccadic adaptation has been classically accepted as a good model of adaptive processes taking place in natural physiological or pathological conditions.

However, this hypothesis was later challenged by cerebellar lesion studies showing marked dissociations between adaptive abilities and saccade dysmetria/variability in the monkey (Barash et al., 1999; Takagi et al., 1998) and in humans (Choi et al., 2008; Straube et al., 2001; van der Geest et al., 2006). On the one hand, the fact that normal adaptation abilities are disclosed in the double-step paradigm despite highly variable saccade parameters suggests that saccadic adaptation can – to a certain extent – cope with the variability of post-saccadic visual error signals. Note further that the normal adaptation found in patients presenting a developmental alteration of the cerebellum (William–Beuren syndrome: van der Geest et al., 2006, Chiari type II syndrome: Salman et al., 2006) contrasts with the classical detrimental effect of sudden onset lesions of the cerebellar vermis. This would suggest that cerebellar-dependent saccadic adaptation mechanisms can themselves be compensated in case of developmental – but not of sudden onset – cerebellar dysfunction, a hypothesis meriting further consideration. On the other hand, several studies have now revealed an impaired adaptation without – or independently of – any marked decrease of saccadic accuracy (Takagi et al., 1998; Gaymard et al., 2001; Barash et al., 1999; Straube et al., 2001; Waespe and Baumgartner, 1992; Choi et al., 2008; Alahyane et al., 2008). Furthermore, longitudinal studies in the monkey (Takagi et al., 1998, Barash et al., 1999) have indicated that the maintenance of saccadic accuracy results from a progressive, long-term, functional restoration after the lesion. Accordingly, the above dissociation between impaired adaptation and preserved saccadic accuracy suggests that short-term, but not long-term, saccadic adaptation processes are impaired by cerebellar lesion in these studies. More generally, these dissociations

suggest the existence of different types of adaptation processes with different time-scales.

A more direct argument for this proposal is provided by a recent study in the monkey (Robinson et al., 2006). Monkeys were exposed to daily double-step adaptation sessions and kept blindfolded to prevent de-adaptation (i.e., recovery) in-between these adaptation sessions. Testing over a 19 days period, the authors found that saccadic gain changed rapidly within the first couple of days and more slowly over subsequent days, associated with a progressive increase of retention between sessions. At the beginning (day 1) and end (day 19) of this period, monkeys were also tested in a further double-step adaptation session with an intra-saccadic target step size larger than in the just preceding session. At day 1, this secondary session failed to induce any additional fast gain change, suggesting that the motor memory used by the just preceding short-term adaptation was no longer available. At day 19 in contrast, the secondary session induced a significant and fast gain change, suggesting that the short-term motor memory was again available. These observations could be accounted for by a simple model combining separate short- and long-term adaptation mechanisms (time-constant of 0.5 h – or approximately 500 saccades – and 5 days, respectively). According to this model, the short-term mechanism corresponds to the classical short-term saccadic adaptation: it is elicited as soon as systematic saccade errors are detected but shows only moderate retention. In contrast, the long-term mechanism comes into play only if the need for adaptation persists and allows a long-lasting maintenance of saccade accuracy. As a final note, it is worthy to point out that as demonstrated in humans (Alahyane and Pelisson, 2005), even a single short period (about 30 min) of exposure to double-step targets leads to significant saccadic gain changes extending over a much longer period, namely at least 5 days. This suggests that even the so-called short-term mechanism can hold information for a much longer period than its typical (acquisition) time-constant, an hysteresis which is typically observed for memory systems when signals appropriate for de-adaptation (recovery) are not available or when their use is impeded by the effect of context discussed in the preceding sections.

Multiple states models of saccadic adaptation have also been proposed by two other teams (Ethier et al., 2008b; Kojima et al., 2004). Both studies showed that the effect of an initial adaptation training can persist after saccade gain is brought back to its pre-adaptation level through de-adaptation (i.e., recovery). Kojima et al. (2004) demonstrated the existence of a facilitation of adaptive saccadic change by a previous adaptation period. Monkeys were exposed to a sequence of adaptation, de-adaptation and re-adaptation periods during a single experimental session. The authors reported a faster change of saccade gain in the early part of re-adaptation period as compared to the corresponding part of the adaptation period performed about an hour before. Interestingly, control conditions indicated that this facilitation of adaptation (1) disappeared when about 700 zero-error saccades (target stationary during saccades) were performed between the recovery and re-adaptation phases, (2) was maintained when monkeys performed saccades without visual error feedback (target switched off during saccade execution). The authors' conclusions are self-explanatory: "We conclude that a memory of previous learning remains during recovery to facilitate subsequent adaptation and that such a memory does not disappear merely with time but is erased actively by repeated zero-error movements. Our results, which cannot be explained by a single mechanism, suggest that the saccadic system is equipped with more than one plasticity process." (Kojima et al., 2004). The second study confirmed and extended this conclusion in humans (Ethier et al., 2008b). In that case, saccadic gain was measured immediately after exposure to an adaptation/de-adaptation sequence similar to Kojima et al.'s. Whereas saccadic gain was brought back to a pre-adaptation level at the end of the de-adaptation phase, subsequent "error clamp" trials (visual target systematically placed on the fovea at saccade end) disclosed a quick change of gain toward the initially adapted value followed by a gradual reversal toward normal, pre-adaptation level. This rebound of gain toward the initial level of adaptation was interpreted as the effect of a memory exceeding the duration of the exposure phase. Experimental data (see Chen-Harris et al., 2008) were adequately fitted by a general conceptual model assuming that motor learning relies on multiple processes with different time-constants (Smith et al., 2006).

Altogether, data reviewed in this sub-section strongly suggest that saccadic adaptation can rely on multiple adaptive processes, with different time-scales and possibly different neural substrates. As a note of caution, it should be emphasized that the majority of studies reviewed in the present paper, concerning the short-term adaptation mechanism, pertains to the shortest end of the spectrum of time-scales. Since the generalization of this knowledge to other adaptive processes of the spectrum is highly debatable, we are then forced to admit that very little is known concerning the adaptation mechanisms which are critically involved in compensating for various pathological conditions over longer time-scales. Therefore, it is essential that strong efforts are devoted in the future to these long-term adaptation mechanisms. This will be critical for the development of efficient rehabilitation procedures in patients with impaired saccade accuracy.

6.2. Specificity to saccade category (reactive vs voluntary)

The fact that different adaptive mechanisms are involved for reactive and voluntary saccades strongly emphasizes the need for specific investigations of the underlying neural substrates. In addition, justification for an increased effort devoted to studying voluntary saccade adaptation is based on two further observations. First, as indicated above, voluntary saccades represent the main category of saccades performed in our daily life. Second, the recently suggested possibility that adaptation of voluntary saccades, as compared to reactive saccades, taps upon upstream representational levels of space (Cotti et al., 2007, 2009; Panouilleres et al., 2009c) makes it potentially useful in the rehabilitation of visuo-attentional deficits consecutive to brain lesions. Based on a similar reasoning, rehabilitation strategies associated with other types of sensory-motor adaptation have been developed and applied with success (e.g. prism adaptation, Rossetti et al., 1998; review in Pisella et al., 2006). The assignation of such clinical application to saccadic adaptation would represent a valuable objective for the coming years.

6.3. Backward versus forward versus directional adaptation

The difference reported in this review between backward and forward adaptation provides another source of complexity. Furthermore, another strong motivation for a better understanding of forward adaptation is related to its potentially larger functional significance than backward adaptation. Indeed, saccade amplitude lengthening is likely more involved than saccade shortening in compensating for pathological alterations of the sensory-motor system because these alterations – whether peripheral (Abel et al., 1978; Kommerell et al., 1976; Optican et al., 1985; Zee et al., 1976) or central (Leigh and Zee, 1999) – tend to decrease rather than increase saccade gain. Saccade amplitude lengthening is also likely involved in many physiological situations to compensate for the reduction of saccade speed due to fatigue (Barash et al., 1999; Golla et al., 2008).

The adaptation of saccade direction is another example of neglected aspect despite its potential contribution to functional recovery under various pathological conditions. These conditions

may include deficits of coordination of 2-D eye motion originating at a peripheral neuro-muscular level (e.g. effect of vertical neuro-muscular palsy on oblique saccades) or at a central level (e.g. effect of horizontal lateropulsion on vertical saccades in Wallenberg syndrome). Theoretically, directional adaptation may call for specific processes not required for amplitude adaptation, such as a remapping of the saccade endpoint (or target location). The rare studies of directional adaptation have used a modified version of the target double step paradigm where the second target step is orthogonal to the first one (Chen-Harris et al., 2008; Deubel, 1987; Frens and van Opstal, 1994; Noto et al., 1999). Only two studies have compared directional adaptation to amplitude adaptation (Deubel, 1987, Noto et al., 1999) and, despite some controversy, both suggest that the two types of adaptation follow a similar time-course. However, this similarity should be investigated further by comparing other adaptation properties (e.g. retention, spatial transfer, context specificity, effect of saccade category, ...). Given the known differences between the two types of amplitude adaptation (backward versus forward), it is expected that directional adaptation will disclose some distinctive characteristics relative to either forward adaptation or backward adaptation, or to both.

7. Conclusions

This review was aimed at presenting and discussing the new findings on saccade adaptation accumulated mainly over the past five years. These findings not only provided new insights on the saccade adaptation mechanisms since the last review of Hopp and Fuchs (2004) but also brought into light the complex nature of these mechanisms. First, many studies were aimed at understanding the backward adaptation of reactive saccades and, overall, provided a good picture (but still incomplete) of this process, by showing that this adaptation acts at a low level of the saccadic circuitry. Second, an essential result in the past few years was that the adaptations of reactive saccades and voluntary saccades have distinct characteristics and thus do not entirely rely on the same pathways. Whereas the brainstem appears to be involved in both processes, separate substrates in the cerebellum seem to take part in the adaptation of the two categories of saccades. However, even if the involvement of cortical areas has been predicted from behavioural results for voluntary saccades, it remains unclear if these areas as well as the thalamus and the basal ganglia play a critical role in adaptation of one or both saccade categories. Third, another important point of this review was to report the differences between saccadic amplitude lengthening (forward adaptation) and saccadic amplitude shortening (backward adaptation). Whereas forward adaptation induces target remapping, backward adaptation is associated with changes occurring downstream from that visual processing stage. A possible cerebellar substrate of this functional dissociation has been mentioned very recently. Finally, we identified several unanswered questions (different time-scales, precise neural basis of adaptation, error signal processing ...), and stated that saccadic adaptation is a complex function relying on separate processes which differently interact according to the context, direction of adaptive amplitude changes and category of saccades. We argued that this complexity must be taken into account to reach a better knowledge of the brain mechanisms underlying sensory-motor plasticity, which will undoubtedly lead to the development of efficient rehabilitation procedures of various visuo-attentional deficits.

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