Dynamical and Metrical Adaptation of Saccadic Eye Movements in Humans

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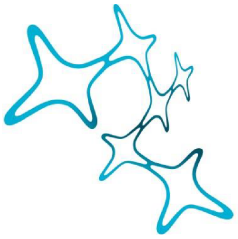

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Thanks to all of you, who helped shed a light -Luce- and showed me my warm colors.

When little light was around me. It would not have been possible without you.

Summary

The ever changing nature of the world around us, the constraint of our oculomotor system and its intrinsic changes, physiological or pathological, pose important challenges to how we build an image of the visual world around us. To collect visual information we constantly move our eyes, in order to direct the fovea (the retinal area of highest visual acuity) into the most salient parts of the visual scene. We then interleave these movements, called saccades, with periods in which the eyes stay still on the fovea, called fixations, to collect visual information. Moreover, we produce different types of saccades, depending on whether our behaviour is induced by external stimuli or by goal driven actions. For all classes of produced saccades precision is highly important for our visual perception and it is adaptively monitored by our brain.

This thesis investigates the adaptive mechanisms behind how the brain monitors saccadic performance and corrects for mistakes in saccadic accuracy, both concerning saccadic dynamics (accuracy in properly ending a saccade) and metrics (accuracy in saccadic amplitude). During each study we used an adaptation paradigm, and measured the effect of saccadic adaptation by comparing the pre-adaptation performance and the post-adaptation performance. Furthermore we also analysed the amount of adaptation transfer between different saccade types to determine whether adaptive mechanisms are highly context-specific and to draw conclusions about their possible brain areas involved in these processes. The main results of these studies are summarized below.

The first study (Chapter 2. 1) “Adaptation of Post-Saccadic Drift in Reflexive Saccades Transfer Only Partially to Voluntary Saccades” investigates the dynamical adaptation of the saccadic system in humans. We managed to induce post-saccadic drift (PSD) in humans through a consistent post-saccadic shift of the visual target in reflexive saccades (RS) and we tested its effect in open loop reflexive (RS) and voluntary saccades (VS). The results revealed that PSD can be induced by our stimulus in humans and that the adaptation transfers only partially from reflexive to voluntary saccades, suggesting that PSD adaptive mechanisms can

not be accounted for exclusively by a pulse-step mismatch in the brainstem, but need to be located upstream in the oculomotor pathway, as the former hypothesis would predict both saccade types to be affected equally by the adaptation procedure.

The second study (Chapter 2. 2) “Updating the Dichotomy of Reflexive and Voluntary Saccades” investigates the metrical adaptation of the saccadic system in humans. We induced gain adaptation on reflexive saccades (RS) through the double step paradigm (McLaughlin, 1967) and tested its effect in open loop reflexive (RS) and voluntary saccades (VS) in five different studies. The studies differed in their operationalisation of VS, through a manipulation of two factors: the instructions given to the participants (Instruction) and the timing of the fixation and target(s) presentation (Overlap). The results revealed different adaptation transfer rates between RS and VS depending on the definition of VS, resulting in stronger or weaker adaptation transfer rates. We therefore proposed a redefinition of VS based on more quantifiable variables and a paradigm switch from thinking of VS and RS as a dichotomy but rather as laying into a more continuous frame of references.

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List of Abbreviations

PSD Post-Saccadic Drift

VS Voluntary Saccades

RS Reflexive Saccades

1. General Introduction

Visual perception seems such an effortless act: we wake up in the morning, open our eyes and here we go, we see the world. We however know that the process of building a stable visual image of the world around us is anything but a simple task.

On one hand we need to consider something philosophers have been discussing since Ancient Greece. Is the world stable? “Panta rhei” said Heraclitus, “all is flowing”, or in other words "Nothing ever is, everything is becoming" says Plato explaining the core of the heraclian argumentation (Plato, ca. 370 B.C.E./1997). Whether or not we like the famous metaphor about not being able to bathe in the same river twice, it seems like a fitting description of our world, and specifically of our visual world. It is indeed a fact that visual scenes do not remain stable and constant.

On the other hand, to complicate the situation we need to consider how we explore and collect information from visual scenes. “They move these small globes around and that is how they see” wrote Findlay and Gilchrist (2003) in their book Active Vision, imagining a Martian ethologist describing the human eyes and visual perception. The importance of gaze movements lies in the inhomogeneous structure and morphology of the retina, which is a thin sheet of neurons at the back of the eye that is sensitive to light and converts it into neural signals sent to the visual areas of the brain. Within the retina lies the fovea, which coincides with the area of most acute vision. To get a rough idea about the central role of the fovea in human vision, we can mention that circa half the neurons in the optic nerve carry information from the fovea, and that the remaining half is responsible for the rest of the retina.

It is then clear the need to produce gaze movements that redirect the fovea to locations of interest in the visual scene. During eye movements, however, our perception is highly impaired (Volkmann, 1968; Volkmann, 1986). In order to collect visual information we therefore need to alternate periods in which the eyes move, called saccades, and in which they stay still[1], called fixations.

[1] During fixations the eyes are not perfectly still. As will be discussed in Chapter 1.1. microsaccades (involuntary small eye movements that resemble in their shape and dynamic saccadic eye movements) can be produced during fixations and serve the purpose of avoiding sensory adaptation to non moving stimuli.

A third important aspect that influences perception is the intrinsic changes of the oculomotor system, that could be physiological or pathological. These changes lead to the need to recalibrate the system in order to maintain the needed accuracy and stability of the saccadic system. Such recalibrations, through adaptive mechanisms, guarantee the correction of systematic motor performance errors and any mismatch between the intended and produced motor command.

In summary, when we perceive the world our oculomotor system faces different challenges, (1) the extrinsic changes of the visual environment, (2) the intrinsic properties of the oculomotor system, (3) the intrinsic changes, pathological or physiological, that affect the oculomotor system. The oculomotor system needs therefore to take into consideration these aspects of the problem, by minimising its delays and by maximising its precision and stability in order to gain as much reliable information as possible. Furthermore it needs to be able to monitor itself and detect and correct any possible systematic motor performance errors.

We will discuss these aspects here. We will first shortly describe the oculomotor system, its properties and aims (Section 1. 1), we will then continue with the properties of the saccadic system describing the control of the movement and the holding still of the eye (Section 1. 2, 1. 3), we will then discuss the neurophysiological basis of the saccadic system, specifically for RS and VS (Section 1. 4, 1. 5), finally we will talk about problems that can arise in the production of saccades, and the adaptive mechanisms that control saccade accuracy and precision (Section 1. 6, 1. 7). Section 1. 8 provides a summary of this thesis's aim.

1. 1 The Oculomotor System

To be able to account for the extrinsic changes of the visual scene the oculomotor system has developed different types of eye movements. We can divide them into two main classes: (1) gaze stabilization eye movements and (2) gaze redirecting eye movements. They are summarized in Table 1.

Eye Movements	Aim
Saccadic eye movements	Move the gaze toward salient objects in the visual scene
Fixations	Keep the fovea still onto a target by inhibiting eye movements or drifts with the exception of microsaccades
Fixational eye movements	Move the eyes during fixations (microsaccades) to avoid sensory adaptation effects
Smooth pursuit	Keep a moving target stable on the fovea
Vestibulo- ocular reflex	Keep a target stable on the retina during brief head rotations and translations
Optokinetic response	Keeps a target stable on the retina during important head rotations and translations
Vergence	Coordinate the eyes into synchronously opposite directions in order to place the target on the fovea of both eyes

Table 1. Summary of eye movement types and their aims.

Gaze stabilization eye movements answer the need of keeping an image positioned still on the fovea, the region of the retina with the highest density of photoreceptors. Visual acuity declines heavily when we move from the foveal region to the periphery (Jacobs, 1979) and the shifting of the image on the retina impairs visual perception (Burr & Ross, 1982; Demer 1993). Gaze stabilization mechanisms solve these problems. The vestibulo-ocular reflex (VOR) compensates high-velocity head movements, by counterrotations of the eye. In addition to the VOR, the optokinetic response (OKR) keeps the retinal image stable during slower head movements. Smooth pursuit eye movements hold a moving image stable on the fovea (for a more detailed description, see Dodge, 1903; Krauzlis, 2008; Robinson, 1978). The opposite problem is also true. Vision is known to fade if a visual object is stabilized on the retina (Martinez-Conde & Macknik, 2008). To solve this constraint we produce small eye movements, called microsaccades, even during fixations to maintain visual acuity (Martinez-Conde et al., 2013).

Gaze redirecting eye movements became necessary with the evolution of the fovea. As previously mentioned, to move the fovea to salient parts of the visual scene we produce rapid eye movements. These movements are called saccades and they serve the purpose of shifting the line of sight between different points of fixation. Raymond Dodge (1903) made the first distinction between saccades and other types of eye movements explaining explicitly their function "to move the eyes so that the point of interest will be seen with the visual center of the retina". However, in order to perceive the visual scene we need to interleave saccades with periods in which the target remains stable on the fovea, or fixations. Fixations usually last around 200-300 ms (Viviani, 1990). During fixations the next saccade is programmed. These movements will be further discussed in Section 1. 2. "*The Saccadic System, the Control of Movement*" and 1. 3. *"The Saccadic System, the Control of Holding the Eye Still".*

Finally we need to mention vergence eye movements, their role is to coordinate the eyes in opposite directions in order to hold an image still simultaneously on the fovea of each eye. This movement is necessary given that we have two eyes: the position of each eye needs to be calibrated independently in order to foveate the same object.

1. 2 The Saccadic System, the Control of Movement

Saccadic eye movements are an ubiquitous feature of vision, as reflected by the fact that during normal activities we move our eyes 3-4 times per second, making tens of thousands of saccades each day and many billions over the course of a lifetime.

In our everyday life we are not aware of the continuous gaze shifting, nevertheless we can always decide where and when to make a saccade. We cannot, however, decide how to make a saccade or correct it mid flight. Saccadic eye movements are thus described as stereotyped and ballistic. The first term refers to the fact that they always have a typical step shape (see Figure 1). While moving from one position to another, the eye accelerates, reaching a peak velocity in the first half of the saccade, then it decelerates: every time a saccade of the same amplitude (angular rotation of the eye) occurs, a similar trajectory is followed closely.

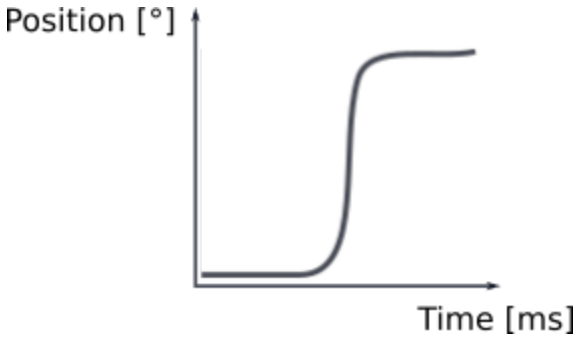

Figure 1. Typical step shape of a saccadic eye movement.
On the x-axis Time in ms, on the y-axis Position in degrees [°]. The eye is first fixating, then moves (saccadic eye movement) and lastly abruptly ends the movement to hold the new fixation.

The ballistic nature of the saccade lies in the fact that the top velocity of a saccade is always proportional to its amplitude: there is a linear relationship between the amplitude of a saccade and its velocity and duration (Robinson, 1964). This relationship is referred to as the "main sequence" (Bahill et al. 1975; Boghen et al. 1974).

The amplitude of a saccade can range from 0.1° (microsaccades) to 90°, nevertheless typically saccades do not exceed 20 - 25°. To make larger gaze movements, eye and head movements are usually combined. A horizontal saccade of 5° can reach a peak velocity of 200°/s and a duration of 30 ms. Saccades with higher amplitudes (80°) can reach peak velocities of 500°/s and last up to 300 ms. (Collewijn et al., 1988).

The time between the appearance of a stimulus in the periphery of the visual field and the beginning of a saccade, or saccadic latency, is around 200 ms, when the stimulus is located at around 10°. Various factors may influence saccadic latencies. Some factors elongate it, like low luminosity, stimuli located at higher eccentricities, distractors, or cognitive demanding tasks parallel to the generation of saccades (e.g. programming antisaccades). Other factors shorten it, like knowing when the target will appear or its position.

Different types of saccades are distinguished, depending on how they are elicited (Deubel, 1999; Gaymard et al., 1998; Pélisson et al., 2010). For a summary see Table 2. Growing amounts of evidence support the idea that partially different cortical areas control different saccade types (Johnston & Everling, 2008; Munoz & Everling, 2004; Pierrot-Deseilligny et al., 1995; Pierrot- Deseilligny et al., 2003) .

Saccade Category	Function
REFLEXIVE SACCADES	
Reflexive saccades	Saccades elicited by the appearance of a novel stimulus in the periphery
Express saccades	Very short latency saccades elicited via the gap paradigm
VOLUNTARY SACCADES	
Delayed saccades	Saccades elicited by a go signal with a target already present and stable in the visual scene
Memory guided saccades	Saccades generated to a memorised target location
Predictive saccades	Saccades elicited by regularly alternating targets
Anti-saccades	Saccades generated toward the opposite location of the visual target
Scanning saccades	Sequence of saccades between targets present on the visual scene
SPONTANEOUS SACCADES	Saccades elicited without any spatial goal (for ex. thinking with closed eyes)

Table 2. Summary of different types of saccadic eye movements and their function.

Reactive saccades, also called reflexive or involuntary saccades, occur in response to the onset of a visual target that suddenly appears in isolation in the peripheral part of the retina. Latencies of reactive saccades are typically around 200 ms, 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 & Weber, 1993).

Voluntary saccades, also called intentional or volitional saccades, occur when subjects intentionally scan a visual scene. 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 go signal), memory guided saccades (looking at a remembered location of a previously presented target), predictive saccades (looking between two regularly alternating targets), scanning saccades (looking sequentially between targets in a stable visual scene) and anti-saccades (looking at the location which is opposite to the visual target).

Spontaneous saccades occur when there is no spatial goal, as for example when thinking with eyes closed or at rest in the darkness.

1. 3 The Saccadic System, the Control of Holding the Eye Still

So far, we explained how saccadic eye movements serve the function of bringing a visual target at the center of the fovea, once done, however, the target stimulus has to be maintained in this position. If we stop thinking one moment about eye movements and vision, a simple question comes to mind: how is it possible to continuously move the eyes but nevertheless perceive a stable world?

One first observation is that during the execution of a saccade, visual perception is highly impaired. This phenomenon, called saccadic suppression (Volkmann 1986) enables us to move the eyes without noticing their movements. Quite interestingly, we are also not aware of the gap in visual perception that saccadic suppression creates, but a nice and easy experiment could convince us of this phenomenon. If we stand in front of a mirror with a friend, we will not be able to see the saccades we produce reflected in the mirror while we will have no difficulties in seeing our friend's ones.

Since we are not properly able to perceive visual images during saccades, periods in which the eyes are steady, or fixations, assume a very important role. Fixations occur between saccades, and by preventing eyes from shifting gaze to another visual target, they make it

possible to visually inspect a particular object at length. The importance of fixations lies in the fact that they constitute the active periods of visual scanning. They usually last around 200-300 ms (Viviani, 1990), but their variability is very high. During fixations we analyze the visual stimuli and we program the next saccades.

It is important to notice that fixations are not passive moments after a saccade, but they require an active system to keep the eyes from moving, still on the target at the end of each saccade. Or as Robinson (1970) wrote “Fixation is just as much of an active process as movement”.

1. 4 Neurophysiological Basis of Moving and Holding the Eye Still

The eye is controlled by six muscles, arranged in three pairs, corresponding to the three axes of rotation of the eyeball: horizontal, vertical and torsional. This imposes mechanical constraints on eye movements. On the one hand to move rapidly, the muscle must develop a large transient force to overcome the viscous drag of the orbital tissue, on the other hand to hold the eye in place at the end of the movement, the muscle must develop enough tension to balance the elastic restoring force of the orbital tissue.

This is achieved by combining two inputs that need to be sent to the eye muscles (see Figure 2), a phasic increase, or burst, of neural activity in the oculomotor nuclei, called the pulse of innervation, and a steady sustained torque arising from a tonic level of neural activity, called the step of innervation. The problem the brain needs to face is how to transform the velocity signals (the pulse) into position signals (the step). Neurophysiological evidence indicates that the position signal is produced by mathematically integrating the velocity signal with respect to time, which is achieved in the neural integrator (Arnold & Robinson, 1997; Skavenski & Robinson, 1973). For a schematic of this mechanism see Figure 2. Studies revealed that nuclei in the brainstem are involved in this operation, more specifically the nucleus prepositus hypoglossi (NPH) and medial vestibular nuclei (MVN) integrate horizontal gaze, whereas the interstitial nucleus of Cajal (INC) integrates vertical and torsional gaze (Cannon & Robinson 1987; Kheradmand & Zee, 2011; Leigh & Zee 2015). A role of the

cerebellum has also been shown (Harris et al., 1993; Shaikh & Ghasia, 2014). For a review on the neural integrator see Sanchez & Rowe, 2018.

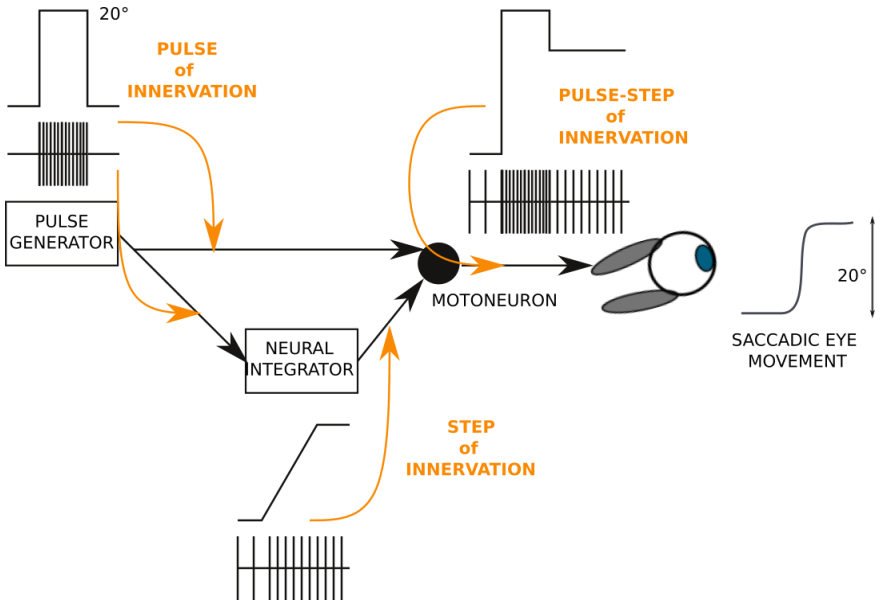

Figure 2. The pulse-step innervation and the related neural activity.
The neural commands needed to produce a saccadic eye movement. A first burst of neural activity, the pulse of innervation, is needed to overcome the viscous drag of the orbital tissue. In the figure both the pulse of 20° and the neural activity in the brainstem that produces it are displayed. The vertical bars are a graphical description of the frequency of action potentials in the dedicated brainstem region. The pulse of innervation has two pathways to reach the ocular motoneuron. One direct to the motoneuron, and one indirect through the neural integrator, where the pulse component is mathematically integrated and a step of innervation is produced, a steady sustained neural activity to hold the eye in place at the end of the saccade. The pulse and step components of innervation then reach the ocular motoneuron and generate a saccade.

In the following sections we will see in more detail the neurophysiology behind saccadic initiation and monitoring, both regarding the involved subcortical and cortical regions. We will therefore talk about the brainstem and the reticular formation (RF), the superior colliculus (SC), the cerebellum (CB) and its nuclei, the vermis and fastigial nucleus on one hand and the flocculus on the other, the visual cortex, the parietal cortex and the lateral intraparietal area (LIP), and the frontal cortex and the frontal eye field (FEF), the supplementary eye field (SEF) and the dorsolateral prefrontal cortex (DLPFC). See Figure 3 for a localisation of these brain areas, and Figure 4 for a schematic of the pathways.

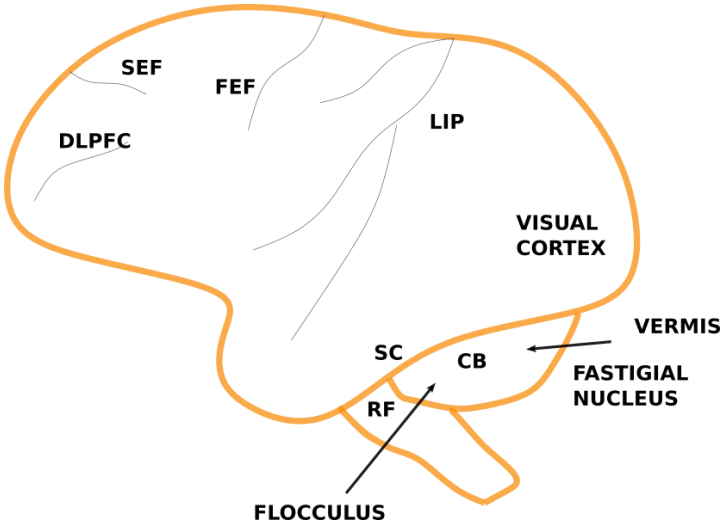

Figure 3. Brain areas involved in generating and controlling saccadic eye movements.
Abbreviations: RF, reticular formation (in the brainstem); SC, superior colliculus; CB, cerebellum; LIP, lateral intraparietal area; FEF, frontal eye field; SEF, supplementary eye field; DLPFC, dorsolateral prefrontal cortex.

1.4.1 The Brainstem

The neural activity related to the pulse-step innervation has been found in specific regions of the brainstem, specifically in the pons and medulla for horizontal saccades, and in the rostral midbrain for vertical saccades. Within these regions specific classes of neurons work together to build the appropriate motor command (Keller, 1974). Burst neurons start firing circa 10 ms before the onset of the saccade and end slightly before the saccade lands on the target. The firing rate during the burst is related to the instantaneous velocity of the saccade and the number of spikes in the burst is related to the amplitude of the saccade. Excitatory burst neurons (EBNs) (in the paramedian pontine reticular formation, PPRF, for horizontal saccades, and in the rostral interstitial nucleus of medial longitudinal fasciculus, RIMLF) provide the velocity signal for the eye muscles that will contract during the saccade, and specify the pulse portion of the motor command. The EBNs also provide a copy of this velocity signal to the brainstem nuclei of the neural integrator, which generates the step portion of the motor command. Inhibitory motor neurons (IBNs) -in the medullary reticular formation (MedRF) for horizontal saccades and in the interstitial nucleus of Cajal and RIMLF for vertical saccades- provide a crossed projection that inhibits motor neurons projecting to the antagonist eye muscles, leading them to relaxation. Another class of neurons, the omnipause neurons (OPNs)

located in the nucleus raphe interpositus (RIP), fire at a constant high rate of about 100 spike/s during fixation, but completely pause their activity just before and during saccades. The activity of OPNs inhibits EBNs and IBNs, preventing unwanted saccadic eye movements during fixation. The onset of the activity in OPN appears to be triggered by inhibitory signals originating from higher brain centers (for reviews see Krauzlis, 2008; Sparks, 2002). These brainstem premotor regions receive input from many brain areas, which include the frontal, visual and parietal cortex, the SC and the cerebellum (for a review see Leigh & Zee, 2015; Scudder et al., 2002).

1.4.2 The Superior Colliculus

The SC is an important oculomotor structure, it is composed of several layers, the superficial layers receive direct retinal inputs, while the intermediate layers contain neurons that are responsible for generating orienting movements of the eyes and the head. Its retinotopic organisation creates motor maps, whose stimulation produces saccades in the contralateral visual field. Its role is to receive inputs from several cortex areas and provide a trigger signal to the brainstem. It sends at the same time information to the cerebellum so it can monitor and adjust the saccadic command if necessary (for reviews see Leigh & Zee, 2015; Munoz, 2002; Scudder et al. 2002; Sparks, 2002).

1.4.3. The Cerebellum

As mentioned, the cerebellum receives a copy of the oculomotor input from the SC, but it is Important to note that the cerebellum also directly sends information to the brainstem. The role of the cerebellum is better described in Section 1.7, but here we can summarize it as “keeping an eye” on the oculomotor system. Two main loci are involved in this control role, the flocculus and the vermis/ fastigial nucleus and they will be discussed later (for a review see Leigh & Zee, 2015; Munoz, 2002)

1.4.3. The Neocortex

The visual, parietal and frontal cortices play a very important role in the oculomotor system. Visual inputs important for the generation of saccades and maintaining visual fixations

are sent via the retina and LGN to the visual cortex. From the dorsal stream of the extrastriate cortex we can find projections to the parietal cortex. One important relay station is the lateral intraparietal area (LIP) which plays an important role in building a “priority map” upon which both motor commands and visual attention are modulated. This pathway directly connects to the SC influencing oculomotor behaviour. LIP also projects directly to frontal areas which include the frontal eye fields (FEF), the supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (DLPFC). These areas are interconnected and they also project to the SC , cerebellum and brainstem.

To summarize, two main parallel descending pathways mediate the role of the frontal and parietal cortex on the control of saccades. One pathway from the FEF to the SC (directly and indirectly through the basal ganglia) and from the SEF to the brainstem regions. This pathway is in charge of preparing voluntary saccades. The other pathway is directly from the parietal cortex to the SC. This pathway controls more the reorientation of gaze to novel stimuli and the shifting of visual attention to new targets (for a review see Leigh & Zee, 2015; Munoz, 2002). See Figure 3 for a localisation of these brain areas, and Figure 4 for a schematic of the pathways.

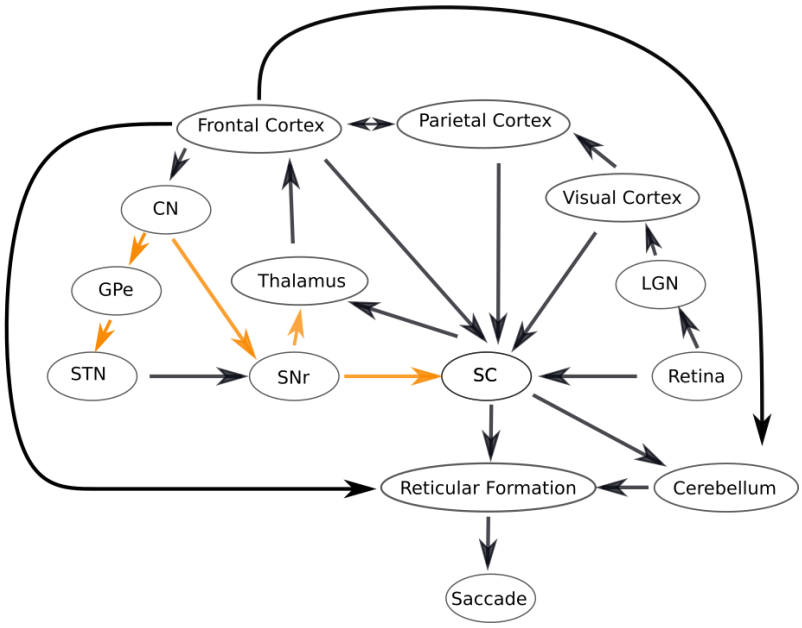

Figure 4. Brain areas involved in generating and controlling saccadic eye movements.
Black lines represent excitatory connections. Orange lines represent inhibitory connections
Abbreviations: LGN, lateral geniculate nucleus; CN, caudate nucleus; GPe, globus pallidus external; STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; SC, superior colliculus. [Redrawn and modified from Munoz, 2002, with permission].

1. 5 Neurophysiological Basis Behind Reflexive and Voluntary Saccades

As described in Section 1. 2, we can distinguish two main types of saccadic eye movements, depending on their latencies and the way they get elicited: voluntary saccades (VS) and reflexive saccades (RS). For a summary check Table 2. As seen in the previous section, the neural pathways of these two saccade types differentiate at the cortical level while sharing common neural pathways in the subcortical areas (Coiner et al., 2019; Johnston & Everling, 2008; Munoz & Everling, 2004; Pierrot-Deseilligny et al., 1991; Pierrot- Deseilligny et al., 2003; Pierrot-Deseilligny et al., 2004; Pélisson et al., 2010; for a review see Leigh & Zee, 2015).

Evidence suggests that different cortical regions play a specific role in generating different classes of saccades (Leigh & Zee, 2015; Munoz, 2002; Pierrot-Deseilligny et al., 1991). Parietal regions have direct and fast projections to the SC and provide the main input to the triggering of RS (Leigh & Zee, 2015; Pierrot-Deseilligny et al., 1991). Lesions in the posterior parietal cortex showed longer latencies in RS (Heide & Kömpf, 1998). Frontal regions have direct and indirect (via the basal ganglia) projections to the SC and play a role in suppressing RS and producing VS. The execution of VS is performed in the FEF, that through the CEF (cingulate eye field) activates the SEF and DLPFC (Berman et al., 1999; Ettinger et al., 2008; Jamadar et al., 2013; Leigh & Zee 2015; Pierrot-Deseilligny et al., 2004). Lesions in FEF produce impairment in VS while RS are mainly unaffected (Gaymard et al., 1998; Gaymard et al., 1999)

The involvement of saccadic subcortical areas, namely the brainstem, SC and the cerebellum on the other end are part of a final common pathway that is responsible for saccadic generation and monitoring of all types of saccades (for a complete picture see Leigh & Zee, 2015).

1. 6 Dysmetria and Post-Saccadic Drift

In Section 1.4 we explained the pulse-step innervation needed to produce a saccadic eye movement and how this command is generated and transmitted to the motoneurons, we will here talk about what happens when the pulse-step command is not appropriately calibrated.

As previously discussed, a properly combined pulse-step of innervation produces an orthometric saccade that is appropriately held in place in the new position. A mismatch between pulse and step produces problems either in the saccade moving command (metricity) or in holding the saccade steady at the new location (dynamic) or both. Two main problems arise from a mismatch in the step-pulse innervation: (1) Saccadic dysmetria, either hypometria - produced by an undershooting of the pulse component - or hypermetria - produced by an overshooting of the pulse component - and (2) post-saccadic drift, PSD, the inability to hold

the eye still at the end of the saccade. If the phasic component is greater than the tonic component, then the eye would travel beyond its final position and slowly drift back. If the phasic component is smaller than the tonic component, then the eye would not reach the final position with one fast, smooth motion, but would stop and slowly drift to its final position (Bahill et al., 1975; Bahill et al., 1978)

Monkey studies (Fuchs & Luschei, 1970; Keller, 1974; Robinson, 1970; Robinson & Keller, 1971; Schiller, 1970) and extraocular muscle recordings in humans (Scott & Collins, 1973) supported this pulse-step innervation model.

When making a saccade to foveate the visual target, two main criteria can assess the success of the eye movement: (1) its metrical accuracy and (2) its dynamical accuracy. It should be by now apparent that in order to collect visual information the oculomotor system needs to produce saccades that land precisely on the intended part of the visual scene and that it needs to hold the eye still in that position for how long necessary to collect visual information.

Saccadic metrical precision refers to the amplitude accuracy of a goal-directed saccade. It is measured by the saccadic gain, the ratio between the amplitude of the saccades (performed saccadic amplitude) and the distance of the target from the initial eye position (desired saccadic amplitude). Saccades whose gain is about 1 are called orthometric, meaning that the performed and desired saccadic amplitude match perfectly, hypometric saccades are movements that fall short of 1 in its gain, meaning that the performed saccades is smaller than the desired amplitude, while hypermetric saccades have a gain that is bigger than 1, meaning that the performed saccades is bigger than the desired amplitude. Normal subjects usually show a small degree of saccadic hypometria, around 10% of the desired amplitude, resulting in a gain of 0.9 - 0.95 (Becker, 1989). Chapter 2. 2 will focus on this topic in detail. See Figure 5, top panel.

Saccadic dynamical precision refers to the accuracy of holding the eye still in its position at the end of a saccade, against the elastic forces of the orbit. In other words, the oculomotor system needs to precisely stop the eye at the end of the saccade instead of letting

it move further. This drifting of the eye at the end of a saccade is called post-saccadic drift, PSD in the rest of the thesis. The shape of PSD can be well approximated by an exponential function, in which the peak velocity is reached near the start of the drift and its velocity decays toward zero in an exponential manner. Normally PSD is too small to deteriorate visual acuity, but it can be more pronounced, like in patients with cerebellar diseases (Leigh and Zee, 2015). See Figure 5, bottom panel.

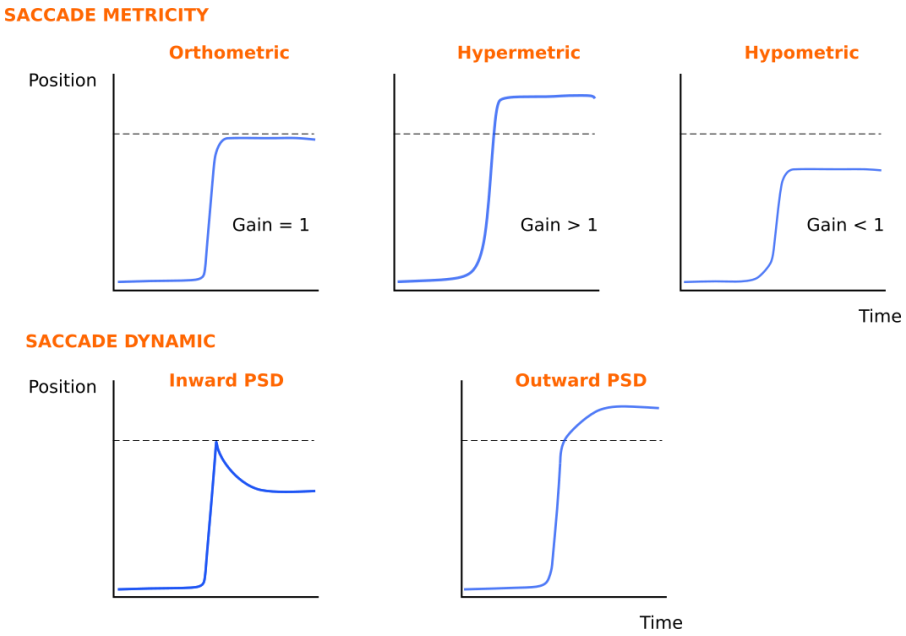

Figure 5. Dysmetria and post-saccadic drift.
The pulse-step innervation needs to be properly matched to produce precise and accurate saccades. A mismatch can produce problems in saccadic metrics and/or dynamics, producing eye movements that do not land precisely on target and/or do not hold the eye still on the target at the end of the movement. On the x-axes time, on the y-axes position.
Top panel. Saccade metrics. On the left an orthometric saccade, in the center a hypermetric saccade, on the right a hypometric saccade. **Bottom panel.** Saccade dynamics. On the left an inward PSD (toward the initial fixation), on the right an outward PSD (away from the initial fixation).

1. 7 The Saccadic System, Adaptive Mechanisms

In the previous paragraphs we have been discussing basics mechanisms underlying the oculomotor system and more specifically the saccadic system, paying special attention to how a transformation between an input signal, the location of a visual target on the retina, to an

output signal, the oculomotor command. As described, saccades are ballistic and stereotyped, producing a deterministic response. The coupling between input and output can however be adjusted over periods of time to maintain the accuracy of both saccade metrics (the amplitude of a saccade) and dynamics (the stability of the saccade at its end). The ability to correct the metricity (topic of Chapter 2.1) and the dynamics of saccades (topic of Chapter 2.2) serve the purpose of generating the needed saccades in spite of physiological and pathological changes linked to aging or diseases. Adaptive mechanisms detect behavioural systematic error in motor performance and update the relationship between visual target location and motor commands needed to foveate precisely and steadily the visual target.

One of the earliest and most influential studies was conducted by Optican and Robinson in 1980 after previous indications of neural plasticity at the level of the central nervous system both via clinical observations and lesion studies (Abel et al., 1978; Kommerel et al., 1976) and of the critical involvement of the cerebellum in both saccadic dysmetria and holding the gaze still (Robinson, 1974). Monkeys underwent a partial tenectomy (i.e. an incision of the tendons) on both horizontal recti muscles of one eye, while the other eye was patched. Even though the muscles of the operated eye reattached, they were permanently weakened. Monkeys were seated in front of a screen and trained to follow with their eyes small target lights jumping 10° on the horizontal plane. The muscle lesion made it necessary for the monkey to learn to produce larger movement commands (in comparison to the pre-operation) to precisely move the eye to the right location, and to also produce larger hold commands to keep the eye at the off-center target location. No visual feedback information from the visual scene was available to the patched eye. As depicted in Figure 6, monkeys performed

orthometric saccades followed by no post-saccadic drift with the healthy eye, the same oculomotor input however produced hypometric saccades followed by inward post-saccadic drift in the operated eye. The weakening of the muscle therefore produced both a miscalibration in saccade metrics (the movement was hypometric) and saccade dynamics (the movement was followed by PSD). At this point the patch was switched from the operated eye to the healthy eye, allowing visual feedback to the weak eye. At the beginning the animals needed about four hypometric saccades to produce the 10° saccade to reach the visual target. But after only five days of training monkeys recovered in the operated eye, developing orthometric saccades followed by no post-saccadic drift in the operated eye. They however started producing hypermetric saccades followed by outward post-saccadic drift in the other eye (which was patched during the training). Figure 6 depicts the described experiment.

These results introduced the idea of an existent adaptive mechanism in the brain that relied on visual feedback in recalibrating both the metricity (the move circuit) and the dynamic (the hold circuit) of saccadic eye movements. In looking for the neurophysiological mechanisms involved in the control of adaptive mechanisms, Optican and Robinson (1980) examined the role of cerebellum, by performing a total cerebellectomy on two monkeys after the tenectomies. The total removal of the cerebellum produced a stable saccadic hypermetria and PSD. When the authors put a patch on the unoperated eye (same procedure described before) the animals were however unable to recover even after several days of training.

The authors went further and tested whether different specific parts of the cerebellum were responsible for adaptive mechanisms of both saccade metrics and dynamic. Interestingly they could demonstrate that the removal of the fastigial nucleus and the oculomotor vermis impaired saccade metrics but not saccade dynamics: the monkeys produced hypermetric

saccades followed by no PSD with the unoperated eye. After 13 days of training with a patch on the normal eye, monkeys were able to improve saccades made with the weak eye, particularly in the hold phase, repairing the observed PSD.

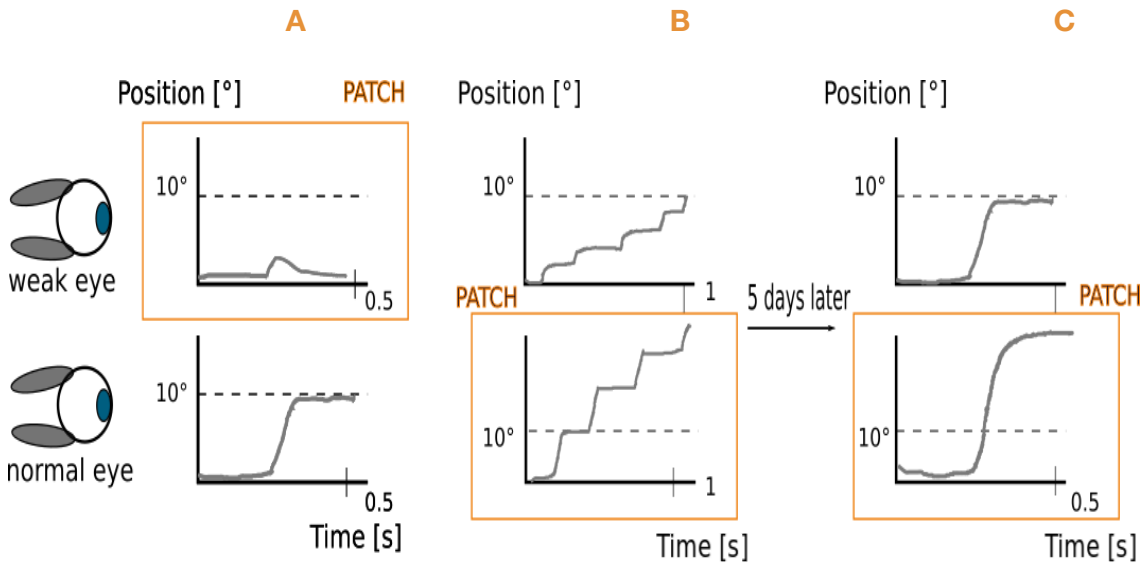

Figure 6. Saccadic adaptation in Optican & Robinson (1980).
Top panel. Saccadic performance of the eye that underwent the partial tenectomy on both horizontal recti muscles of the eye. (A) After the operation, while the eye receives no visual feedback, as it is patched (orange square in the figure) saccades are hypometric and followed by an inward PSD. (B) When visual feedback is available the monkey produces four hypometric saccades to reach the visual target at 10°. (C) Only 5 training days later the monkey recovers, developing orthometric saccades followed by no PSD.
Bottom panel. Saccadic performance of the eye that was not operated. (A) Orthometric saccades without PSD are produced after the operation when the eye receives visual feedback. (B) Without visual feedback the monkey produces a sequence of four saccades (like in the weak eye) and lands over the saccadic target. (C) The patched eye after the 5 training days has developed hypermetria and outward PSD. [Redrawn and modified from Optican & Robinson, 1980, with permission].

This was the first experiment to demonstrate the existence of cerebellum related adaptive mechanisms that calibrate systematic errors in saccade metricity and PSD, and in identifying the role of the fastigial nucleus in the control of saccadic gain (metricity).

Zee et al. (1981) were interested in locating which part of the cerebellum could have been involved in the control of PSD. They tested monkeys before and after the removal of the

flocculus (a small lobe in the cerebellum), and showed that the animals could generate orthometric saccades, but could not hold their gaze still at the end of them, producing onward PSD on horizontal saccades. Same pattern was found also when switching the light off: monkeys were unable to hold a peripheral gaze, showing a drift towards the center.

Together these studies started suggesting that the oculomotor vermis and the fastigial nuclei are involved in recalibrating the commands that move the eye (gain adaptation), and that the flocculus and the associated vestibular nuclei play a role in holding the image steady after the saccade (PSD). See Figure 7 for a schematic and Figure 3 for the localisation of these nuclei in the brain.

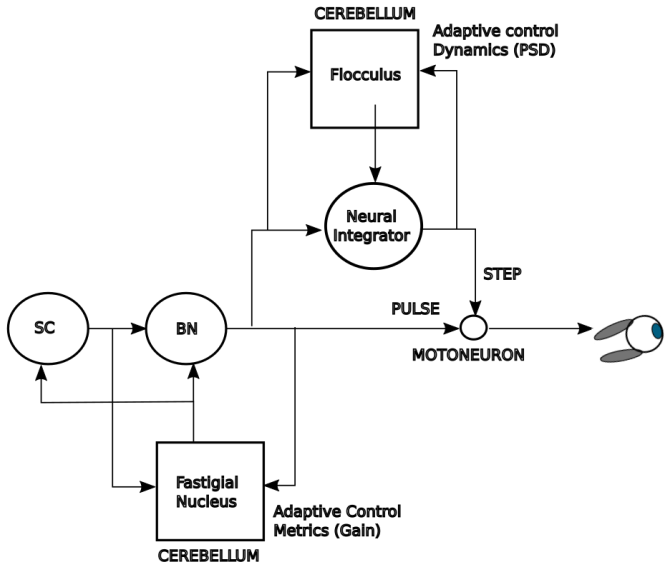

Figure 7. Generation and monitoring of saccades.
The activation of the superior colliculus, SC, drives the burst generator (BN), producing the pulse component of innervation that is directly sent to the ocular motoneuron. The same input reaches the neural integrator that produces the step component of innervation and sends it to the ocular motoneuron. Two cerebellar adaptive mechanisms monitor these saccadic generation pathways. The fastigial nucleus controls the accuracy of the pulse component, monitoring saccadic metrics, the flocculus controls the accuracy of the step component, monitoring saccadic dynamics. [Redrawn and modified from Shadmehr, 2017, with permission]

1. 8 Thesis Aim

The following paragraphs summarise the main objectives of this thesis, divided by experimental projects:

Chapter 2. 1 “Adaptation of Post-Saccadic Drift in Reflexive Saccades Transfers Only Partially to Voluntary Saccades” aimed at investigating *dynamical* adaptation of the saccadic system in humans. We were interested in finding out if post-saccadic drift (PSD) could easily be induced in a laboratory setting on humans. Furthermore we wanted to investigate whether PSD adaptation is specific to the saccade type for which it was elicited. To answer these questions we induced PSD in reflexive saccades by presenting a consistent exponential shift of the target immediately after the end of each reflexive saccade. We then analysed the amount of transfer of this adaptation to interleaved open-loop reflexive and voluntary saccades.

Chapter 2. 2 “Updating the Dichotomy of Reflexive and Voluntary Saccades” aimed at investigating *metrical* adaptation of the saccadic system in humans. In this set of studies we investigated the discrepancy in the transfer rates between laboratories when investigating the amount of transfer between reflexive and voluntary saccades after inducing gain adaptation in reflexive saccades. To this end, we induced gain adaptation via the double step paradigm (McLaughlin, 1967) on reflexive saccades and tested the amount of transfer in open- loop reflexive and voluntary saccades. We however defined differently voluntary saccades in each experiment, by manipulating the instructions given to the participants and the timing of target appearance. We also used a scanning saccade paradigm as a baseline experiment for voluntary saccades.

2. Cumulative- Style Thesis

The following section contains two manuscripts (Chapters 2.1 “Adaptation of Post-saccadic Drift in Reflexive Saccades Transfers Only Partially to Voluntary Saccades” and Chapter 2. 2 “Updating the Dichotomy of Reflexive and Voluntary Saccades”) not submitted to peer-review yet.

2.1 Adaptation of Post-Saccadic Drift in Reflexive Saccades Transfers Only Partially to Voluntary Saccades

Author contributions:

Giulia Manca designed the study, collected, analyzed, interpreted, and visualized the data, and wrote the manuscript.

Heiner Deubel designed the study, participated in interpreting the results, and commented on the manuscript.

Abstract

Post-saccadic eye stabilization is essential for ensuring high visual acuity during the fixation period. Previous monkey studies demonstrated a cerebellum-dependent adaptive mechanism that is able to minimize post-saccadic drift (PSD) resulting from lesions of the peripheral oculomotor system. It has been proposed that this adaptation occurs by an adjustment of the pulse-step innervation ratio at the level of the brainstem.

The present study aims at investigating plasticity of post-saccadic eye stabilization in healthy humans. In particular, we asked whether PSD adaptation would be specific to the type of saccade for which it was elicited. To answer this question we induced PSD by consistently presenting a small, exponential onward target drift immediately following reflexive saccades. We analyzed the amount of transfer of the resulting adaptation to interleaved open-loop reflexive and voluntary saccades.

Our post-saccadic target drifts indeed resulted in the induction of PSD following reflexive saccades. However, voluntary saccades were not equally affected, suggesting separate adaptive mechanisms for reflexive and voluntary saccades. The results confirm that PSD can be induced by consistent post-saccadic target drifts and they argue against an exclusive brainstem involvement in adaptive control of PSD, as a simple adjustment of the pulse-step ratio would affect both saccade types.

2. 1. 1 Introduction

Stability of the eyes during fixation periods is necessary for maximising visual perception, as visual acuity is impaired for images moving across the retina with speeds as low as few degrees per second (Inchingolo, 1992). Fixations are interleaved with saccades, very fast eye movements that minimise the time of poor visual acuity derived by the acceleration of the eyes while redirecting the fovea (the retinal area with the highest visual acuity) to the target locations in the visual field. In normal conditions the central nervous system actively holds the eyes still to establish a fixation at the end of a saccade, however, sometimes, the main saccade can be followed by a post-saccadic exponential drift (PSD), that can be either inward or outward - in the opposite or same direction of the saccade respectively. In normal subjects these drifts are not big enough to compromise visual acuity, but their sizes can be bigger, producing serious effects on patients suffering for example from cerebellar disease or ocular motor palsies (Leigh & Zee, 1983).

Motor neuron recordings (Keller, 1974; for a review see Leigh & Zee, 2015, Scudder et al., 2002) and modeling of the physical properties of the eye (for a review see Inchingolo, 1992) describe the pattern of activity that drives both saccades and fixations: in order to move the eye from a stationary state, a pulse of activation is required to overcome the viscous drag of the orbital tissue. This first input is then followed by an activation step -the integral of the pulse in mathematical terms- that takes into account the decay of the pulse leading to a sustained change in muscle tension compensating for elastic properties of the eye plant and keeping the eye in the right position. However, the pulse does not end abruptly before the step activity of the muscle: a gradual decline in muscle torque, called the slide, links the two activities of the eye muscles (Sylvestre & Cullen, 1999). The saccadic pulse and step can be seen as eye velocity and position commands. Robinson (1975) first described this model of the oculomotor plant, since then many studies confirmed the existence in the brainstem of class of motor neurons that produce a burst of activity (the pulse), then a gradual decay of activity (the slide) and finally a position-related change of tonic activity (the step) (Fuchs et al., 1985; Scudder et al., 2002; Shinoda et al., 2019; Sparks, 2002).

Just before the initiation of a saccade, omnipause neurons stop firing, which lets burst neurons generate a pulse of innervation that drives the eye to its new position. The tonic firing rate increases during the saccade and reaches its peak at the end of the burst cell activity, in order to keep the eye in the new position. Once desired and actual eye position matches, the burst cells stop firing, resuming the tonic activity of omnipause neurons (for reviews see Krauzlis, 2005; Sharpe & Wong, 2005).

Many authors suggested that to minimise post-saccadic drift (PSD) the pulse and step signals need to be combined correctly, showing how a mismatch of these two signals can result in saccadic dysmetria, PSD or both. (Bahill et al., 1975; Bahill & Troost, 1979; Kapoula, et al., 1989; Optican & Miles, 1985; Optican & Robinson, 1980). Cerebellar activity is responsible for an active control, but not the initiation of saccadic eye movements. Specifically, lesions of the vestibulocerebellum (flocculus) are related to disorders in gaze-holding and are associated with PSD, as this region is thought to be one of the responsible areas for appropriately matching the saccadic pulse and step of innervation (Optican et al., 1986; Takagi et al., 1998; Zee et al., 1981).

Previous studies in primates demonstrated how cerebellum-dependent adaptive mechanisms are able to compensate for PSD resulting from muscle ablation (Optican & Robinson, 1980). After monkeys underwent partial tenectomy on the horizontal recti muscles of one eye, they performed hypometric saccades followed by inward PSD in the operated eye, and orthometric saccades followed by no PSD in the other eye. After five days of training monkeys were however able to recover in the operated eye, while the developed hypermetric saccades followed by outward PSD in the other eye, which was patched during the training. This recovery was, however, not possible when the monkey underwent total flocculectomy, total removal of the flocculus. The existence of mechanisms that reduce post-saccadic drift was also shown in humans patients with abducens nerve palsies (Kommerell et al., 1976) and in a patient with ocular motor nerve palsy (Abel et al., 1978). This adaptive mechanism was also

shown by inducing PSD through a systematic retinal shift of a target stimulus, both in monkeys (Optican et al., 1986) and humans (Deubel, 1991; Kapoula et al., 1989).

It is important to note that all the studies mentioned so far have investigated PSD with saccades triggered by the onset of a stimulus appearing suddenly in the retinal periphery. Different types of saccades have been identified, depending mainly on how they are elicited and their latencies (for a more complete classification see Deubel, 1999; Gaymard et al., 1998; Hopp & Fuchs, 2004; Hopp & Fuchs, 2010; Pélisson et al., 2010; Tusa et al., 1986). For our purposes it is important to mention two main categories:

(1) Reflexive saccades (RS) which occur automatically after a sudden presentation of a peripheral target. Experimentally they are typically investigated by presenting a target in the periphery after the extinction of a fixation target. Their latencies are typically in the range of 150-200 ms. (Smit et al., 1987)

(2) Voluntary Saccades (VS) are internally triggered by subjects - who decide where to direct their gaze - and have latencies that are longer than 200-250 ms (Henik et al., 1994; Walker et al., 2000). Many subcategories of VS have been studied, namely: scanning saccades (moving the gaze between different targets all presented on the visual scene), delayed saccades (moving the gaze at the already visible target only after a central go signal), memory-guided saccades (moving the gaze toward memorised locations where targets were previously presented), and anti-saccades (moving the gaze toward the opposite location of the visual target)

There is general agreement that the neural pathways involved in the generation of these different saccade types yield both some degree of overlapping and of specificity (Coiner et al., 2019; Johnston & Everling, 2008; Munoz & Everling, 2004; Pélisson et al., 2010; Pierrot-Deseilligny et al., 1991; Pierrot- Deseilligny et al., 2003; Pierrot-Deseilligny, et al., 2004). As previously discussed, the involvement of saccadic subcortical areas, namely the brainstem, superior colliculus and the cerebellum are part of a final common pathway that is responsible for saccadic production and monitoring respectively (for a complete picture see Leigh & Zee,

2015). However within the cortex different regions play a more specific role in the production of different types of saccades.

Parietal regions are more involved in producing RS: when a rapid oculomotor response is needed a reflexive saccade is elicited by the PEF (parietal eye field) in a very short loop system via direct projections to the superior colliculus. (Leigh & Zee, 2015; Pierrot-Deseilligny et al., 1991). Frontal regions and the basal ganglia show larger engagement in the production of VS: the execution of voluntary saccades is performed by the FEF (frontal eye field) (Berman et al., 1999; Ettinger et al., 2008; Pouget, 2015; Rosano et al., 2002; Sugiura et al., 2004), that through the CEF (cingulate eye field) activates other frontal oculomotor regions (Berman et al., 1999; Jamadar et al., 2013; Matsuda et al., 2004; Petit et al., 1993; Sugiura et al., 2004), like the SEF (supplementary eye field) (Berman et al., 1999; Ettinger et al., 2008; Jamadar et al. 2013; Leigh & Zee 2015). For more detailed info about the neural mechanisms of saccadic eye movements see Coiner et al., 2019; Leigh & Zee, 2015; Pierrot-Deseilligny et al., 2004.

In order to further investigate whether a consistent shift of the target could induce PSD and whether these mechanisms could be exclusively accounted for by a simple mismatch of the step and pulse input generated in the brainstem, we induced PSD on reflexive saccades and tested its effect on open-loop reflexive and voluntary saccades. On the one hand a complete transfer of adaptation between RS and VS would indicate a common mechanism that would be explainable by a simple mismatch of step and pulse magnitudes. On the other hand a partial transfer of adaptation would suggest the existence of (at least) one separate mechanism involved in the calibration of PSD in different saccade types and would support the idea of a modulator outside the brainstem. This hypothesis is also supported by previous studies (Zee et al., 1981) that suggest the idea of a specific involvement of the flocculus, a small lobe of the cerebellum, in gaze stabilisation.

2. 1. 2 Methods

2. 1. 2. 1 Participants, Stimuli and Apparatus

Nine healthy participants (4 males, 5 females) participated in the experiment for compensation of 4€ per 30 minutes of testing. Their age ranged from 22 to 33 years old. They all had normal or corrected-to normal vision. All participants except one author were naive as to the purpose of the experiment. Participants sat in a quiet room in darkness at a distance of 128 cm from the screen. Their head position was stabilized by a chin and forehead rest.

Red laser dots of about 2 mm diameter served as target, their position was restricted to the horizontal direction, the system was controlled by a galvanometer (General Scanning 120D Watertown, MA, USA). Stimuli presentation and raw data collection was run on a PC directed by a software developed under UNIX for real time experiment .

The software sampled and analyzed at 1kHz the eye movement signal, recorded by EyeSeeCam (Schneider et al., 2009), a head-mounted infrared reflection eye tracker. A digital saccade detector was implemented in order to detect online the beginning of saccades by estimating saccade onset and offset, defined as the first zero-crossing of the eye velocity before and after its peak velocity. If no saccade was detected the program waited 2000 ms before continuing with the next stimulus presentation.

2. 1. 2. 2 Experimental Procedure

Typically, in order to test adaptation effects three phases are required: (1) a pre-adaptation phase, in which the normal saccadic parameters are measured, (2) a long adaptation phase, during which the participants learn the new behaviour, and (3) a post adaptation phase in which the effects of adaptation are tested. To be able to test the effect of inducing PSD on RS and test this effect over time on VS we needed to make two adjustments

to this basic paradigm: firstly, in order to test the time course of adaptation we needed to interleave the adaptation phase with post adaptation test phases, secondly, we needed to test the effect of adaptation on both reflexive and voluntary saccade types.

To achieve this we modified the basic paradigm as shown in Figure 1: we initially presented one block for testing the pre-adaptation values of PSD in reflexive saccades (RT -Reflexive Test-), followed by one block for testing the pre-adaptation values in voluntary saccades (VT -Voluntary Test-) and then we interleaved each block (80 trials) of the adaptation phase in which we trained reflexive saccades (RA -Reflexive Adaptation-) with 10 test trials, once with reflexive saccades (RT), once with voluntary saccades (VT). All together the experiment consisted of 5 RT blocks (50 trials in total), 5 VT blocks (50 trials in total) and 8 RA blocks (640 trials in total) and lasted around 30 minutes.

Figure 1. Experimental paradigm: general design.
The quadrilaterals represent different experimental blocks: in light blue blocks in which reflexive saccades were tested, in purple blocks in which voluntary saccades were tested and in green the adaptation block, during which reflexive saccades were adapted. The blocks were interleaved as shown.

During the whole experiment participants were asked to move their eyes either following the red targets appearing on the screen in the reflexive saccade conditions (RT and RA) or shifting their gaze between the targets on the screen in voluntary test condition (VT). The specific instructions changed depending on the condition, as described below and as depicted in Figure 2.

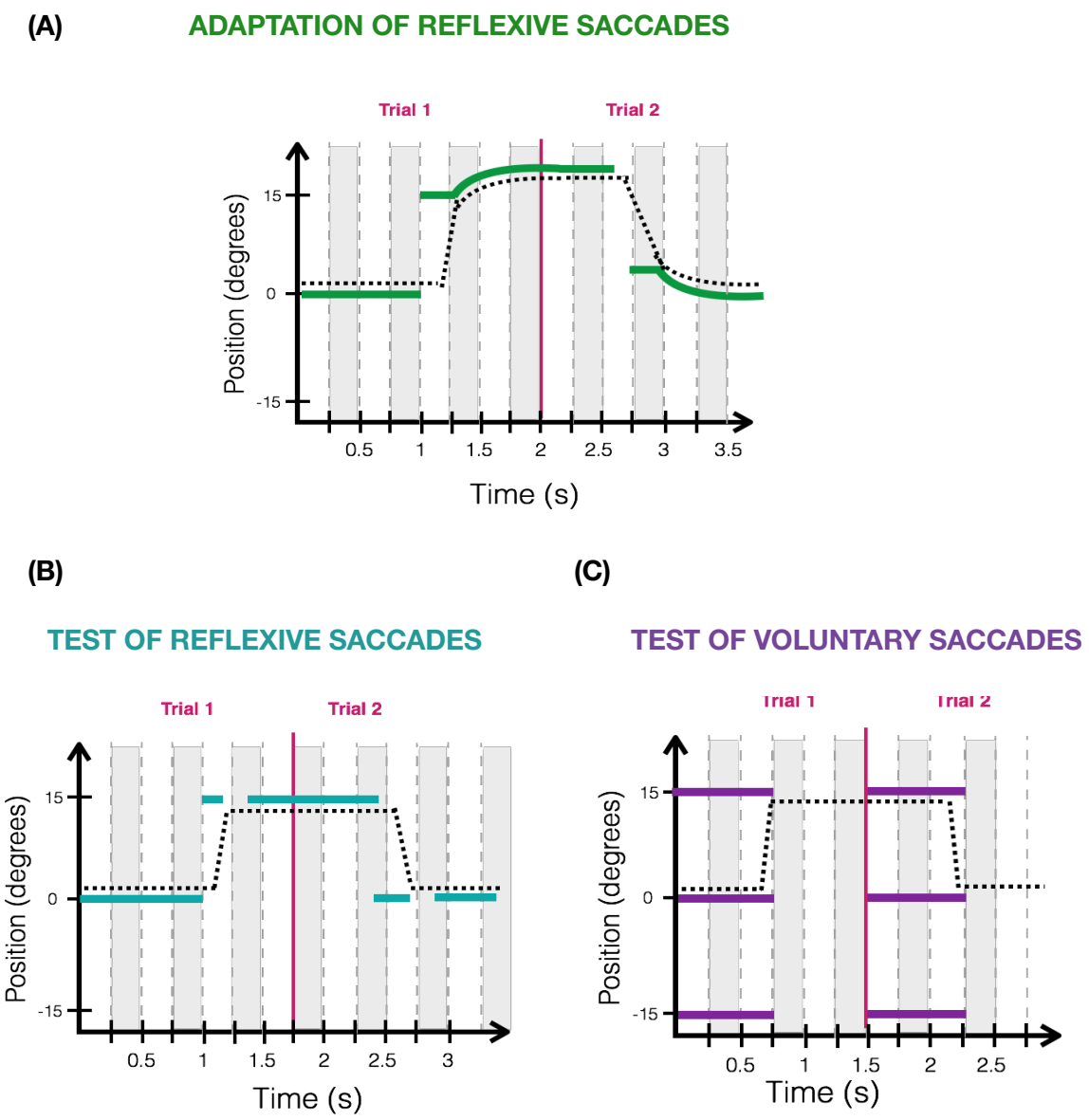

Figure 2. Experimental paradigm: different blocks.
Position of the target(s) on the horizontal plane against time.
2A) In green the Adaptation block (RA), during which Reflexive Saccades were adapted: Fixation target - target step - sliding away of the target (after detection of a saccade). Participants were asked to follow the target on the screen.
2B) In light blue the Reflexive saccades Test blocks (RT), during which reflexive saccades were tested: Fixation target - target step - blanking phase (after detection of a saccade). Participants were asked to follow the target on the screen.
2C) In purple the Voluntary Saccades Test blocks (VT), during which Voluntary Saccades were tested: Fixation target - target step - blanking phase (after detection of a saccade). Three targets were visible on the screen and participants were asked to scan through them at their own pace.

Independently of the type, every block started with the appearance of a central red target that served as a fixation for 1000 ms.

Reflexive Adaptation (RA)

Simultaneously to the disappearance of the fixation target, a red circular target was shown on the screen at ±15° degree from the previous target. Four possible target positions were used. Participants were instructed to make a saccade to the target as fast as possible. The target was shown on the screen until the participant initiated a saccade, at which time the target was systematically shifted away, following the exponential function described below, to mimic the retinal effect of pathologically large post-saccadic drift. This was made possible by a digital saccade detector, active only after the appearance of the target, with a temporal resolution of 1 ms implemented in REX (Hays et al., 1982) that on-line detected saccades and triggered the drift. Note that the actual shift of the target corresponded with the end of the saccade, given a consistent measured delay of approximately 10 ms between the saccade detection and the initiation of the drift. The target drift lasted 320 ms and was described by an exponential function D(t), as follows:

$$\text{Target drift } D(t) = A^* (1-\exp(-t/\tau)),$$

A, the amplitude of the drift, was set to 2.25°, which is 15% of the step size. Tau, the time constant of the drift, was set to 120 ms. Both A and tau were set to similar values as previously used in human studies (Deubel, 1991; Kapoula, et al., 1989).

Following the target shift, the target remained visible at the same location and served as fixation for the next trial. The fixation target was presented for a variable duration to prevent the elicitation of predictive saccades, namely for 500 ±100 ms. The saccade detector was enabled only between target presentation and saccade detection.

Reflexive Test (RT)

Simultaneously to the disappearance of the fixation target, a red circular target was shown on the screen at ±15° degree from the previous target. Three possible target positions were used: +15°, 0 and -15°. Participants were instructed to make a saccade to the target as soon as possible. As soon as they initialized their movement, their saccade was detected and triggered the disappearance of the target from the screen (with a maximum gap of 10 ms, due to technical delays). After 320 ms (the same duration of the target shift in the reflexive adaptation condition), the target reappeared in the same position. This position served as fixation for the new trial and was shown for a variable duration,to prevent the elicitation of predictive saccades, namely 1000 ms ±200 ms. The saccade detector was enabled only between target presentation and saccade detection.

Voluntary Test (VT)

Simultaneously to the disappearance of the fixation target, an array of three circular red dots was shown on the screen, 15° apart from each other: at -15°, 0° and 15°. Participants were instructed to freely choose which target to select and when to make a saccade, with the only constraint of producing 15° saccades. As soon as participants made a saccade, the program detected the movement and triggered the blanking of the screen, which lasted 320 ms. Finally the array was presented again and served as fixation for the new trial. The fixation array was presented for a variable duration, to keep the timing of the condition similar between RT and VT, namely 1000 ms ±200 ms. The saccade detector was enabled only between target presentation and saccade detection.

2. 1. 2. 3 Data Processing

An offline calibration was applied to the raw data before analyzing it. Using 500 ms before each target step, we extracted the horizontal raw fixational eye position by averaging

across the longest period in which eye velocity stayed below 3 deg/sec. Offset and gain of a linear calibration was determined by linear regression of the raw fixational eye position on the corresponding horizontal target position

After calibration, saccades were detected offline using an algorithm to calculate the slow and fast phase of the eye velocity profile (for further details see Ladda et al., 2007). Raw eye velocity was filtered using a symmetrical (zero-phase) Gaussian lowpass filter and a two point differentiator with a cutoff frequency of 33 Hz.

We then selected, manually, the post-saccadic drift at the end of every saccade. We plotted for each trial the saccadic behavior of the participant and we considered drifts as valid, when they were following the main saccade (the one triggering the blanking of the screen). We adjusted the beginning of the drifts, when necessary, to account for dynamical overshoot, the little velocity adjustment often seen in the data at the end of the saccades

We used two different criteria to calculate the amplitude of the post-saccadic drift, to retrieve different kinds of information on the drift itself. Both variables were analysed separately. In the first case, we considered the drift to be over after 250 ms, time interval used by previous studies, and time necessary to reach 88% of the drift asymptote in the adaptation phase. We then calculated the amplitude of the drift as a difference between the final position of the eye at the end of the drift and the landing position of the saccade on the horizontal plane. The amplitude of the post-saccadic drifts were then calculated for each trial and averaged for each condition across participants. In the second case, in order not to lose the information about the shape of the post-saccadic drift, we fitted each post saccadic drift with the function applied as target movement during the adaptation of reflexive saccades:

$$d(t) = A^* (1-\exp(-t/\tau))$$

We estimated for each trial the two parameters: amplitude (A) and time constant (tau). The fitting procedure was run through the standard function “fit” in MATLAB that took each trial as input parameter and calculated which amplitude (A) and time constant (tau) best described

the data. These parameters were then further analysed by averaging them for each condition across participants. Just note that in order to get more precise results from the fitting algorithm, the only constraint to determine the end of the PSD was the beginning of a new saccade, or the blinking of the eye.

As the experimental paradigm allowed participants to make rightward and leftward saccades, we mirrored the data by multiplying the data from leftward saccades by -1. This allowed a negative PSD to describe an inward PSD (PSD in the opposite direction as the saccade) and a positive one for an outward PSD (PSD in the same direction as the saccade).

We considered outliers to be those observations that lie outside 2 * IQR, where IQR, the 'Inter Quartile Range' is the difference between 75th and 25th quartiles. As we observed very few but big outliers, to preserve the data, we firstly excluded outliers from the overall data, and only then ran an outlier analysis on each block, before calculating results.

The percentage of transfer between RT and VT was calculated to quantify the size of the effect. Transfer was defined as the ratio between the mean PSD amplitude during each RT block and its correspondent VT block multiplied by 100.

$$\text{Transfer (\%)} = \text{RT[degrees]} / \text{VT[degrees]} * 100$$

2. 1. 2. 4 Statistical Analysis

All analyses and figures were created using the open statistical software R (Team, 2015) and the "lme4" package (Bates et al., 2012) as well as the "lmerTest" package (Kuznetsova et al., 2017). We modeled the amplitude of the PSD in both test conditions (Reflexive Test and Voluntary Test) over time and quantified the transfer ratio between conditions as described below. All the measurement points during the test Conditions for both saccade types were included in the analysis.

The use of ANOVAs or t-tests was not feasible as our data did not meet the assumptions of such models (independence of observations, normality and homoscedasticity) or the requirement of having the same number of trials in each condition. We therefore preferred to use a model that makes no previous assumptions (beside the linearity of the model) and treat each data point independently, without the need of post-hoc comparisons or adjusting the level of significance or testing only few comparisons.

To account for the longitudinal setting (testing the same participants in the same conditions multiple times over the course of the experiment) and the intrapersonal dependencies within the data that come along with it, mixed linear regression models were estimated, modeling each person as a unit with potential random variance. To this end the model allowed for participant-specific random intercepts.

To quantify the effect of within-participant variances, we estimated unconditional random effects models (UREMs) calculating intra-class correlations (ICCs) to relate within and between participant variability. We used the standard formula to calculate ICCs, by dividing the random effect variance, σ^2i, by the total variance (the sum of the random effect variance and the residual variance, $\sigma^2\varepsilon$.)

$$ICC = \sigma^2_i / (\sigma^2_i + \sigma^2_\varepsilon)$$

In order to analyse the increase in amplitude of PSD in both saccade types over time, we firstly estimated linear growth curves, using mixed regression models with dummy coding. Reflexive Saccade was taken as a reference category. (Hilbert et al., 2019). To do so we created a variable for each saccade type and assigned the value 0 to Reflexive Saccades, and the value 1 to Voluntary Saccades. As a consequence, the regression weight of the intercept indicates the predicted values for Reflexive Saccades and the regression weight of VS represents the predicted difference between Reflexive and Voluntary Saccades. To account for the effect of the adaptation over time we coded a variable for each test condition and assigned the value 0 to the Pre-Test, the value 1 to the first Post-Test, the value 2 to the second Post-Test, the value 3 to the third Post-Test and the value 4 to the final Post-Test. This allowed us to model individual changes in the form of a growth variable. As a consequence, the

regression weight of the intercept indicates the predicted values for the Pre-Test and the regression weight of the other Post-Tests represents the predicted difference between each Post-Test and the Pre-Test.

These variables (Post-Test(x) and Saccade Type) entered the model as single predictors and as an interaction term.

$$y_{ij} = \gamma_0 + \gamma_1 \text{Voluntary Saccades}_i + \gamma_2 \text{Post-Test}_{1j} + \gamma_3 \text{Post-Test}_{2j} + \gamma_4 \text{Post-Test}_{3j} + \gamma_5 \text{Post-Test}_{4j} + \gamma_6 \text{Voluntary Saccades}_i \times \text{Post-Test}_{1j} \times + \gamma_7 \text{Voluntary Saccades}_i \times \text{Post-Test}_{2j} + \gamma_8 \text{Voluntary Saccades}_i \times \text{Post-Test}_{3j} + \gamma_9 \text{Voluntary Saccades}_i \times \text{Post-Test}_{4j} + u_{0i} + e_{ij}$$

The regression weights of the predictors are therefore to be interpreted as follows:

Intercept: Predicted amplitude of PSD for RS in the Pre-test.

VS: Predicted Pre-Test difference between the RS and the VS.

Post-Test(x): Change between the Pre-Test and Post-Test(X) for RS.

Post-Test(x) x VS: Difference in change between the Pre-Test and Post-Test(x) between the RS and VS.

2. 1. 3 Results

The results section is divided in three different subsections to give a clearer picture of the findings. In the first section we describe the results from the different test phases both for RS and VS; in the second we present the amount of transfer between VS to RS, to quantify the effect we are investigating; lastly we have a closer look at the adaptation phases, to make sure that participants were able to follow instructions and check whether the manipulation was actually effective.

2. 1. 3. 1 Reflexive and Voluntary Test Conditions

As described in the Method section, the change of PSD amplitude induced by the adaption manipulation was measured in two different ways: (1) by calculating the difference in

horizontal eye position between the PSD starting and the ending time - considered at 250 ms-, this variable will be called “PSD -Raw Data-” in the rest of the Result section; (2) by fitting the parameter A (amplitude) of the exponential function used to mimic the effect of a natural PSD, this variable is referred to as “PSD - A -” in the rest of the section. These two variables will be described in the next two sections.

PSD - Raw Data -

The outlier detection (for details see Methods) generally excluded 1.7% of the data. The same analysis on each block further excluded 0.97% of the data. The majority of the excluded data was found in the RA blocks. In test blocks (both RT and VT) we observed few outliers that remained stable throughout the experiment. The accepted post-saccadic drifts ranged between -0.73° and 2.6°.

Figure 3A shows the effect of adaptation on the amplitude of PSD. In a normal state of the eye system -measured by the preadaptation blocks-, subjects show virtually no PSD for both types of saccades (Reflexive Pre-Test: -0.01 °± 0.17° SEM; Voluntary Pre-Test: 0.02 °± 0.16° SEM) confirming that the oculomotor system was able to control fairly abruptly the movement of the eye at the end of the saccade. However, after several trials of consistent slipping away of the target, the eyes started developing a drift in the same direction of the motion of the target, evident during the test phases -in which the stimulus is not present-: its effect can already be seen in the first post-test blocks and it is consistent throughout the experiment (for detailed values see Table 1).

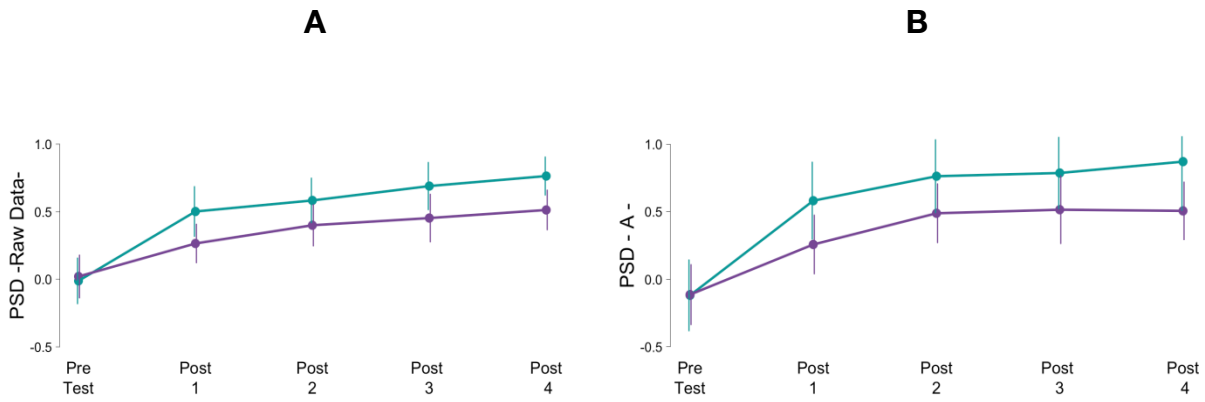

Figure 3. Mean PSD amplitude (± MES) as measured in different test blocks.
In light blue RT, in purple VT. (A) On the left panel PSD - Raw data -; (B) On the right panel PSD - A -

BLOCK	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**
TYPE	**RT**	**VT**	**RT**	**VT**	**RT**	**VT**	**RT**	**VT**	**RT**	**VT**
PSD -Raw data-										
Mean	-0.01	0.02	0.5	0.26	0.58	0.4	0.69	0.45	0.76	0.51
SEM	0.17	0.16	0.18	0.14	0.16	0.15	0.17	0.18	1.14	0.14
PSD -A-										
Mean	-0.12	-0.11	0.58	0.26	0.76	0.49	0.79	0.51	0.87	0.51
SEM	0.26	0.22	0.28	0.22	0.27	0.22	0.26	0.25	0.36	0.21

Table 1. Mean and SEM averaged across participants of all the test blocks. Chronologically ordered as presented during the experiment. In light blue RT, in purple VT. Top panel shows values for amplitude PSD - A -, lower panel for amplitude PSD - Raw Data -.

An UREM indicated a variance of 0.04 between participants and a variance of 0.28 within participants for PSD. This resulted in an ICC of 0.125, indicating the application of mixed regression analysis (see Methods section). The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < 0.001$).

Importantly the analysis confirmed our central results. While we found no significant differences between saccade types (t(649.6)=0, p=0.72), saccade types interacted with the adaptation paradigm (All values are shown in Table 2). These significant interaction coefficients indicate a higher PSD amplitude increase over time in the Reflexive Test condition than in the Voluntary Test condition, underlining how even though their main effect had no significant difference, the role of the adaptation paradigm had a differential effect depending on the saccade type.

	Estimate	SE	df	t	p
PSD - Raw Data -					
γ_{00}	0	0.078	55.142	-0.005	0.996
VS	0.031	0.09	649.571	0.358	0.721
Post-Test 1	0.5	0.089	650.517	5.644	**<0.001**
Post-Test 2	0.569	0.087	650.452	6.54	**<0.001**
Post-Test 3	0.686	0.09	650.372	7.595	**<0.001**
Post-Test 4	0.741	0.096	652.481	7.735	**<0.001**
VS x Post-Test 1	-0.275	0.117	649.269	-2.344	**<0.05**
VS x Post-Test 2	-0.212	0.116	649.229	-1.829	0.068
VS x Post-Test 3	-0.288	0.119	648.998	-2.421	**<0.05**
VS x Post-Test 4	-0.264	0.124	650.456	-2.135	**<0.05**
PSD - A -					
γ_{00}	-0.104	0.108	45.644	-0.965	0.339
VS	0.024	0.112	846.168	0.214	0.831
Post-Test 1	0.691	0.123	845.925	5.625	**<0.001**
Post-Test 2	0.860	0.121	846.351	7.101	**<0.001**
Post-Test 3	0.908	0.123	846.278	7.390	**<0.001**
Post-Test 4	0.971	0.122	846.649	7.986	**<0.001**

VS x Post-Test 1	-0.323	0.162	846.031	-1.996	**<0.05**
VS x Post-Test 2	-0.256	0.159	845.619	-1.608	0.1
VS x Post-Test 3	-0.311	0.16	845.821	-1.936	0.05
VS x Post-Test 4	-0.364	0.159	845.563	-2.291	**<0.05**
PSD - τ -					
γ_{00}	134.295	25.992	98.694	5.167	**<0.001**
VS	-7.746	30.085	846.926	-0.257	0.797
Post-Test 1	52.697	32.909	846.448	1.601	0.11
Post-Test 2	82.025	32.473	847.111	2.526	**<0.05**
Post-Test 3	9.07	32.992	847.005	0.276	0.783
Post-Test 4	25.14	32.594	847.568	0.771	0.441
VS x Post-Test 1	-35.507	43.356	846.668	-0.819	0.413
VS x Post-Test 2	-38.534	42.737	845.969	-0.902	0.368
VS x Post-Test 3	-18.744	43.002	846.332	-0.436	0.663
VS x Post-Test 4	-33.733	42.632	845.867	-0.791	0.429

Table 2. Quantitative results of the linear mixed growth analysis of PSD change during the adaptation paradigm.
Top panel results for amplitude PSD - Raw Data -; middle panel for amplitude PSD - A -; lower panel for time constant - τ -.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

PSD - A -

The analysis on the fitted amplitude A yielded similar results as the previous analysis. The general outlier detection excluded 27.7% of the data, while the outlier analysis on each block excluded 5.3% of the data: the excluded trials originated mainly from RA blocks, while both for RT and VT outliers were low and constant throughout the experiment. The accepted PSD ranged between -3.59° and 6.84°.

As shown in Figure 3B and Table 1, the pattern of PSD adaptation in both saccade types is very similar to the one described in the previous section: virtually no PSD in the Pre-Test blocks (Reflexive Pre-Test: -0.12 °± 0.26 SEM; Voluntary Pre-Test: -0.11 °± 0.22 SEM) followed by an increasing adaptation in the following blocks.

Intra-participant variance was also calculated for PSD - A -, showing an ICC of 0.040. Even though the results do not strongly suggest the need for it, mixed regression analysis was conducted for comparability. Table 2 contains the results of the linear mixed growth analysis, which did not differ from the results from the previous analysis. The effect of adaptation over time proved very significant on each Post-Test block (all $p < 0.001$) while no mean effect of the saccade type was found ($t(846.2) = 0.02$, $p = 0.83$). The interaction between saccade type and time proved significant at the beginning and end of the experiment and close to significant in the middle part of the adaptation protocol.

PSD - τ -

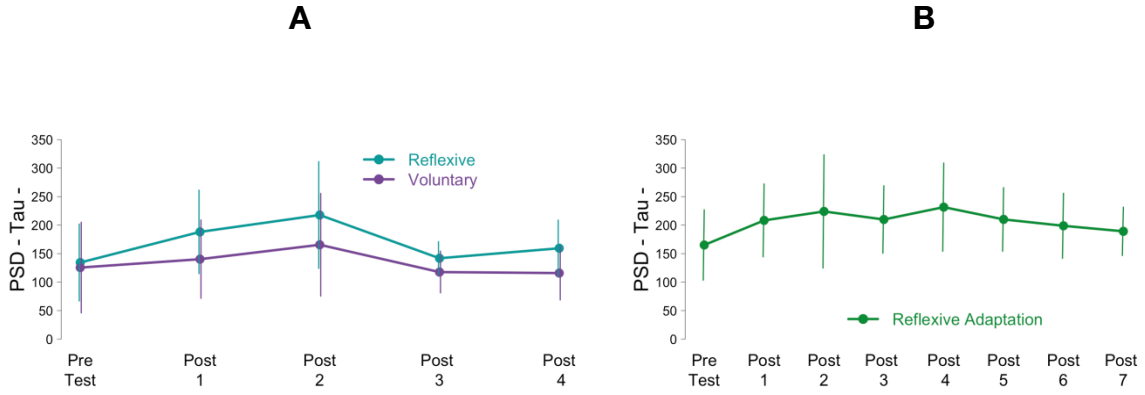

Figure 4A, 4B. Mean PSD time course (± MES) in different blocks.
In light blue RT, in purple VT (left panel, Figure 4A), in green the adaptation blocks (right panel, Figure 4B).

Regarding the fitted time constant (τ), we observed no clear learning effect or adaptation effect during the adaptation phase and test phases respectively (see Figure 4). The linear mixed growth analysis showed no effect of adaptation over time on τ, except at Post-Test 2, where a significant main effect of adaptation was found to be significant in contrast to the Pre-Test ($t(847.1) = 82.025$, $p = 0.012$).

2. 1. 3. 2 Transfer

In order to quantify the transfer between the RT condition and the VT condition we first calculated the absolute change for both conditions by subtracting the four post-test mean values to the pre-test values for each participant, and then averaged across participants. Figures 5A and 5B show the respective values for the Reflexive Test condition (0%, 71%, 87%, 87%, 97%) and for the Voluntary Test condition (0%, 48%, 73%, 69%, 66%).

We then calculated the transfer as the percentage ratio between the mean PSD in the different post-test measurements in the Voluntary Test condition and the Reflexive Test condition (68%, 84%, 80%, 68%), as shown in Figure 5C.

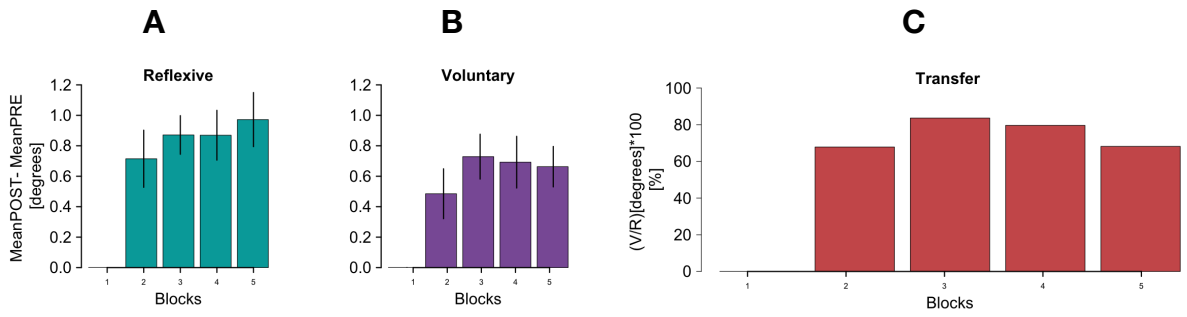

Figure 5A and 5B. Mean (± SEM) of PSD amplitude absolute change.
Panel left (5A) depicts RS; panel right (5B) VS. The pre-test value was subtracted by all the post-test values and then averaged across subjects
Figure 5C. Histograms showing the percentage ratio between the mean of VS and RS amplitude PSD values.

2. 1. 3. 3 Reflexive Adaptation Condition

In this subsection we check what happened during the adaptation blocks. Even though less interesting in terms of results, this analysis contains important information about the participants' performances during the task. During the RA blocks participants had no difficulties following the target with their eyes, both during the step of the target (-12.2° ± 2.77

SEM for -15° target steps and 12.4° ± 2.66 SEM for +15°) and its sliding away, i.e the drift. Table 3 shows the single mean and SEM values for each adaptation block. It is important to note the learning effect driving a bigger PSD amplitude during the final blocks both for PSD -Raw Data- and PSD -A-

BLOCK	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**
TYPE	**RA**	**RA**	**RA**	**RA**	**RA**	**RA**	**RA**	**RA**
PSD -Raw Data-								
Mean	0.97	1	1.03	1.13	1.12	1.14	1.19	1.21
SEM	0.2	0.16	0.15	0.15	0.14	0.14	0.13	0.14
PSD -A-								
Mean	0.93	1.21	1.37	1.48	1.52	1.52	1.46	1.53
SEM	0.38	0.32	0.32	0.29	0.36	0.32	0.33	0.31

Table 3. Mean and SEM of all the adaptation blocks. Chronologically ordered as presented during the experiment.Top panel shows values for amplitude PSD - A -, lower panel for amplitude PSD - Raw Data -

2. 1. 3. 4 Saccadic Latency and Duration

To further check if our manipulation worked, and if we were able to induce RS and VS respectively, we checked saccadic latencies and durations in all conditions (RA, RT and VT). In the ideal case latencies would vary between RS and VS, while we should observe the same saccadic duration in all types of saccades.

Indeed, latencies largely varied depending on the type of saccades, during VT condition the mean saccadic latency and the SD were 244 ± 143 ms, while during Reflexive Test condition and Reflexive Adaptation condition they were 178.5 ± 70 ms and 156 ± 67 ms respectively. The linear mixed model analysis on saccadic latencies showed a significant difference between voluntary saccades and the two other conditions of reflexive saccades:

between VT and RT ($t(5144)= -62.35$, $p< 0.001$) and between VT and RA ($t(5144)= 18.19$, $p< 0.001$).

On the other hand, saccadic mean duration was very similar between conditions: RA= 76 ± 23 ms, RT= 78 ± 25 ms, VT= 75 ± 30 ms. The statistical analysis also showed no significant differences on saccadic duration between VT and RT ($t(5144)= 0.09$, $p= 0.9$). or VT and RA ($t(5144)= -1.47$, $p= 0.2$).

2. 1. 4 Discussion

This study had two main objectives. First, we aimed at confirming the results of previous literature (Deubel, 1991; Kapoula et al., 1989) showing that human gaze stabilization mechanisms are under adaptive control. Second, investigating if the underlying dynamical adaptive mechanisms are highly specific with regards to different saccade types or if they share some degree of commonality.

2. 1. 4. 1 PSD Adaptation in Reflexive Saccades

The results of this study are in line with the previous literature (Deubel, 1991; Kapoula; 1989) confirming that PSD can be induced in humans by mimicking its retinal consequences through a consistent post-saccadic exponential drift of the target. As expected, PSD amplitude measured at the beginning of the experiment - before the adaptation phase - was close to zero, consistent with the saccadic system abruptly ending each saccade. This behaviour is very functional for maximising visual acuity, while minimising retinal slips. However, after 80 trials of consistent exponential shifting of the post-saccadic target, we observed the first effect of adaptation: the eye develops a compensatory exponential drift, shown by the higher PSD amplitude during the first, and the consequent test phases. This difference between pre-adaptation and post-adaptation PSD amplitude was estimated around 94% and found to be highly significant.

Consistent with the previous work of Deubel (1991), we observed that this amount of adaptation was reached in about half an hour, the average time that each subject needed to complete 800 trials. This result is in contrast with the work of Kapoula et al. (1989), where 2-3 hours of adaptation (10000-20000 trials) were needed for each subject to develop PSD. Like in Deubel (1991)'s study, we used single-target drifts at the end of each saccade, where Kapoula et al. (1989) induced PSD via full-field shifts. This further confirms that single-target shifts are a more adequate stimulus for inducing PSD in human subjects.

2. 1. 4. 2 PSD Adaptation Transfer Between Reflexive and Voluntary Saccades

This is the first study to investigate PSD adaptation transfer to a different saccadic type instead of focusing exclusively on reflexive saccades, as previous literature (Deubel, 1991; Kapoula et al., 1989; Optican & Miles, 1985; Optican & Robinson, 1980). We observed that the adaptation paradigm not only induced a PSD on reflexive saccades in the open loop test condition, as previously discussed, but also transferred to some degree to voluntary saccades. Our data showed a transfer rate from RS to VS of 68%, but mostly important the statistical analysis showed us a significant interaction between saccade type and the adaptation paradigm, meaning that the adaptation blocks (RA) had a different effect depending on whether the saccades were reflexive or voluntary, even though no main effect of saccade type was found, i.e no real difference between saccades when we do not consider the effect of adaptation.

This central result speaks in favour of an involvement of different adaptive mechanisms for different saccade types in the calibration of PSD and gives us further suggestions about the brain localisation of dynamical adaptive mechanisms. As predicted, and in line with previous literature (Deubel, 1991; Optican & Robinson, 1980), our results argue against an exclusive involvement of the brainstem in adaptive PSD control. In this case a simple adjustment of the pulse-step innervation in our paradigm would affect both saccade types equally, whereas our

data shows how different saccade types were affected differently by the same adaptation paradigm. Even though from our behavioural data we cannot make any direct claim about the localisation of the adaptive mechanisms involved, our results are in line with an involvement of the brain structures upstream from the brainstem saccade generator that modify its activity. Such conclusions are in line with Deubel (1991), who manipulated PSD in oblique saccade and demonstrated how PSD can be only induced where the saccadic system is organised in a polar coordinate frame. By adaptively inducing PSD orthogonally to the saccade vector he was indeed able to demonstrate the incompatibility with the horizontal/vertical saccadic organisation in the brainstem structures.

As previously shown by Optican & Robinson (1980), the cerebellum has a critical role in calibrating both the metric (saccadic size) and the dynamic (PSD) components of the saccadic system. A total flocculectomy completely impaired monkeys from calibrating the saccade system after a tenectomy of the recti muscles. Our data is in line with those findings. It is however impossible to further speculate whether two different loci in the cerebellum could be involved in calibrating PSD for different saccade types: the flocculus for reflexive saccades, as shown by Optican & Robinson (1980), and another locus for voluntary saccades. A similar idea has been proposed by Alahyane et al., (2008). At the same time it is possible to imagine a single involvement of the flocculus, but associated with different “weights”in calibrating different saccade types. It is well established that the flocculus has both afferent and efferent connections to both the oculomotor center in the brainstem and the superior colliculus through the fastigial nuclei and the olive as well as with the FEF in the motor neocortex (Leight & Zee, 2015). It is then plausible that their contribution to the calibration of PSD in the cerebellum could lead to different calibration values, explaining the different rate of transfer seen in our results. However, to be able to draw stronger conclusions, it would be necessary to perform additional experiments adapting voluntary saccades and measuring the transfer to reflexive saccades. An asymmetrical transfer pattern would be further evidence of different mechanisms involved.

In addition to analysing PSD amplitude, we were also interested in observing how the time constant of the adapted drift could be influenced by our adaptation training. Interestingly, we observed no adaptation to the stimulus' time constant (120 ms). We measured higher time constants already in the pre-test phase, and they stayed quite stable throughout the experiment, independently of the adaptation paradigm, both during the adaptation and test phases. This result speaks against the possible argument that our paradigm did not induce PSD but trained predictive smooth-pursuit. Smooth-pursuit eye movements are a type of eye movement that serves the purpose of keeping a moving object foveated. Fuchs (1967) seminal paper made an extensive analysis of saccadic and smooth pursuit eye movements. In his paper he describes how the oculomotor system responds to a stimulus that moves at a constant velocity (ramp-like stimulus): after a latency, the saccadic system produces a catch-up saccade followed by the smooth-pursuit system that matches the stimulus velocity. This oculomotor behaviour holds true for all different presented stimulus velocities. Further research (Chou, 2004; Eggert et al., 2009; Freyberg & Ilg, 2008; Jarrett & Barnes, 2002; Ladda et al., 2007; Thier & Ilg, 2005) showed that when the appearance of the stimulus and/or its velocity can be predicted, a compensatory mechanism develops by producing a predictive smooth pursuit eye movement (for a review see: Kowler et al., 2019).

Given our design, it is not possible to completely rule the idea of predictive smooth-pursuit. However, the fact that our subjects were not able to adapt to the stimulus velocity speaks against this type of mechanism. But in order to definitely rule out this hypothesis, it would be necessary to design a separate set of experiments, in which different stimulus drift time constants would be used in the adaptation phase. That would allow us to compare how and if time constants of the resulting PSD undergo an adaptation that mirrors the time constants of the stimulus but with a constant offset. This could be happening in our data, as we observed no modulation of time constant after or during the adaptation phases but rather a stable time constant during the whole experiment, slightly higher than the 120 ms used during the induction of adaptation.

However it must be noted that our results are based on a relatively small sample of test trials. In each session for each participant we collected fifty saccades for RS and fifty saccades for VS, and in some cases some had to be excluded because of errors (see error rates in the Result Section). It could be interesting to repeat the same experiment and have error trials repeated in order to keep a stable number of trials, to ensure the same amount of correct trials for each single subject. This should make the results between the two variables used to measure PSD amplitude even more comparable. On top of that, it would be interesting to see if a different fitting procedure could lead to clearer results, especially concerning the parameter tau. We would propose averaging fitted coefficients (A and tau) by weighting their goodness of fit. This would allow not only to exclude less trials, but also to have a more realistic estimation of each single trial.

PSD hasn't been a popular research topic since the late 1980s. Nowadays more research is done on metrical aspects through the double step paradigm (for reviews see Hopp & Fuchs, 2004; Pélisson et al., 2010; Soetedjo et al., 2019), however these two areas are highly similar and compatible. Not only do both mechanisms serve the function of correcting systematic saccadic mistakes, metrical adaptation for saccadic size, dynamical adaptation for stability in saccadic termination, and of stabilizing gaze; but they are both thought to rely on very similar neurophysiological cerebellar areas: the oculomotor vermis for gain adaptation and the flocculus for PSD (Kheradmand & Zee, 2011; Lewis & Zee, 1993; McDowell et al., 2008; Shadmehr, 2017).

In conclusion, by measuring the effects of an adaptation paradigm both on reflexive and voluntary saccades and quantifying the observed transfer rate we were able to support the literature that excludes that the adaptive mechanisms responsible for PSD should exclusively be found in the brainstem, where an adjustment of the step-pulse ratio should take place. Whether this mechanism resides entirely in the cerebellum, and whether an extra locus in addition to the flocculus might be involved should be investigated with appropriate methods in future experiments.

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2.2 Updating the Dichotomy of Reflexive and Voluntary Saccades

Author contributions:

Giulia Manca designed the study, collected, analyzed, interpreted, and visualized the data, and wrote the manuscript.

Heiner Deubel designed the study, participated in interpreting the results, and commented on the manuscript.

Abstract

Adaptive mechanisms that counteract the effects of physiological and pathological changes in the oculomotor system are essential for the accuracy of saccadic eye movements. Saccadic adaptation can be induced experimentally via the double step paradigm, by systematically shifting the saccadic target after the saccade has been initiated. Even though participants do not perceive this small shift, over the course of the experiment they adjust accordingly by reducing the distance between the eye landing location and the displaced target position both in reflexive saccades (RS) and voluntary saccades (VS).

The generation of these two types of saccades relies on different neural pathways, as do their adaptive mechanisms. Much work has been done using scanning saccades as a prototype of VS, finding little or no transfer between RS and VS, but not much is known about different kinds of VS. We investigated this by varying the presentation mode (sudden or stable) and the task (block-wise or trial-based). We then analysed how RS adaptation transfers to VS. Our data show that the transfer rate can vary based on how voluntary saccades are elicited, suggesting an update of the previously proposed dichotomy of reflexive and voluntary saccadic systems into a continuous frame of reference.

2. 2. 1 Introduction

In order to collect important visual information primates shift the fovea -the area of highest visual acuity- with fast and precise eye movements, called saccades. Since the moving eye cannot perceive (Volkmann, 1968), one important requirement for the saccadic system is the ability to produce orthometric saccades: movements that fall exactly on the intended target. Thus, the landing precision of a saccadic eye movement is a necessary prerequisite for maximising visual perception.

Adaptive mechanisms compensate for any physiological or pathological changes in the oculomotor system that could challenge this goal by recalibrating systematic errors in motor performance and iteratively updating any mismatch between the visual target location and the produced motor command. In a classic study Optican & Robinson (1980) showed how cerebellum-dependent adaptive mechanisms compensate for saccadic dysmetria resulting from muscle ablation. A partial incision of the tendons of horizontal recti muscles of one eye resulted in dysmetric eye movements followed by post-saccadic drift. However, within five days monkeys were able to recalibrate the system and produce orthometric saccades. The same pattern of results was observed in a human patient with unilateral abducens palsy (Kommerell et al., 1976) and in a patient with a third nerve palsy (Abel et al., 1978)

Adaptive mechanisms of saccade metrics on healthy humans have been consistently studied in the laboratory with the use of the double step paradigm *(*Deubel et al., 1986; McLaughlin, 1967; Miller et al., 1981*).* In this non-invasive technique, the target is displaced consistently in one direction during saccade execution. The idea is to simulate a consistent spatial error, detectable only at the end of the saccade. Operatively, a first target appears on the screen (first step), and as soon as the participant makes a saccade toward it, the target is shifted (second step) either inward (opposite to the direction of the saccade), or outward (in the same direction of the saccade). Even though the second target displacement is often not perceived due to intrassacadic suppression (Volkmann et al., 1968; Volkmann, 1986),

orthometric saccades are quickly produced: the participant automatically changes their saccadic gain, defined as the ratio between saccadic amplitude and target step, matching not the first target step but its final position. This important feature of the oculomotor system, that allows a rapid correction of any systematic metrical calibration mistakes, is ubiquitous in the saccadic system, independently from the type of saccade.

Different types of saccades have been identified, depending mainly on their latencies and the way they are elicited (Deubel, 1999; Gaymard et al., 1998; Hopp & Fuchs, 2004; Pélisson et al., 2010; Tusa et al., 1986). For our purposes it is important to distinguish two main categories:

(1) Reactive saccades (RS) occur in response to the onset of a visual target that suddenly appears in isolation in the peripheral part of the retina. Their latencies are typically around 150 - 200 ms (Smit et al., 1987). If a short temporal gap is introduced between the extinction of the fixation point and the appearance of the target (gap paradigm), saccades can be elicited with latencies as short as 100 ms (Fischer & Ramsperger, 1984; Fischer & Weber, 1993), called express saccades.

(2) Voluntary saccades (VS) occur when participants intentionally direct the gaze exploring a visual scene. Latencies of voluntary saccades are typically longer than 200 - 250 ms (Henik et al., 1994; Walker et al., 2000).

Different sub-categories of voluntary saccades can be further differentiated (for a review see Hopp & Fuchs, 2004; McDowell et al., 2008), such as delayed saccades (saccades that are made toward a permanently visible peripheral target only after a go-signal), memory guided saccades (saccades that are made toward a remembered location of a previously presented target), predictive saccades (saccades that are made between two regularly alternating targets), scanning saccades (saccades that are made sequentially between targets in a stable visual scene), and anti-saccades (saccades that are made at the location which is opposite to the visual target). Spontaneous saccades occur when there is no spatial goal, as for example when thinking with eyes closed or at rest in the darkness.

Growing evidence supports the idea that both common and specific cortical and subcortical areas are involved in their generation (Pierrot-Deseilligny et al., 1995; Pierrot-Deseilligny et al., 2003; Munoz & Everling, 2004; Johnston & Everling, 2008). Therefore it has been proposed that adaptive metrical calibration mechanisms could be located at different sites in the oculomotor pathways (Deubel, 1999; for reviews see Hopp & Fuchs, 2004; Pélisson et al., 2010). One very useful tool to answer this question is the study of adaptation transfer between different saccade types. The rationale being that depending on whether adaptation is achieved in one or multiple cerebral sites we should observe different adaptation patterns. Adapting one type of saccade will produce minor or no effect (transfer of adaptation) on the other saccade type if adaptation mechanisms are active at different neural loci, while a complete transfer will be seen if they are active in the same neural locus after the convergence of all saccadic pathways.

Deubel (1995, 1999) led the first comprehensive study of the transfer of adaptation between different categories of saccades. The author was interested in whether separate adaptation mechanisms could be involved in the calibration of different types of saccades or one common mechanism could act at a single focus of the final pathway recruited for all saccade categories. Deubel (1999) and later many other authors (Fujita et al., 2002; Gaveau et al., 2005) found evidence for an asymmetrical transfer between different types of saccades, and argued in favor of different mechanisms underlying saccadic adaptation. To explain this finding, Deubel (1999) proposed a model composed by three loci of adaptation for each saccade type-specific computational stage in the brain, locating one for reflexive saccades in the collicular pathway (downstream the SC), one for memory-guided saccades at the output of the PFC and one for voluntary saccades modifying the strength of the connections between FEF and the reticular formation. Recent papers on saccadic gain adaptation seem to confirm this hypothesis by discovering loci of adaptation within the cortex through fMRI studies (Gerardin et al., 2012; Panouillères et al., 2014). Alahyane and colleagues (2007, 2008) proposed a two-level scheme of saccade adaptation, which assumes both a common locus in the final pathway and two separate cerebellar loci specific to each saccade category.

In the present study we focused on investigating the unilateral transfer of saccade amplitude adaptation from reflexive to voluntary saccades. It is however important to mention that the transfer in the opposite direction has been widely studied and the comparison between the symmetry or asymmetry of transfer in both directions allows to formulate further hypotheses about the site(s) of adaptation in the brain.

The picture emerging from all these studies shows a general agreement in finding a high transfer rate between reflexive saccades and express saccades (Deubel, 1999; Frens & van Opstal, 1994; Hopp & Fuchs, 2002), while the picture gets less clear when voluntary saccades are investigated. In contrast to Deubel (1995, 1999) who found no transfer from reflexive to voluntary saccades, Fujita et al. (2002) showed a partial transfer between both saccade types (in the case of delayed and memory-guided saccades), while Hopp & Fuchs (2010) found a substantial transfer between them (in the case of memory-guided saccades). Concerning scanning saccades both Deubel (1995, 1999) and Alahyane et al. (2007) found no significant transfer from reflexive saccades. Fujita et al. (2002) and Deubel (1995, 1999) both found no transfer between reflexive and voluntary saccades in the case of scanning saccades.

Resolving these differences and understanding where and why they might originate is one of the aims of our set of experiments. Through a more comparable manipulation of voluntary saccades we expected to be able to draw further conclusions about these apparently conflicting results. Our paradigm allowed us not only to further understand those different adaptation profiles, but also to better define differences between saccade types. Up to now, the definitions of voluntary and reflexive saccades have been based on two main criteria: how the saccade is elicited and its latency. These definition criteria seem however quite naive and simplistic.

While most studies differentiate between different types of voluntary saccades (delayed, memory-guided, scanning, antisaccades), we were interested in creating a set of experiments in which the same type of voluntary saccade could be manipulated to identify more objective

parameters to propose a better definition of its amount of “voluntariness”. We therefore manipulated the two factors that seemed to be crucial in its definition: experimental instructions for the participants, and appearance of the target(s). The scanning saccades experiment was taken as baseline for comparison, as all the above mentioned studies find little adaptation transfer under this condition.

Through the analysis of adaptation transfer between experiments we imagined two mutually exclusive scenarios: either to see no differences in adaptation transfer between experiments, suggesting a clear distinction between all our manipulations of voluntary saccades and reflexives saccades (implying no real role of our manipulations) or to see some emerging patterns in transfer rate across experiments. This last hypothesis would imply the need of redefining our definition of voluntary saccades and what parameters could be identified in describing what makes a voluntary saccade voluntary.

2. 2. 2 Methods

2. 2. 2. 1 Participants, Stimuli and Apparatus

Five separate experiments were conducted. Six healthy participants (4 males and 2 females) between 21 and 28 years old participated in Experiment 1, five participants (2 males and 3 females) between 24 and 29 years old participated in Experiment 2, seven participants (1 male and 6 females) between 19 and 30 years old participated in Experiment 3, seven participants (all females) between 21 and 29 years old participated in Experiment 4, five participants (all females) between 21 and 25 years old participated in Experiment 5. All participants were healthy, had a normal or corrected-to-normal vision and were naive to the purpose of the experiments. They received either monetary compensation or course credits for participating.

The experiments were conducted in a dark and quiet room. Each participant was comfortably seated with the head supported by a chin and forehead rest at a distance of 60 cm from a 21 inch Sony GMD-F500R (1280 x 1024 pixels, vertical refresh rate of 75 Hz). Eye movements were recorded with an SR Research EyeLink 1000 desktop mounted eye-tracker, calibrated before each experiment.

Stimulus presentation was controlled by a Mac Mini (operating system, Mac OS X Snow Leopard) and implemented in Matlab (MathWorks, Natick, MA, USA) using Psychophysics and Eyelink toolboxes (Pelli, 1997; Brainard, 1997; Cornelissen et al., 2002). Saccade onset detection was calculated online from the sampled eye position signal. When the instantaneous eye velocity exceeded a 20°/sec threshold, a saccade was detected and either the target displacement in the adaptation conditions or target disappearance in the test conditions (see below) were triggered.

2. 2. 2. 2 General Design and Stimuli

This study was composed of five similarly structured experiments. Each experiment consisted of five phases: (1) a Pre-Test in which the normal parameters of the reflexive (RT1) and voluntary saccades (VT1) were measured; (2) a long adaptation phase (RA1) in which adaptation to reactive saccades was induced; (3) a first test (Test 1) in which the effect of the first adaptation on both reflexive (RT2) and voluntary saccades (VT2) were observed; (4) a second long adaptation phase (RA2) for reactive saccades; (5) a second test (Test 2) in which the overall effects of adaptation on both saccade types (RT3, VT3) were measured. Each test phase (Pre-Test, Test 1, Test 2) consisted of 50 trials, voluntary and reflexive saccade trials were intermixed, resulting in 25 voluntary and 25 reflexive saccades trials. Each adaptation phase (RA1, RA2) lasted 200 trials (Figure 1).

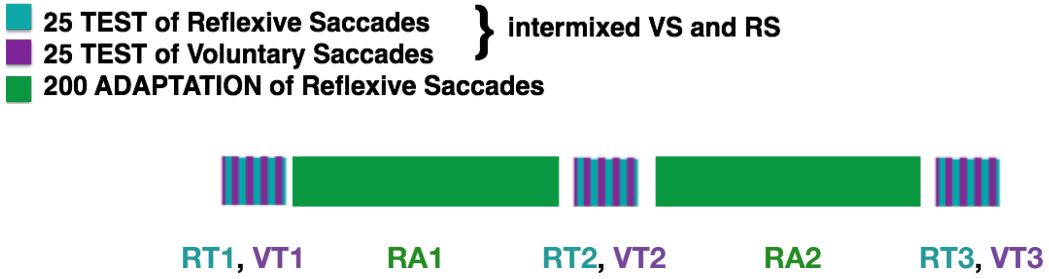

Figure 1. General design common to each experiment.
The quadrilaterals represent different experimental blocks: in light blue, blocks in which reflexive saccades were tested. In purple, blocks in which voluntary saccades were tested. In green, the adaptation block, during which reflexive saccades were adapted. Voluntary and reflexive saccade trials were intermixed, the experiment blocks were built as shown in the picture.

To induce the adaptation of reflexive saccades (RA1, RA2), a modified version of the double step paradigm (Deubel, 1995) was used. During these types of trials a white circular target, with a diameter of 0.7°, was presented centrally on the screen for 1000 ± 200 seconds, after this interval the central target stepped randomly to the right or to the left (± 7°) on the horizontal plane. Participants were instructed to follow this target as soon and as precisely as possible. When the onset of the saccade was detected (see previous section for technical details) the target was displaced by 25% of the initial step size, into the opposite direction of the first step (inward step). This final target position was used as a new starting position in the next trial (Figure 2).

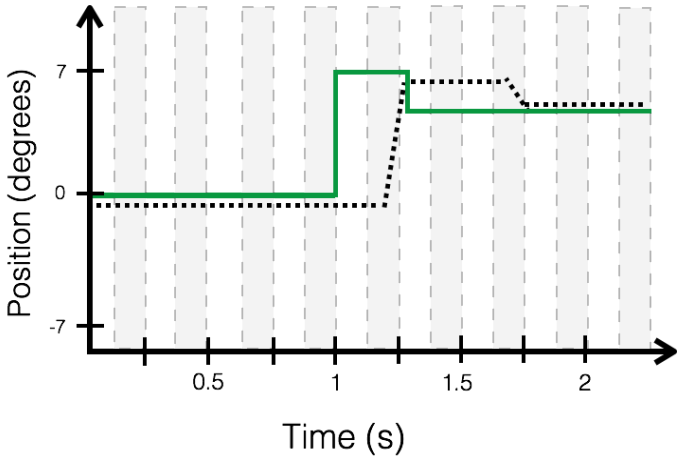

Figure 2. Reflexive adaptation blocks (RA1, RA2).
Depiction of a single trial. In the x-axis time, in the y-axis horizontal position. In green the target, in dotted black a possible saccade trace. A fixation target (a white circular dot with a diameter of 0.7°) appeared on the screen for 1000 ± 200 seconds, after this interval the central target stepped randomly to the right or to the left (± 7°). When the onset of the saccade was detected the target was displaced by 25% of the initial step size, into the opposite direction of the first step (inward step).

To measure the metricity of reflexive saccades both before the adaptation (Pre-Test, RT1) and after the adaptation phases (RT2, RT3) we used the same paradigm in all experiments. A central fixation was shown for 1000 ± 200 ms (either a white fixation cross in experiment 2, 3, 4 and 5 or a Gabor patch in experiment 1). In Experiments 4 and 5, to match the timing of the fixation cross in the voluntary test condition, a central Gabor was presented, after the fixation cross, as fixation for 700 ± 200 ms. As the fixation disappeared, one Gabor patch appeared at an eccentricity of 7° to the left or to the right of fixation. Participants were instructed to make a saccade towards it as soon as possible. As the saccade onset was detected (see previous section), the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial (Figure 3). Targets (and fixations in the experiments that had Gabor as fixation) were Gabor patches (spatial frequency= 0.1 cycle per pixel, contrast=100%, phase of the sine grating=1°, spatial constant of the gaussian hull function= 9), which could be either tilted vertically (0°) or diagonally (± 15°). The tilt of the central fixation Gabors, in the experiments in which they were present, matched the target one.

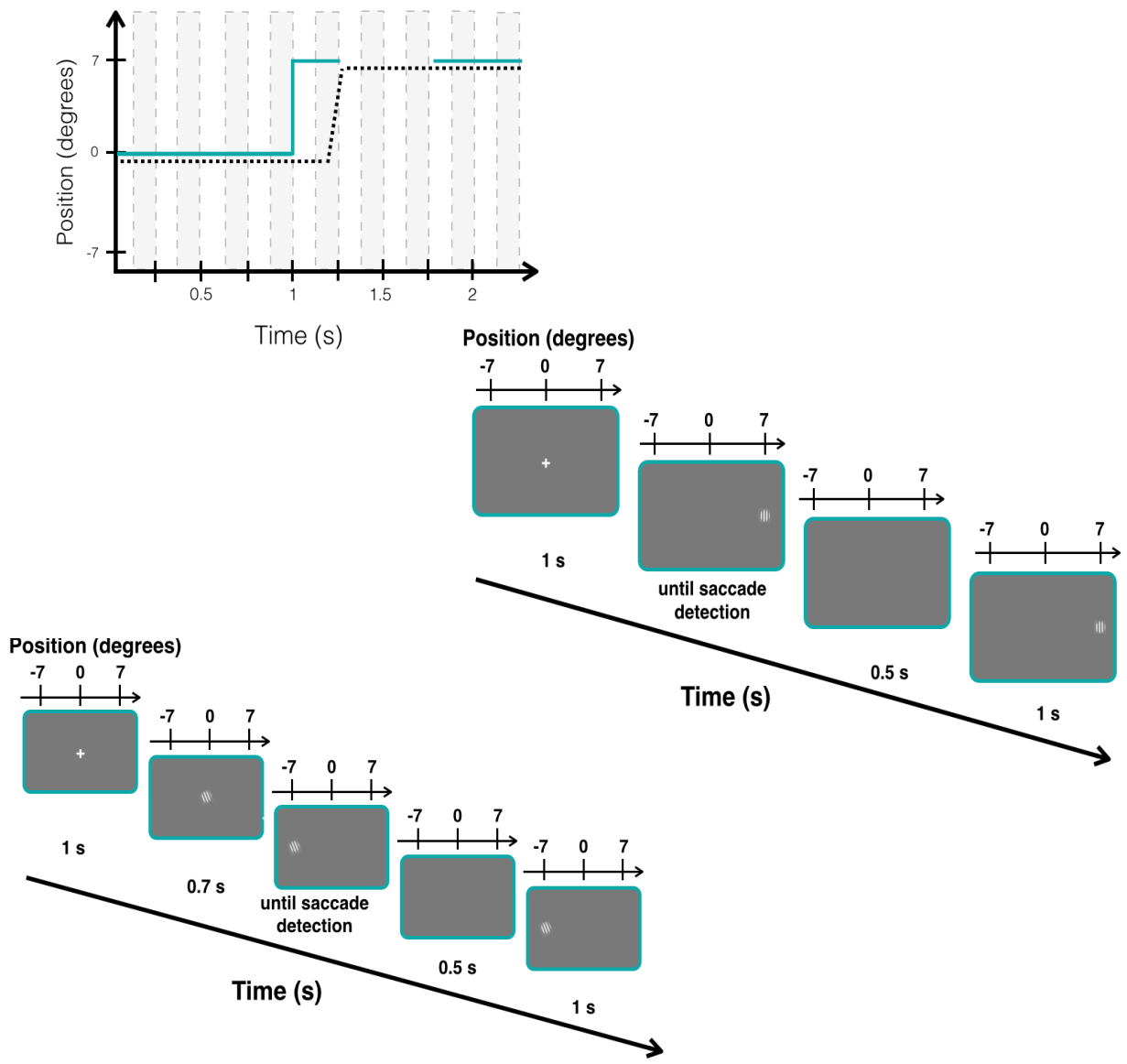

Figure 3. Reflexive saccade test blocks (RT1, RT2, RT3).
Depiction of a single trial. A central fixation was presented on the screen for a variable time depending on the experiment (see below), after this interval a Gabor patch that served as a saccadic target was presented to the right or to the left (± 7°). When the onset of the saccade was detected the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial.

Upper panel: In light blue the target, in dotted black a possible saccade trace. The timing of the fixation matches experiments 1, 2 and 3 (see below).
Intermediate panel: Depiction of experiments 1, 2 and 3. The central fixation was presented for 1000 ± 200 ms (either a white fixation cross in experiment 2 and 3or a Gabor patch in experiment 1).
Lower panel: Depiction of experiments 4 and 5. The central fixation was presented for 1000 ± 200 ms, after this interval a central Gabor patch was presented as fixation for 700 ± 200 ms to match the timing of the fixation cross in the voluntary test condition of the same experiments.

With regards to voluntary saccades, we wanted to vary the amount of voluntary effort required to complete the task. We therefore manipulated two factors: the instructions to the participants (Instruction) and the timing of fixation and target(s) (Overlap). First, we varied the instructions to the participants by specifying on each trial which target to select -vertical or oblique tilted target- (Trial Instruction: Experiments 1 and 4), or by asking participants to always select throughout the experiment the same type of target, -always the tilted target- (Experiment Instruction, Experiments 2 and 3), Second, we manipulated the timing of fixation and target(s), which could result in a temporal overlap of fixation and target(s) (Overlap, Experiments 3 and 4) or in no overlap (No overlap, Experiments 1 and 2). Finally a fifth experiment was conducted in which scanning saccades were tested. During this experiment targets were present on the screen and participants produced self-paced saccades between them, this last experiment served as a baseline. For an overview of the five types of experiments, see Figure 4.

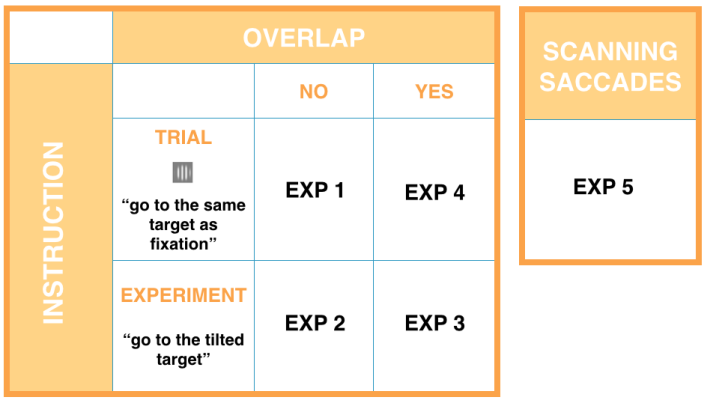

Figure 4. General design of the set of experiments.
To vary the amount of required voluntary saccadic effort, four experiments were conducted by manipulating two variables: (1) Instruction. The instructions given to the participants and (2) Overlap. The fixation and target(s) presentation time.
In Experiments 1 and 4 the instructions were trial based, participants were instructed on each trial to either select the vertical or the diagonal tilted target. In Experiments 2 and 3 instructions were kept constant during the whole experiment, by asking participants to always select the diagonal tilted target.
In Experiments 1 and 2 there was no overlap between fixation and targets, targets appeared as the fixation disappeared. In Experiments 3 and 4 on the other hand we presented the fixation and the targets at the same time creating an overlap paradigm.
Experiment 5 tested scanning saccades, we simultaneously presented three targets on the screen and instructed participants to explore them making self-paced saccades. This experiment served as a baseline.

The manipulation of voluntary test trials differed depending on each single experiment, further details are therefore given below in the description of each experiment.

Experiment 1 (Trial Instruction, No Overlap)

The adaptation phase and the reflexive saccade tests are described in the General design section. During the test trials, a Gabor patch served as central fixation for 1000 ± 200 ms. The Gabor patch could be tilted vertically (0°) or diagonally (± 15°). As the fixation disappeared, two Gabor patches, one tilted vertically (0°) and the other diagonally (± 15°) appeared simultaneously, at an eccentricity of 7° left and right of fixation. As the saccade onset was detected, the target(s) were blanked for 500 ms. Participants had to select the target with the same orientation as the fixation Gabor. The new fixation appeared at the same location of the last correct target (Figure 5).

Experiment 2 (Experiment Instruction, No Overlap)

The adaptation phase and the reflexive saccade tests are described in the General design section. During the test trials, a fixation cross was presented for 1000 ± 200 ms. As the fixation disappeared two Gabor patches (voluntary saccade test), one tilted vertically (0°) and the other diagonally (± 15°) appeared simultaneously, at an eccentricity of 7° left and right of fixation. Participants had to select the tilted target throughout the whole experiment. As the saccade onset was detected, the target(s) were blanked for 500 ms. The new fixation target appeared at the same location of the last correct target (Figure 6).

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Experiment 3 (Experiment Instruction, Overlap)

The adaptation phase and the reflexive saccade tests are described in the General design section. During the test trials, a fixation cross was presented for 1000 ± 200 ms. The fixation cross remained for another 700 ± 200 ms as the two Gabor patches appeared simultaneously, at an eccentricity of 7° left and right of fixation. Fixation cross and targets were therefore present on the screen at the same time. Participants were instructed to male a saccade only when the fixation disappeared, and to select the tilted target throughout the whole experiment. As the saccade onset was detected, the targets were blanked for 500 ms. The new fixation target appeared at the same location of the last target (see Figure 7).

Participants were given feedback if their saccades started before the disappearance of the targets or if their saccades were made in the wrong direction.

Experiment 4 (Trial Instruction, Overlap)

The adaptation phase and the reflexive saccade tests are described in the General design section. During the test trials, a fixation cross was presented for 1000 ± 200 ms. The fixation cross remained for another 700 ± 200 ms as the two Gabor patches appeared simultaneously, at an eccentricity of 7° left and right of fixation. Fixation cross and targets were therefore present on the screen at the same time. After this interval, the central fixation was replaced by a Gabor patch that could be tilted vertically (0°) or diagonally (± 15°), and indicated which target to select. Participants were instructed to make a saccade as fast as possible as this central Gabor patch appeared. As the saccade onset was detected, the target(s) were blanked for 500 ms. The new fixation target appeared at the same location of the last target (see Figure 8). Participants were given feedback if their saccades started before the disappearance of the targets or if their saccades were made in the wrong direction.

Experiment 5 (Scanning Saccades)

The adaptation phase and the reflexive saccade tests are described in the General design section. During the test trials, a fixation cross was presented for 1000 ± 200 ms. In the voluntary saccade test, the fixation cross remained for 700 ± 200 ms as the two Gabor patches appeared. After this interval, the central fixation was replaced by a Gabor patch that could be tilted vertically (0°) or diagonally (± 15°), and indicated which target to select. Participants were instructed to start a sequence of four self paced saccades, as this central Gabor patch appeared. They were asked to select the target with the same orientation as the fixation Gabor as a first saccadic target and to make three further saccades in a sequence, with the last saccade ending at the central fixation. At every saccade onset the targets were blanked for 500 ms (see Figure 9).

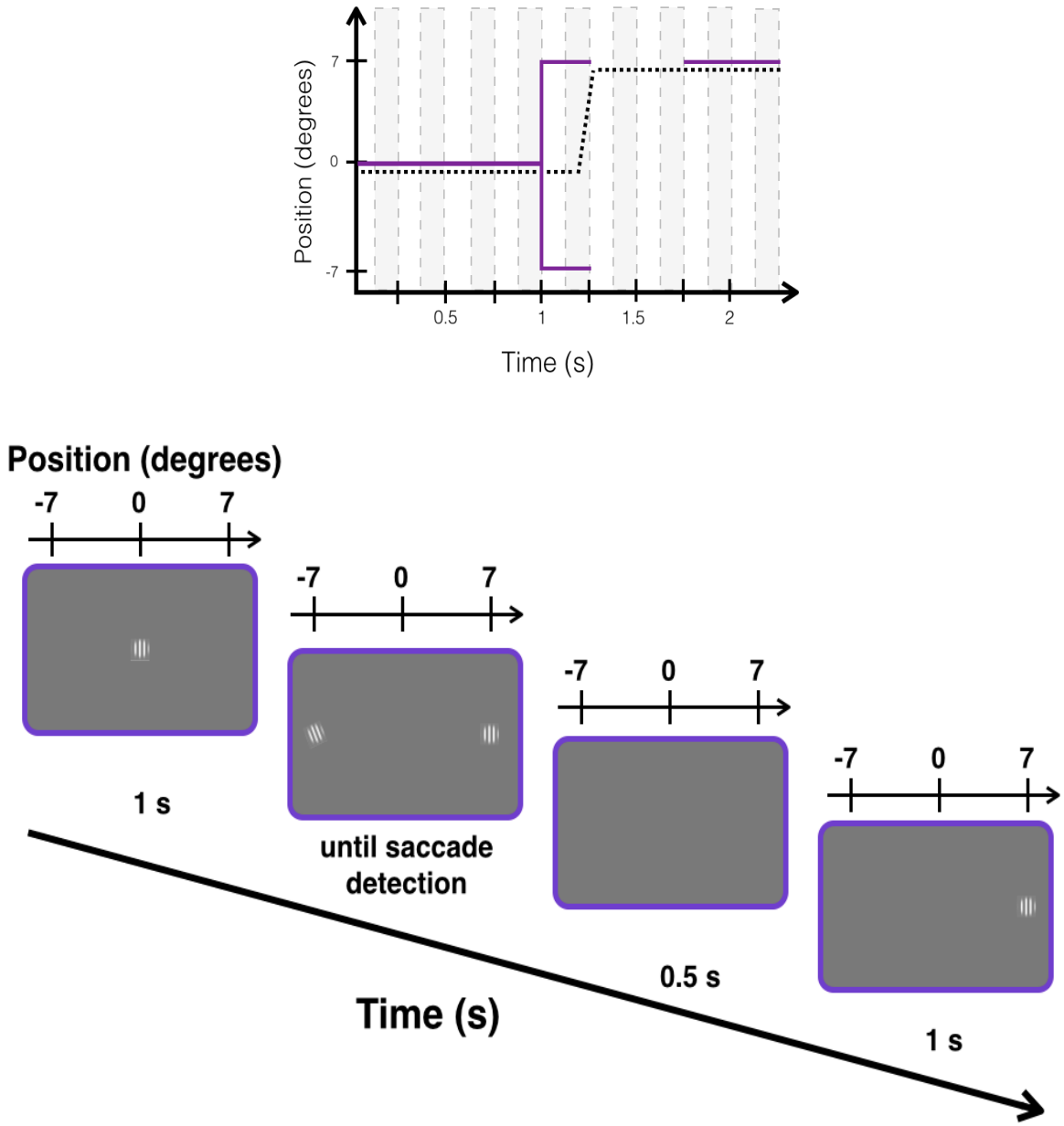


Figure 5. Experiment 1 (Trial Instruction, No Overlap). Voluntary saccade test blocks (VT1, VT2, VT3). Depiction of a single trial. A central Gabor patch was presented as fixation on the screen for 1000 ± 200 ms, after this interval two Gabor patches, that served as a saccadic targets, one tilted vertically (0°) and the other diagonally (± 15°), appeared simultaneously, at an eccentricity of 7° left and right of fixation. Participants were asked to select the target with the same orientation as the fixation Gabor patch. When the onset of the saccade was detected the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial

Upper panel. On the x-axis time, on the y-axis horizontal position. In purple the fixation and the targets, in dotted black a possible saccade trace.

Lower panel. Sequence of stimulus presentation.

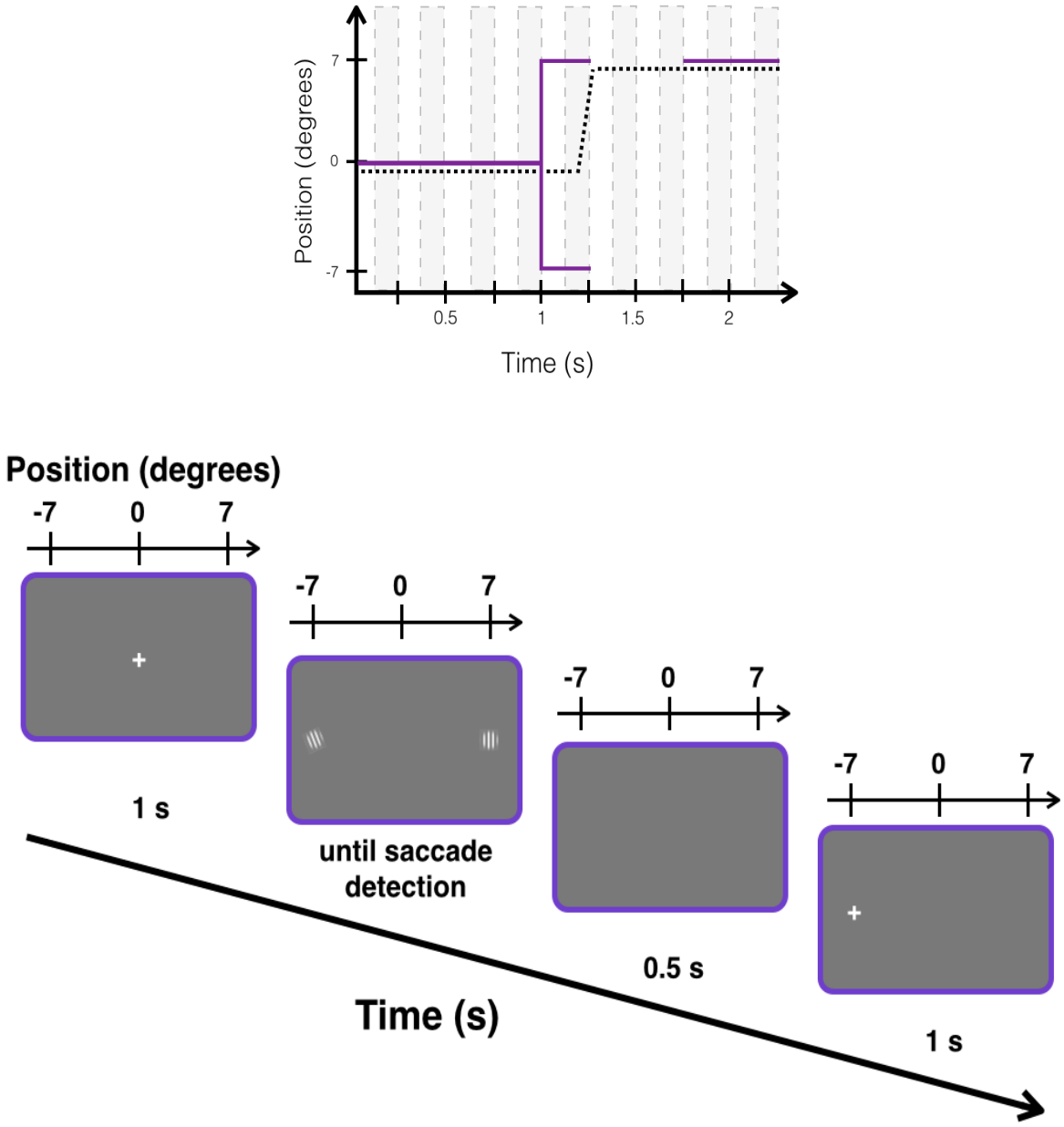


Figure 6. Experiment 2 (Experiment Instruction, No Overlap). Voluntary saccade test blocks (VT1, VT2, VT3).

Depiction of a single trial. A central fixation was shown on the screen for 1000 ± 200 ms, after this interval two Gabor patches, that served as a saccadic targets, one tilted vertically (0°) and the other diagonally (± 15°) appeared simultaneously, at an eccentricity of 7° left and right of fixation. Participants were asked to select the tilted target throughout the experiment. When the onset of the saccade was detected the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial

Upper panel: In the x-axis time, in the y-axis horizontal position. In purple the fixation and the targets, in dotted black a possible saccade trace.

Lower panel: Sequence of stimulus presentation.

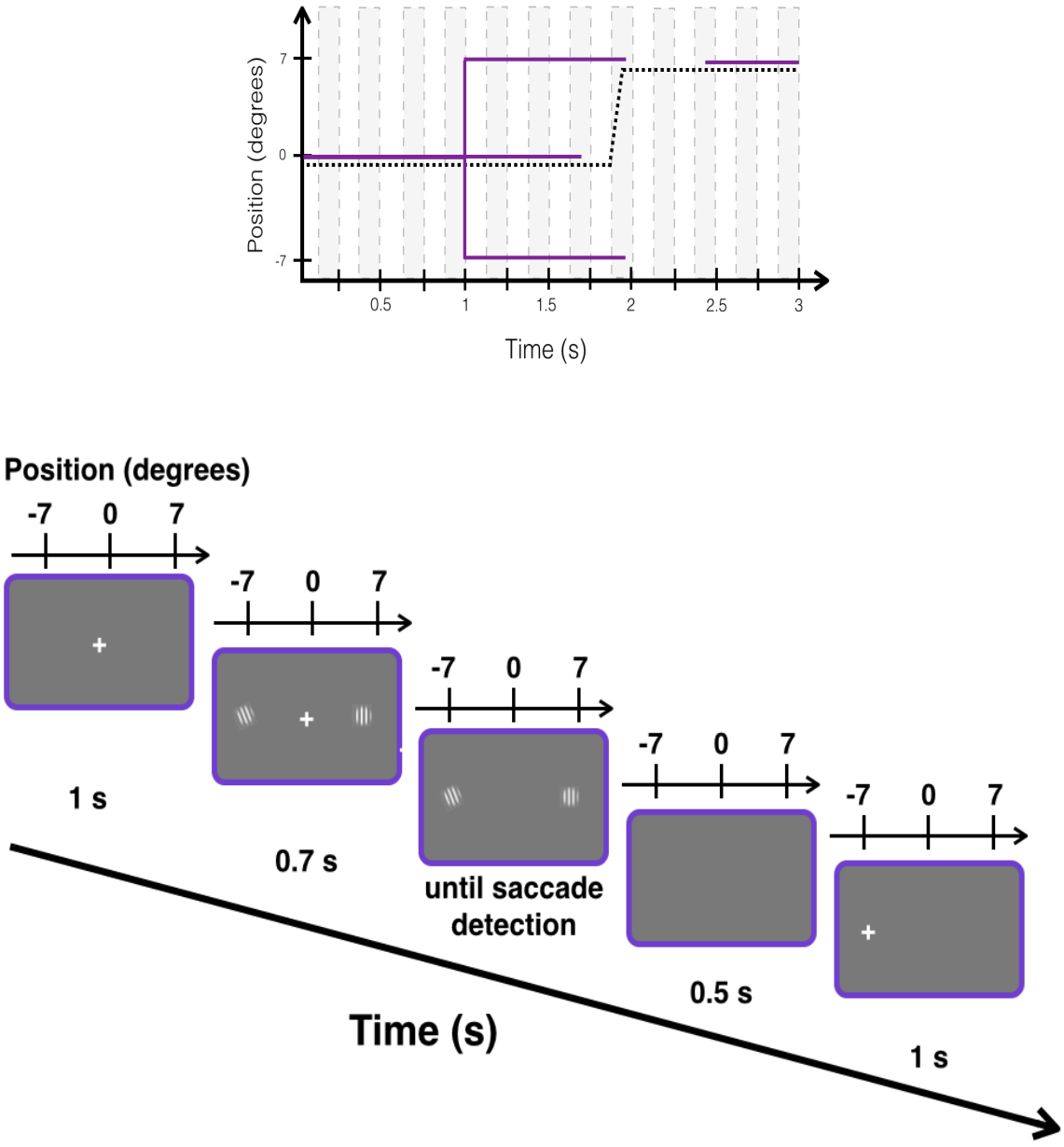
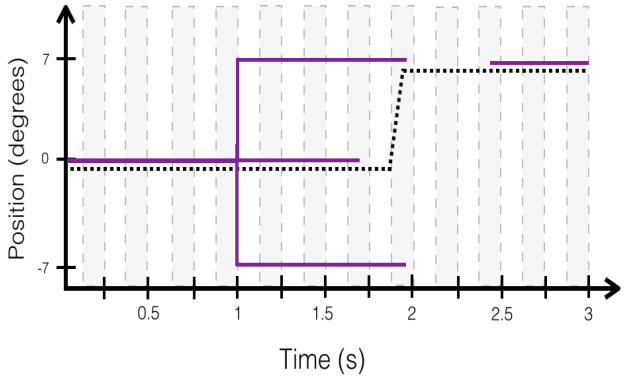


Figure 7. Experiment 3 -Experiment Instruction, Overlap-. Voluntary saccade test blocks (VT1, VT2, VT3). Depiction of a single trial. A central fixation was shown on the screen for 1000 ± 200 ms, after this interval the fixation cross did not disappear as two Gabor patches were presented simultaneously, one tilted vertically (0°) and the other diagonally (± 15°) at an eccentricity of 7° left and right of fixation, for 700 ± 200 ms. The fixation cross and the targets were therefore shown at the same time on the screen. Participants were asked to select the tilted target throughout the experiment. When the onset of the saccade was detected the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial
Upper panel: In the x-axis time, in the y-axis horizontal position. In purple the fixation and the targets, in dotted black a possible saccade trace.
Lower panel: Sequence of stimulus presentation.



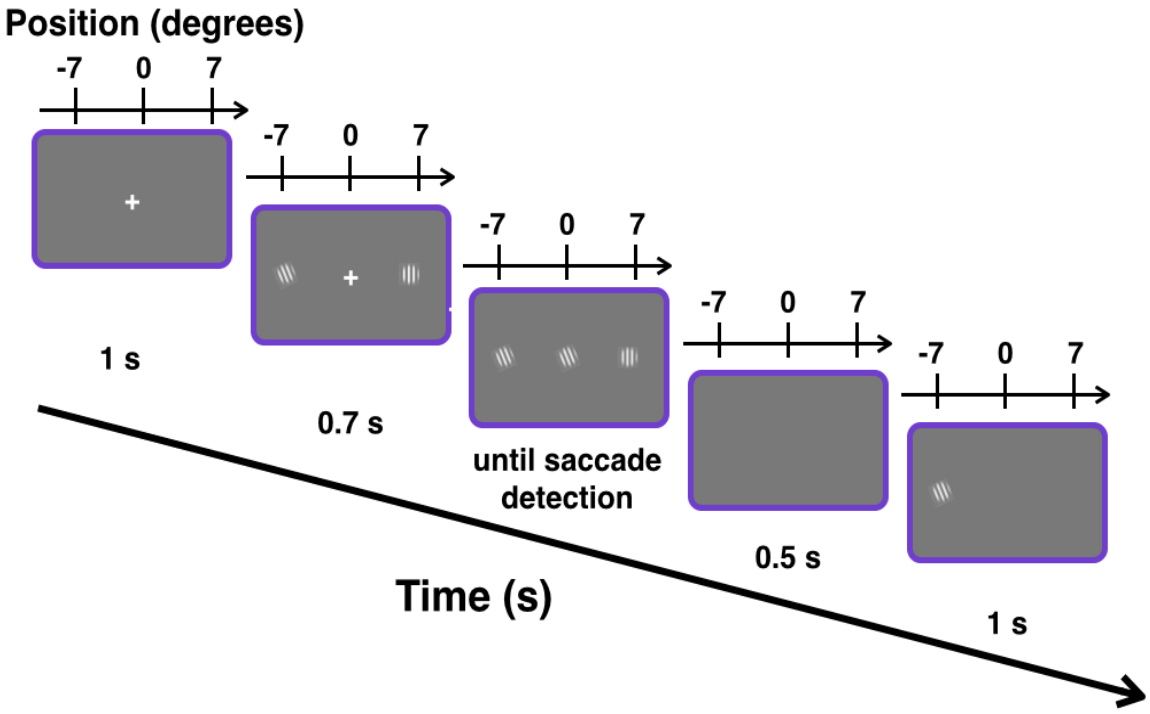


Figure 8. Experiment 4 (Trial Instruction, Overlap). Voluntary saccade test blocks (VT1, VT2, VT3).
Depiction of a single trial. A central fixation was shown on the screen for 1000 ± 200 ms, after this interval the fixation cross did not disappear as two Gabor patches were presented simultaneously, one tilted vertically (0°) and the other diagonally (± 15°) at an eccentricity of 7° left and right of fixation, for 700 ± 200 ms. The fixation cross and the targets were therefore shown at the same time on the screen. After this interval the central fixation was replaced by a Gabor patch that matched the tilt of one of the targets. Participants were asked to select the target that presented the same orientation as the central fixation Gabor patch. When the onset of the saccade was detected the target was blanked for 500 ms. The correct final target position served as a new central fixation in the next trial
Upper panel: In the x-axis time, in the y-axis horizontal position. In purple the fixation and the targets, in dotted black a possible saccade trace.
Lower panel: Sequence of stimulus presentation.

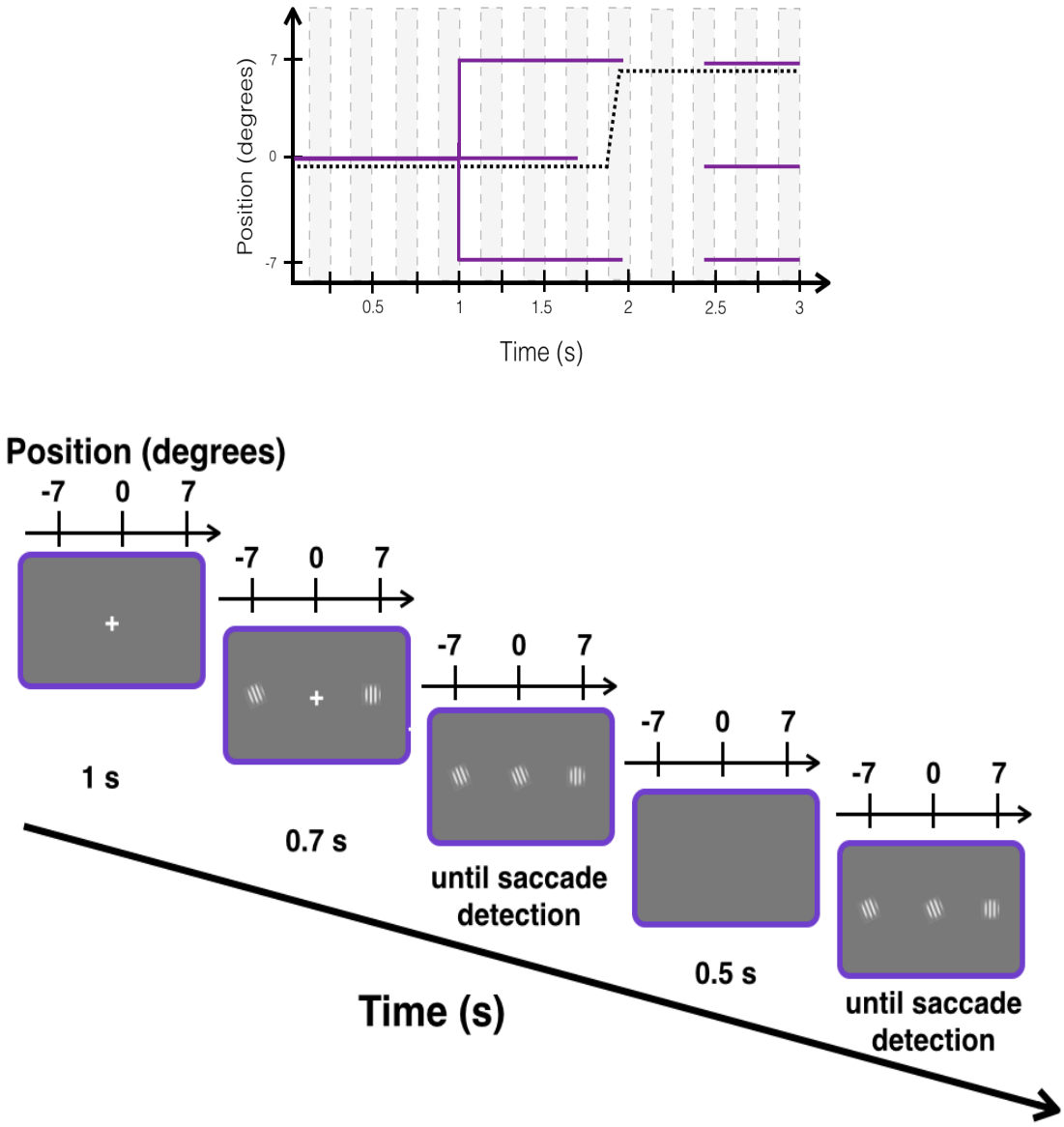


Figure 9. Experiment 5 (Scanning Saccades). Voluntary saccade test blocks (VT1, VT2, VT3).
Depiction of a single trial. A central fixation was shown on the screen for 1000 ± 200 ms, after this interval the fixation cross did not disappear as two Gabor patches were presented simultaneously, one tilted vertically (0°) and the other diagonally (± 15°) at an eccentricity of 7° left and right of fixation, for 700 ± 200 ms. The fixation cross and the targets were therefore shown at the same time on the screen. After this interval the central fixation was replaced by a Gabor patch that matched the tilt of one of the targets. Participants were asked to select the target that presented the same orientation as the central fixation Gabor patch and to produce a sequence of four total saccades. When the onset of one saccade was detected the target was blanked for 500 ms. All the targets were then shown again until the four saccades we produced. The correct final target position served as a new central fixation in the next trial
Upper panel: In the x-axis time, in the y-axis horizontal position. In purple the fixation and the targets, in dotted black a possible saccade trace.
Lower panel: Sequence of stimulus presentation.

2. 2. 2. 3 Data Processing and Statistical Analysis

Raw data from the eye tracker was recorded on-line and evaluated off-line using Matlab software (MathWorks, USA). Beginning and end of each saccade, as well as latencies were calculated by the Eyelink's built-in saccade detection algorithm based on the recorded velocity, acceleration and eye location's parameters. Trials including behavioural mistakes were excluded from the analysis, they included trials in which (1) no saccadic eye movement was produced, (2) participants made a saccade in the wrong direction, (3) participants produced a saccade amplitude not within a reasonable range, either smaller than 2° or bigger than 15°, (4) fixation was not held until the go sign, (5) all other types of problem, including blinking eye movements or movements of the head leading to recalibration.

An outlier analysis was also performed on saccadic amplitude, excluding those data points that that lied outside 2 * IQR, where IQR, the 'Inter Quartile Range' is the difference between 75th and 25th quartiles.

Saccadic gain was calculated for each trial, it being defined as the ratio between the saccadic amplitude and the target step amplitude.

$$Gain = \frac{Saccadic\ Amplitude\ [degrees]}{Target\ Step\ Amplitude\ [degrees]}$$

The percentage of transfer between RT and VT was calculated as the ratio between the saccadic mean amplitude during each RT and its correspondent VT multiplied by 100.

$$Transfer\ (\%) = \frac{V[degrees]}{R\ [degrees]} * 100$$

$$V(\%) = \frac{V(post) - V(pre)\ [degrees]}{V(pre)\ \ [degrees]} * 100$$

$$R\ (\%) = \frac{R(post) - R(pre)\ [degrees]}{R(pre)\ \ [degrees]} * 100$$

All analyses and figures were created using the open statistical software R (Team, 2015) and the "lme4" package (Bates, Maechler, & Bolker, 2012) as well as the "lmerTest" package (Kuznetsova, Brockhoff, & Christensen, 2017). Two types of analysis were performed, a first to

analyse the saccadic gain within each experiment, and a second to compare the transfer ratios across experiments.

The use of ANOVAs or T-tests was not feasible as our data did not meet the assumptions of such models (independence of observations, normality and homoscedasticity) or the requirement of having the same number of trials in each condition. We therefore preferred to use a model that makes no previous assumptions (beside the linearity of the model) and treat each data point independently, without the need of post-hoc comparisons or adjusting the level of significance or testing only few comparisons.

For each experiment we modelled the saccadic gain in both conditions (Reflexive Tests and Voluntary Tests) over time and quantified the saccadic gains in each condition. All the measurement points during the Test Conditions for both saccade types were included in the analysis. To account for the longitudinal setting (testing the same participants in the same conditions multiple times over the course of the experiment) and the intrapersonal dependencies within the data that come along with it, mixed linear regression models were estimated, modeling each person as a unit with potential random variance. To this end the model allowed for participant-specific random intercepts.

To quantify the effect of within-participant variances, we estimated unconditional random effects models (UREMs) calculating intra-class correlations (ICCs) to relate within and between participant variability. We used the standard formula to calculate ICCs, by dividing the random effect variance, $\sigma^2 i$, by the total variance (the sum of the random effect variance and the residual variance, $\sigma^2 \varepsilon$.)

$$ICC = \sigma^2_i / (\sigma^2_i + \sigma^2_\varepsilon)$$

In order to analyse the decrease in amplitude of saccadic gain in both saccade types over time, we first estimated linear growth curves, using mixed regression models with dummy coding, and Reflexive Saccade as a reference category. (Hilbert et al., 2019). To do so we created a variable for each Saccade Type and assigned the value 0 to Reflexive Saccades, and

the value 1 to Voluntary Saccades. As a consequence, the regression weight of the intercept indicates the model predicted values for Reflexive Saccades and the regression weight of Voluntary Saccades represents the predicted difference between Reflexive and Voluntary Saccades.

To account for the effect of the adaptation over time we coded a variable for each test condition and assigned the value 0 to the Pre-Test, the value 1 to the first Post-Test and the value 2 to the second Post-Test. This allowed us to model individual changes in the form of a growth variable. As a consequence, the regression weight of the intercept indicates the predicted values for the Pre-Test and the regression weight of the other Post-Tests represents the predicted difference between each Post-Test and the Pre-Test. Both variables (Saccade Type and Time) entered the model as single predictors and as an interaction term.

$$y_{ij} = \gamma_0 + \gamma_1 \text{Voluntary Saccades}_i + \gamma_2 \text{Post-Test}_{1j} + \gamma_3 \text{Post-Test}_{2j} + \gamma_6 \text{Voluntary Saccades}_i \times \text{Post-Test}_{1j} \times + \gamma_7 \text{Voluntary Saccades}_i \times \text{Post-Test}_{2j} + u_{0i} + e_{ij}$$

The regression weights of the predictors are therefore to be interpreted as follows:
Intercept: Predicted amplitude of saccadic gain in the reflexive condition in the pretest.
VS: Predicted Pre-Test difference between the RS and VS.
Post-Test(x): Change between the Pre-Test and Post-Test(x) in RS.
Post-Test(x) x VS: Difference in change between the Pre-Test and Post-Test(X) between RS and VS.

The same type of analysis was used to compare the transfer ratios between experiments. Unconditional random effects models (UREMs) were estimated by calculating intra-class correlations (ICCs) to quantify the effect of within-participant variances. Linear growth curves were then calculated, using mixed regression models with dummy coding and the scanning saccade experiment as a reference category. (Hilbert et al., 2019). We then run two different analyses to check for the effect of our two variables: (1) instructions to the participant (Instruction) and the timing of fixation and target(s) appearance (Overlap). We

therefore created a dummy variable for each variable (Instruction and Overlap) and assigned the value 0 to the scanning saccade experiment, and the value 1 to Trial (Instructions) and Overlap (Overlap), and the value 2 to Experiment (Instructions) and No-Overlap (Instructions), respectively. Each variable (Instructions and Overlap) entered the analysis as a single predictor. We were unable to enter an interaction term, as the amount of data was not sufficient to calculate this estimation.

$$y_{ij} = \gamma_0 + \gamma_1 \text{Trial Instruction}_{1j} + \gamma_4 \text{Experimentl Instruction}_{2j} + u_{0i} + e_{ij}$$

$$y_{ij} = \gamma_0 + \gamma_1 \text{Overlap}_{1j} + \gamma_2 \text{No-Overlap}_{i2j} + u_{0i} + e_{ij}$$

We also used the same model but entered as predictors a single dummy variable assigned depending on the experiment number: we assigned the value of 0 to the scanning saccade experiment, the value 1 to Experiment 4, the value 2 to Experiment 3, the value 3 to Experiment 2 and the value 4 to Experiment 1.

$$y_{ij} = \gamma_0 + \gamma_1 \text{Exp1}_i + \gamma_2 \text{Exp2}_i + + \gamma_3 \text{Exp3}_i + \gamma_4 \text{Exp4}_i + u_{0i} + e_{ij}$$

2. 2. 3. Results

The presentation of the results is divided in different sections to better describe the findings. The first section gives a general, overall description of the results; sections two to six describe the specific results of each experiment, while the last section compares the findings of all experiments and analyzes the amount of adaptation transfer between RS and VS.

2. 2. 3. 1 General

As described in the Method section, saccadic gain was calculated equally in all experiments as the ratio between saccadic amplitude and target step amplitude. Before the data analysis, we excluded trials with erroneous responses (Table 1), and performed an outlier

detection analysis (Table 2). Specific details about these procedures are given in the Method section.

Overall two types of information were relevant to our purposes in all experiments: (1) checking if the double step paradigm resulted in a reduction of saccadic amplitude during the adaptation phases (RA1 and RA2), and (2) investigating the effect of the adaptation phases on both types of saccades, as compared to the Pre-Test blocks (Post-Test 1 and Post-Test 2), specifically analysing the amount of transferred adaptation to voluntary saccades. With regards to (1), we generally observed that saccadic gain was indeed reduced in all experiments between the first 25 trials and the last 25 trials of each adaptation phase (RA1, RA2). Indicating that the adaptation paradigm worked well (Figures 10, 11, 12, 13, 14 and Tables 3, 5, 7, 9, 11). With regards to (2), we found a general decrease of 10% in saccadic gain with regards to reflexive saccades in all experiments, while we found different rates of saccadic gain reduction concerning voluntary saccades. Both effects are shown in Figures 10, 11, 12, 13, 14 and Tables 3, 5, 7, 9, 11.

Next we compared the transfer rate between reflexive and voluntary saccade types between experiments (See Section 2. 2. 3. 2) and analysed the factors that might play a role in these differences, in particular the manipulated factors: Instruction and Overlap. We observed a significant role of the fixation overlap, as shown in Figure 15 and Table 13. Transfer rate was calculated as the percentage ratio between voluntary and reflexive saccades adaptation rates. See the Methods for further details.

EXPERIMENT	1	2	3	4	5	TOT
TOTAL mistakes	8.36%	7.09%	6.96%	2%	21%	9.28%
No saccade made	0.75%	0.5%	0.34%	0.025%	0%	0.3%
Wrong Direction	5.9%	3.78%	3.38%	0.85%	6.11%	3.97%
Wrong saccadic amplitude	2.24%	3.67%	4.31%	1.64%	5.98%	3.61%
No fixation	1.97%	1.02%	0.44%	0.46%	13.48%	3.7%
Other kind	0.36%	3.6%	1.23%	0.15%	6.25%	3.98%

Table 1. Excluded behavioural mistakes in each experiment.
Percentage of excluded data for each experiment. Trials were excluded when one of the following mistakes happened: the participant made no saccade within the trial, the saccade was produced to the non-target location, the participants produced a saccade that was either too small or too large, the fixation was not held long enough and other kind of less frequent mistakes.

BLOCK	TOT	Pre- Test		Start	End	Test 1		Start	End	Test 2	
		VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
Experiment 1	4.84	7.05	8.28	3.38	3.6	4.49	5.04	3.6	4.83	5.38	3.6
Experiment 2	4.76	8.69	4.61	4.17	3.33	3.09	3.57	2.86	6.25	4.76	7.07
Experiment 3	5.51	4.66	4.27	13.45	3.33	0	0	13.83	0	7.14	7.38
Experiment 4	4.3	3.07	4.42	4.62	3.46	3.8	5.78	3.01	4.68	4.85	5.11
Experiment 5	6.36	7.50	13.44	0	5.53	5.47	14.95	0	0.85	1.72	7.55

Table 2 Percentages of outliers excluded for each experiment, in each experimental block.

2. 2. 3. 2 Experiments 1 to 5

Experiment 1

In order to analyse only the trials that yield consistent information, we excluded all behavioural mistakes from the data. As summarized in Table 1, they amounted to 8.36% of the total data, divided as follows: 0.75% with no saccade, 5.9% with a saccade in the wrong direction, 2.24% with a wrong amplitude, 1.97% with a wrong fixation, and 0.36% of other mistakes. Outlier detection (as described in the Methods) further excluded 4.84% of the data. Generally the same amount of outliers was found in each experimental block, with the only exception, as expected from a small novelty effect, of the pre-test blocks. (for specific data see Table 2). The accepted saccade gains ranged between 0.57 and 1.24. Moreover, we checked saccadic latencies. We expected longer latencies for voluntary than for reflexive saccade blocks, which was indeed the case as shown by the values in Table 3 (lower panel).

First of all, we were interested in knowing if the double step paradigm indeed led to adaptation. We therefore extracted the first and the last 25 trials from each adaptation block and calculated the saccadic gain. As shown in Figure 10A and in Table 3 (upper panel) we observed around 10% of gain reduction in the first adaptation phase, and around 8.5% in the second one (RA1: first 25 trials 1.01° ± 0.02°, last 25 trials: 0.91° ± 0.01° SEM; RA2: first 25 trials 0.94° ± 0.02°, last 25 trials: 0.86° ± 0.02°). Interestingly we also observed a small gain increase between the two adaptation phases (around 3%), indicating a fast decrease in adaptation due to the interleaving of two test blocks.

Secondly, we were interested in understanding the effect of these adaptation phases on both types of saccades. We were of course expecting a large effect on reflexive saccades, and a smaller effect on voluntary ones. Figure 10B shows the effect of adaptation on the saccadic gain in all test blocks. Before any type of experimental manipulation -measured in the Pre-Test blocks-, participants show orthometric saccades, with a gain close to 1, meaning the saccade has the same amplitude as the target step (Voluntary Pre-Test: 1.04° ± 0.01SEM; Reflexive Pre-Test: 1.05° ± 0.01 SEM), confirming that the oculomotor system was well calibrated and

able to produce orthometric saccades in all participants. After several trials of consistent inward stepping of the target, the gain started decreasing, as noticeable during the following test phases. As described in the Methods, during the test phases the second step of the target was not present, we however observed a decreased saccadic gain, showing that our participants started producing saccades aiming at the same position where the second target would appear in the adaptation phase. This effect can be seen both in the Test-1 and Test-2 and it is consistent during the whole experiment. (Voluntary Test-1: 0.96° ± 0.02 SEM; Reflexive Test-1: 0.97° ± 0.01 SEM; Voluntary Test-2: 0.94° ± 0.02 SEM; Reflexive Test-2: 0.94° ± 0.01 SEM).

An UREM indicated a variance of 0.0011 between participants and a variance of 0.0089 within participants for saccadic gain. This resulted in an ICC of 0.11, indicating the application of mixed regression analysis. The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < 0.001$). Moreover the analysis confirmed no significant differences between saccade types or any type of interaction between the adaptation paradigm and the saccade type (All values are shown in Table 4).

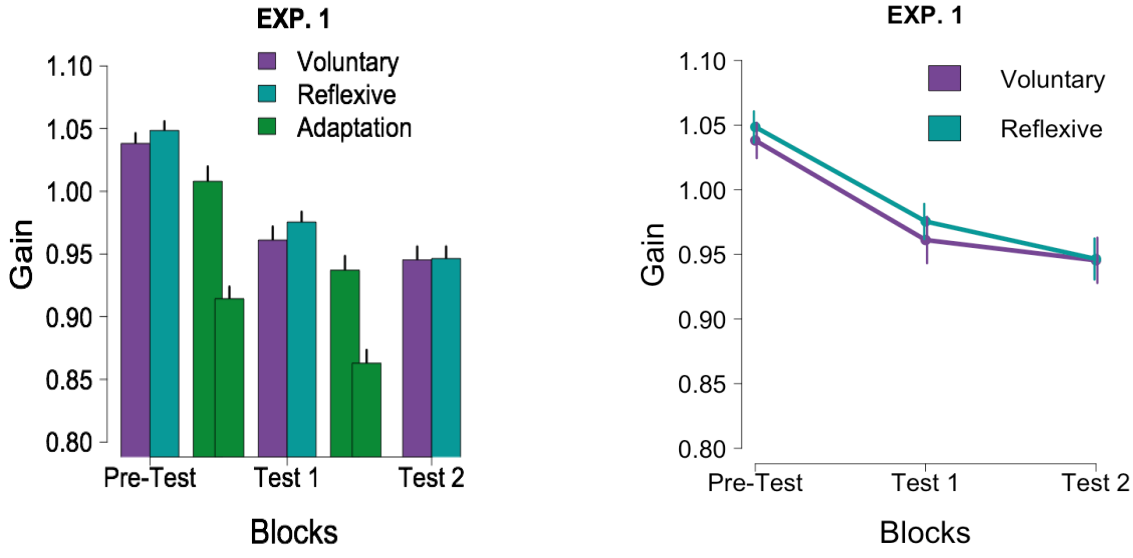


Figure 10. Mean (± MES) Saccadic Gain (Saccadic amplitude / Target step), in different test blocks. In purple VT, in light blue RT, in green RA blocks. Y axis starts at 0.8 to better see the saccadic gain differences.
(**Left panel)** Depiction of all experimental blocks. All trials contribute to the mean and SEM of the VT and RT blocks, while only the first and last 25 trials of the RA blocks are taken into account
(**Right panel)** Depiction of the test blocks (Pre-Test, Test 1, Test 2), both for RT and VT. Same data as in panel A

BLOCK	Pre- Test		Start	End	Test 1		Start	End	Test 2	
	VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
					Experiment 1 SACCADIC GAIN					
Mean	1.04	1.05	1.01	0.91	0.96	0.97	0.94	0.86	0.94	0.94
SEM	0.01	0.01	0.02	0.01	0.02	0.01	0.02	0.02	0.02	0.01
					SACCADIC LATENCIES (MS)					
Mean	207	160	144	141	213	156	142	144	215	164
SEM	17	10	7	4	18	7	7	8	15	9

Table 3. Saccadic Gain (upper panel) and Saccadic Latencies (lower panel). Mean and SEM averaged across participants for each test block. Chronologically ordered as presented during the experiment. Please note that VT and RT were interleaved in the same block, for clarity purposes in the analysis we consider them as two separate blocks, and arbitrarily start with VT. In the RA blocks, only the start and end of the trials are averaged (25 trials at the beginning and 25 trials at the end of the block).

	Estimate	**SE**	**df**	**t**	**p**
			Gain Experiment 1		
γ_{00}	1.05	0.01	7.26	68.52	**<0.001**
VS	-0.02	0.01	657.40	-1.42	0.155
Post-Test 1	-0.07	0.01	657.15	-7.28	**<0.001**
Post-Test 2	-0.11	0.01	657.28	-10.50	**<0.001**
VS x Post-Test 1	0.01	0.02	657.35	0.253	0.800
VS x Post-Test 2	0.020	0.016	657.55	1.227	0.220

Table 4 Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

Experiment 2

In order to analyse only the trials that yield consistent information, we excluded all behavioural mistakes from the data. As summarized in Table 1, they amounted to 7.09% of the total data, divided as follows: 0.5% in which participants made no saccade at all, 3.78% in which the produced a saccade in the wrong direction, 3.67% in which their first saccade was either smaller than 2° or bigger than 15°, 1.02% in which they could not hold the fixation until the targets appeared, and 3.6% in which we considered all other types of problems (which included blinking eye movements, movements of the head leading to recalibration, and so on). Outlier detection (as described in the Methods) further excluded 4.76% of the data. Generally the same amount of outliers was found in each experimental block (for specific data see Table 2). The accepted saccade gains ranged between 0.46 and 1.33. Moreover, we checked saccadic latencies. We expected longer latencies for voluntary than for reflexive saccade blocks, which was indeed the case as shown by the values in the lower panel of Table 5.

First of all, we were interested in knowing if the double step paradigm worked. We extracted the first and the last 25 trials from each adaptation block and checked the saccadic gain. As shown in Figure 11A and Table 5 (upper panel) we observed around 8% gain reduction in the first adaptation phase, and around 7% in the second (RA1: first 25 trials 0.94° ± 0.02°, last 25 trials: 0.84° ± 0.03° SEM; RA2: first 25 trials 0.87° ± 0.03°, last 25 trials: 0.81° ± 0.03°). Interestingly we also observed a small gain increase between the two adaptation phases (around 3%), indicating a fast decrease in adaptation due to the interleaving of two test blocks.

Secondly, we were interested in understanding the effect of these adaptation phases on both types of saccades. We were of course expecting a large effect on reflexive saccades, and a smaller effect on voluntary ones. Figure 11B shows the effect of adaptation on the saccadic gain in all test blocks. Before any type of experimental manipulation -measured in the Pre-Test blocks-, participants show orthometric saccades, with a gain close to 1, meaning the saccade has the same amplitude as the target step (Voluntary Pre-Test: 0.95° ± 0.03 SEM; Reflexive Pre-Test: 0.94° ± 0.02 SEM), confirming that the oculomotor system was well calibrated and able to produce orthometric saccades for all participants. After several trials of consistent

inward stepping of the target, the gain started decreasing, as noticeable during the following test phases. As described in the Methods, during the test phases the second step of the target was not present, we however observed a saccadic gain decrease, showing how our participants started producing saccades aiming at the same position where the second target would appear in the adaptation phase. This effect can be seen both in the Test-1 and Test-2 and it is consistent during the whole experiment. (Voluntary Test-1: 0.87° ± 0.03 SEM; Reflexive Test-1: 0.89° ± 0.03 SEM; Voluntary Test-2: 0.87° ± 0.03 SEM; Reflexive Test-2: 0.85° ± 0.03 SEM).

An UREM indicated a variance of 0.0034 between participants and a variance of 0.0165 within participants for saccadic gain. This resulted in an ICC of 0.17, indicating the application of mixed regression analysis. The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < .01$). Moreover the analysis confirmed no significant differences between saccade types or any type of interaction between the adaptation paradigm and the saccade type. (All values are shown in Table 6).

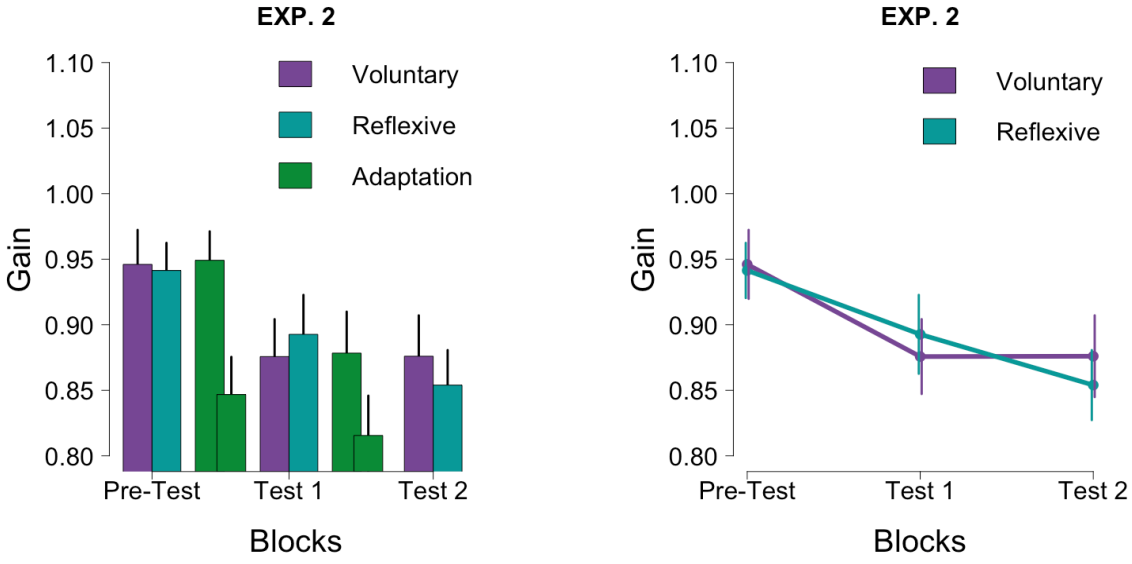


Figure 11. Mean (± MES) Saccadic Gain (Saccadic amplitude / Target step), in different test blocks.
In purple VT, in light blue RT, in green RA blocks
(**Left panel)** Depiction of all experimental blocks. All trials contribute to the mean and SEM of the VT and RT blocks, while only the first and last 25 trials of the RA blocks are taken into account.
(Right panel) Depiction of the test blocks (Pre-Test, Test 1, Test 2), both for RT and VT. Same data as in panel A.

BLOCK	Pre- Test		Start	End	Test 1		Start	End	Test 2	
	VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
Experiment 2 SACCADIC GAIN										
Mean	0.95	0.94	0.94	0.84	0.87	0.89	0.87	0.81	0.87	0.85
SEM	0.03	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03
SACCADIC LATENCIES (MS)										
Mean	360	242	141	134	358	238	151	138	363	234
SEM	39	28	7	6	51	25	15	5	40	27

Table 5. Saccadic Gain (upper panel) and Saccadic Latencies (lower panel). Mean and SEM averaged across participants for each test block. Chronologically ordered as presented during the experiment. Please note that VT and RT were interleaved in the same block, for clarity purposes in the analysis we consider them as two separate blocks, and arbitrarily start with VT. In the RA blocks, only the start and end of the trials are averaged (25 trials at the beginning and 25 trials at the end of the block).

	Estimate	SE	df	t	p
Gain Experiment 2					
γ_{00}	0.94	0.03	5.23	32.98	**<0.001**
VS	0.01	0.02	575.19	0.28	0.77592
Post-Test 1	-0.05	0.02	575.08	-3.13	**0.00186**
Post-Test 2	-0.09	0.02	575.4	-5.34	**<0.001**
VS x Post-Test 1	-0.02	0.02	575.10	-0.82	0.41099
VS x Post-Test 2	-0.02	0.03	575.11	0.99	0.31970

Table 6. Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

Experiment 3

In order to analyse only the trials that yield consistent information, we excluded all behavioural mistakes from the data. As summarized in Table 1, they amounted to 6.96% of the total data, divided as follows: 0.34% in which participants made no saccade at all, 3.38% in which the produced a saccade in the wrong direction, 4.31% in which their first saccade was either smaller than 2° or bigger than 15°, 0.44% in which they could not hold the fixation until the targets appeared, and 1.23% in which we considered all other types of problems (which included blinking eye movements, movements of the head leading to recalibration, and so on). Outlier detection (as described in the Methods) further excluded 5.51% of the data. Generally the same amount of outliers was found in each experimental block, with the exception of a higher number in the first adaptation trials and slight increase toward the end of the experiment (for specific data see Table 2). The accepted saccade gains ranged between 0.51 and 1.35. Moreover, we checked saccadic latencies. We expected longer latencies for voluntary than for reflexive saccade blocks, which was indeed the case as shown in Table 7 (lower panel).

First of all, we were interested in knowing if the double step paradigm worked, we therefore extracted the first and the last 25 trials from each adaptation block and checked the saccadic gain. As shown in Figure 12A and Table 7 (upper panel) we observed around 5.5% of gain reduction in both adaptation phases (RA1: first 25 trials 0.89° ± 0.02°, last 25 trials: 0.84° ± 0.01° SEM; RA2: first 25 trials 0.86° ± 0.02°, last 25 trials: 0.81° ± 0.02°). Interestingly we also observed a small gain increase between the two adaptation phases (around 2%), indicating a fast decrease in adaptation due to the interleaving of two test blocks.

Secondly, we were interested in understanding the effect of these adaptation phases on both types of saccades. We were of course expecting a large effect on reflexive saccades, and a smaller effect on voluntary ones. Figure 12B shows the effect of adaptation on the saccadic gain in all test blocks. Before any type of experimental manipulation -measured in the Pre-Test blocks-, participants show orthometric saccades, with a gain close to 1, meaning the saccade has the same amplitude as the target step (Voluntary Pre-Test: 0.96° ± 0.01 SEM; Reflexive

Pre-Test: 0.97° ± 0.02 SEM), confirming that the oculomotor system was well calibrated and able to produce orthometric saccades for all participants. After several trials of consistent inward stepping of the target, the gain started decreasing, as noticeable during the following test phases. As described in the Methods, during the test phases the second step of the target was not present, we however observed a saccadic gain decrease, showing how our participants started producing saccades aiming at the same position where the second target would appear in the adaptation phase. This effect can be seen both in the Test-1 and Test-2 and it is consistent during the whole experiment. (Voluntary Test-1: 0.93° ± 0.02 SEM; Reflexive Test-1: 0.91° ± 0.01 SEM; Voluntary Test-2: 0.92° ± 0.02 SEM; Reflexive Test-2: 0.85° ± 0.01 SEM).

An UREM indicated a variance of 0.0015 between participants and a variance of 0.0124 within participants for saccadic gain. This resulted in an ICC of 0.11, indicating the application of mixed regression analysis. The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < 0.001$) and a significant interaction between saccades type in the second Post-Test block ($p < 0.001$) . Moreover the analysis confirmed no significant differences between saccade types (All values are shown in Table 8).

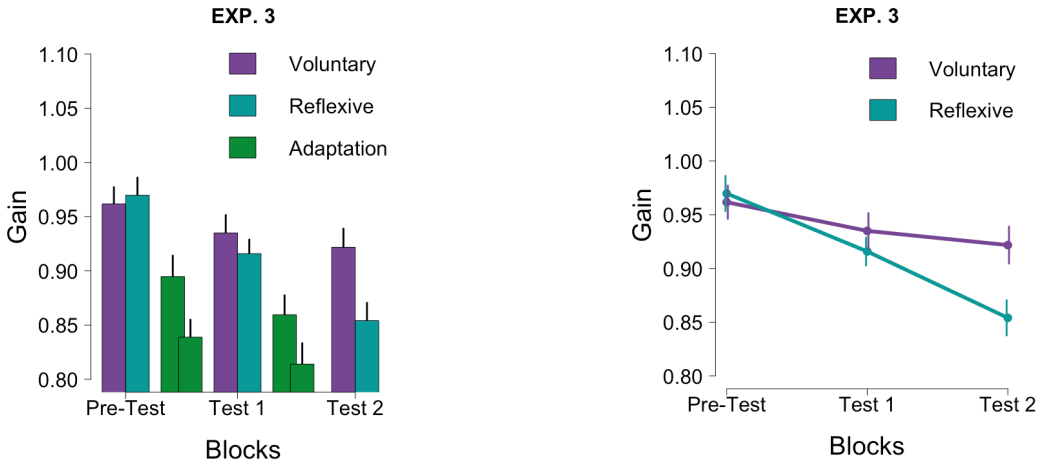


Figure 12. Mean (± MES) Saccadic Gain (Saccadic amplitude / Target step), in different test blocks.
In purple VT, in light blue RT, in green RA blocks
(Left panel) Depiction of all experimental blocks. All trials contribute to the mean and SEM of the VT and RT blocks, while only the first and last 25 trials of the RA blocks are taken into account.
(Right panel) Depiction of the test blocks (Pre-Test, Test 1, Test 2), both for RT and VT. Same data as in panel A.

BLOCK	Pre- Test		Start	End	Test 1		Start	End	Test 2	
	VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
Experiment 3 SACCADIC GAIN										
Mean	0.96	0.97	0.89	0.84	0.93	0.91	0.86	0.81	0.92	0.85
SEM	0.01	0.02	0.02	0.01	0.02	0.01	0.02	0.02	0.02	0.01
SACCADIC LATENCIES (MS)										
Mean	443	219	153	148	384	203	156	149	353	191
SEM	28	19	11	5	22	16	10	5	17	9

Table 7. Saccadic Gain (upper panel) and Saccadic Latencies (lower panel). Mean and SEM averaged across participants for each test block. Chronologically ordered as presented during the experiment. Please note that VT and RT were interleaved in the same block, for clarity purposes in the analysis we consider them as two separate blocks, and arbitrarily start with VT. In the RA blocks, only the start and end of the trials are averaged (25 trials at the beginning and 25 trials at the end of the block).

	Estimate	SE	df	t	p
Gain Experiment 3					
γ_{00}	0.97	0.02	10.05	59.53	**<0.001**
VS	-0.01	0.01	874.5	-0.63	0.525
Post-Test 1	-0.05	0.01	874.08	-4.43	**<0.001**
Post-Test 2	-0.11	0.01	874.59	-8.92	**<0.001**
VS x Post-Test 1	0.02	0.02	874.57	1.64	0.102
VS x Post-Test 2	0.07	0.02	874.67	4.04	**<0.001**

Table 8 Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

Experiment 4

In order to analyse only the trials that yield consistent information, we excluded all behavioural mistakes from the data. As summarized in Table 1, they amounted to 2% of the total data, divided as follows: 0.025% in which participants made no saccade at all, 0.85% in which they produced a saccade in the wrong direction, 1.64% in which their first saccade was either smaller than 2° or bigger than 15°, 0.46% in which they could not hold the fixation until the targets appeared, and 0.15% in which we considered all other types of problems (which included eye blinks, movements of the head leading to recalibration, and so on). Outlier detection (as described in the Methods) further excluded 4.3% of the data. Generally the same amount of outliers was found in each experimental block (for specific data see Table 2). The accepted saccade gains ranged between 0.55 and 1.28. Moreover, we checked saccadic latencies. We expected longer latencies for voluntary than for reflexive saccade blocks, which was indeed the case as shown by the values in the lower panel of Table 9.

First of all, we were interested in knowing if the double step paradigm worked, we therefore extracted the first and the last 25 trials from each adaptation block and checked the saccadic gain. As shown in Figure 13A and Table 9 (upper panel) we observed around 8.5% of gain reduction in the first adaptation phase, and around 3.5% in the second (RA1: first 25 trials 0.95° ± 0.01°, last 25 trials: 0.87° ± 0.01° SEM; RA2: first 25 trials 0.86° ± 0.01°, last 25 trials: 0.83° ± 0.01°). Interestingly in this experiment we did not find any differences between the two adaptation phases, indicating no decrease in adaptation between the two phases.

Secondly, we were interested in understanding the effect of these adaptation phases on both types of saccades. We were of course expecting a large effect on reflexive saccades, and a smaller effect on voluntary ones. Figure 13B shows the effect of adaptation on the saccadic gain in all test blocks. Before any type of experimental manipulation -measured in the Pre-Test blocks-, participants show orthometric saccades, with a gain close to 1, meaning the saccade has the same amplitude as the target step (Voluntary Pre-Test: 0.94° ± 0.01SEM; Reflexive Pre-Test: 0.96° ± 0.01 SEM), confirming that the oculomotor system was well calibrated and

able to produce orthometric saccades for all participants. After several trials of consistent inward stepping of the target, the gain started decreasing, as noticeable during the following test phases. As described in the Methods, during the test phases the second step of the target was not present, we however observed a saccadic gain decrease, showing how our participants started producing saccades aiming at the same position where the second target would appear in the adaptation phase. This effect can be seen both in the Test-1 and Test-2 and it is consistent during the whole experiment. (Voluntary Test-1: 0.9° ± 0.01 SEM; Reflexive Test-1: 0.9° ± 0.01 SEM; Voluntary Test-2: 0.9° ± 0.01 SEM; Reflexive Test-2: 0.88° ± 0.01 SEM).

An UREM indicated a variance of 0.0031 between participants and a variance of 0.0076 within participants for saccadic gain. This resulted in an ICC of 0.29, indicating the application of mixed regression analysis. The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < 0.001$), of the saccade type ($p < 0.005$) and a significant interaction between saccade type and the effect of adaptation over time in both test blocks (all $p < 0.005$). (All values are shown in Table 10).

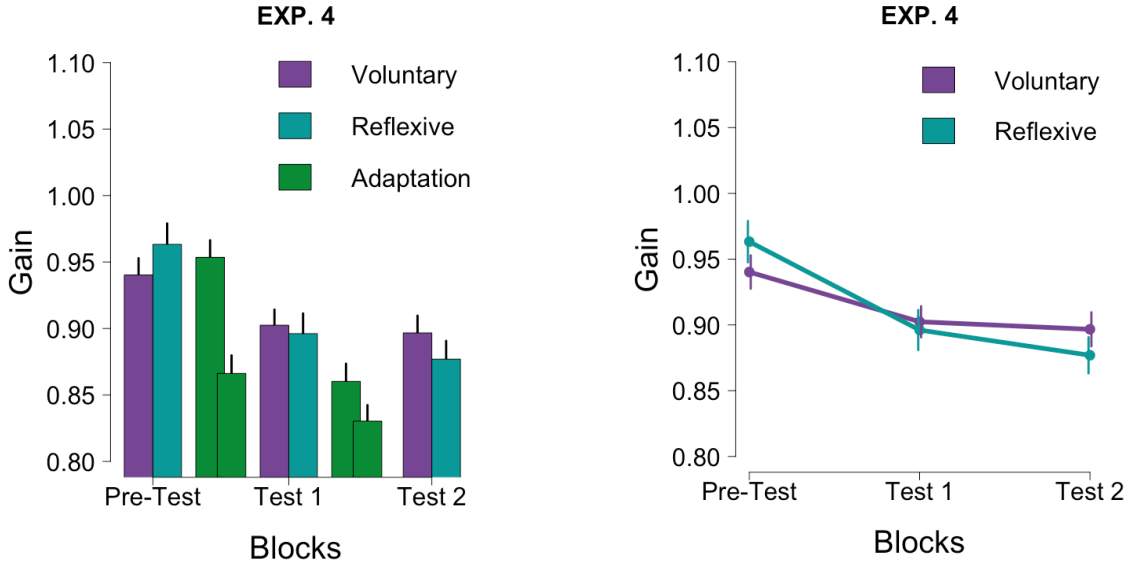


Figure 13. Mean (± MES) Saccadic Gain (Saccadic amplitude / Target step), in different test blocks.
In purple VT, in light blue RT, in green RA blocks
(Left panel) Depiction of all experimental blocks. All trials contribute to the mean and SEM of the VT and RT blocks, while only the first and last 25 trials of the RA blocks are taken into account.
(Right panel) Depiction of the test blocks (Pre-Test, Test 1, Test 2), both for RT and VT. Same data as in panel A.

BLOCK	Pre- Test		Start	End	Test 1		Start	End	Test 2	
	VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
Experiment 4 SACCADIC GAIN										
Mean	0.94	0.96	0.95	0.87	0.9	0.9	0.86	0.83	0.9	0.88
SEM	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
SACCADIC LATENCIES (MS)										
Mean	313	270	147	138	311	261	149	142	302	281
SEM	23	13	8	5	31	14	6	4	26	16

Table 9. Saccadic Gain (upper panel) and Saccadic Latencies (lower panel). Mean and SEM averaged across participants for each test block. Chronologically ordered as presented during the experiment. Please note that VT and RT were interleaved in the same block, for clarity purposes in the analysis we consider them as two separate blocks, and arbitrarily start with VT. In the RA blocks, only the start and end of the trials are averaged (25 trials at the beginning and 25 trials at the end of the block).

	Estimate	SE	df	t	p
Gain Experiment 4					
γ_{00}	0.96	0.02	6.84	43.7	**<0.001**
VS	-0.03	0.01	961.27	-3.015	0.003
Post-Test 1	-0.07	0.01	961.2	-8.2	**<0.001**
Post-Test 2	-0.09	0.01	961.16	-10.1	**<0.001**
VS x Post-Test 1	0.04	0.01	961.34	3.23	**0.001**
VS x Post-Test 2	0.05	0.01	961.31	3.98	**<0.001**

Table 10. Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

Experiment 5

In order to analyse only the trials that yield consistent information, we excluded all behavioural mistakes from the data. As summarized in Table 1, they amounted to 21% of the total data, divided as follows: 0% in which participants made no saccade at all, 6.11% in which the produced a saccade in the wrong direction, 5.98% in which their first saccade was either smaller than 2° or bigger than 15°, 13.48% in which they could not hold the fixation until the targets appeared, and 6.25% in which we considered all other types of problems (which included blinking eye movements, movements of the head leading to recalibration, and so on). Outlier detection (as described in the Methods) further excluded 6.36% of the data. Generally the same amount of outliers was found in each experimental block (for specific data see Table 2). The accepted saccade gains ranged between 0.38 and 1.5. Moreover, we checked saccadic latencies. We expected longer latencies for voluntary than for reflexive saccade blocks, which was indeed the case as shown by the values in the lower panel of Table 11.

First of all, we were interested in knowing if the double step paradigm worked, we therefore extracted the first and the last 25 trials from each adaptation block and checked the saccadic gain. As shown in Figure 14A and Table 11 (upper panel) we observed around 8% of gain reduction in the first adaptation phase, and around 5% in the second (RA1: first 25 trials 0.97° ± 0.02°, last 25 trials: 0.89° ± 0.02° SEM; RA2: first 25 trials 0.89° ± 0.02°, last 25 trials: 0.85° ± 0.02°). Interestingly in this experiment we did not find any differences between the two adaptation phases, indicating no decrease in adaptation between them.

Secondly, we were interested in understanding the effect of these adaptation phases on both types of saccades. We were of course expecting a large effect on reflexive saccades, and a smaller effect on voluntary ones. Figure 14B shows the effect of adaptation on the saccadic gain in all test blocks. Before any type of experimental manipulation -measured in the Pre-Test blocks-, participants show orthometric saccades, with a gain close to 1, meaning the saccade has the same amplitude as the target step (Voluntary Pre-Test: 0.94° ± 0.03 SEM; Reflexive Pre-Test: 0.96° ± 0.02 SEM), confirming that the oculomotor system was well calibrated and able to produce orthometric saccades for all participants. After several trials of consistent

inward stepping of the target, the gain started decreasing, as noticeable during the following test phases. As described in the Methods, during the test phases the second step of the target was not present, we however observed a saccadic gain decrease, showing how our participants started producing saccades aiming at the same position where the second target would appear in the adaptation phase. This effect can be seen both in the Test-1 and Test-2 and it is consistent during the whole experiment. (Voluntary Test-1: 0.9° ± 0.03 SEM; Reflexive Test-1: 0.87° ± 0.02 SEM; Voluntary Test-2: 0.9° ± 0.03 SEM; Reflexive Test-2: 0.86° ± 0.01 SEM).

An UREM indicated a variance of 0.0003 between participants and a variance of 0.0179 within participants for saccadic gain. This resulted in an ICC of 0.01, indicating the application of mixed regression analysis. The linear mixed growth analysis confirmed the significance of the overall effect of adaptation over time on each Post-Test block (all $p < 0.001$) and a significant interaction between saccade type and the effect of adaptation over time in both test blocks (all $p < 0.05$). Moreover the analysis confirmed no significant differences between saccade types (All values are shown in Table 12).

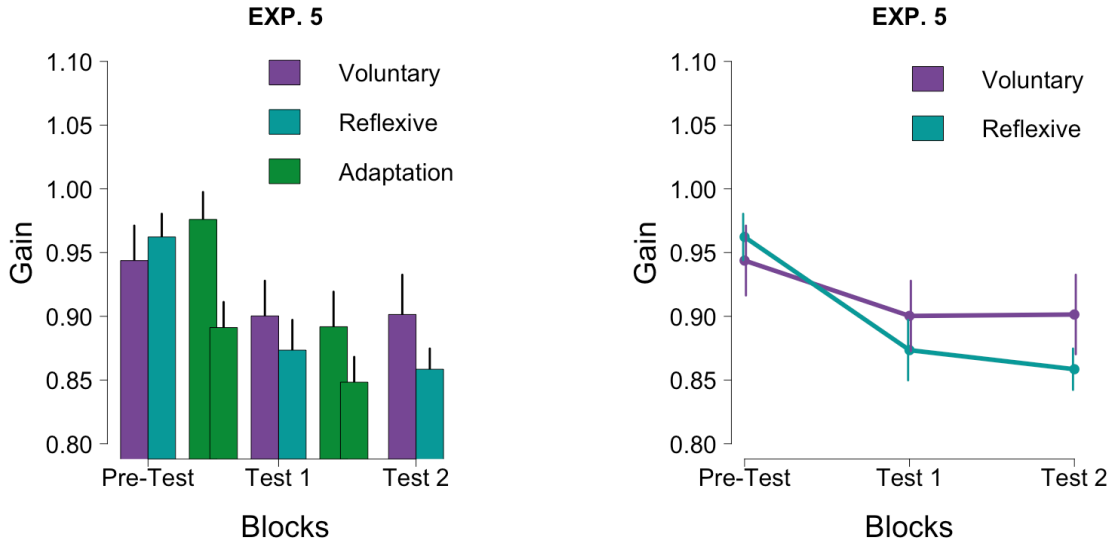


Figure 14. Mean (± MES) Saccadic Gain (Saccadic amplitude / Target step), in different test blocks.
In purple VT, in light blue RT, in green RA blocks
(Left panel) Depiction of all experimental blocks. All trials contribute to the mean and SEM of the VT and RT blocks, while only the first and last 25 trials of the RA blocks are taken into account.
(Right panel) Depiction of the test blocks (Pre-Test, Test 1, Test 2), both for RT and VT. Same data as in panel A.

BLOCK	Pre- Test		Start	End	Test 1		Start	End	Test 2	
	VT	RT	RA	RA	VT	RT	RA	RA	VT	RT
Experiment 5 SACCADIC GAIN										
Mean	0.94	0.96	0.97	0.89	0.9	0.87	0.89	0.85	0.9	0.86
SEM	0.03	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03	0.01
SACCADIC LATENCIES (MS)										
Mean	370	200	157	162	411	191	149	159	4332	201
SEM	45	20	8	5	78	12	7	9	55	17

Table 11. Saccadic Gain (upper panel) and Saccadic Latencies (lower panel). Mean and SEM averaged across participants for each test block. Chronologically ordered as presented during the experiment. Please note that VT and RT were interleaved in the same block, for clarity purposes in the analysis we consider them as two separate blocks, and arbitrarily start with VT. In the RA blocks, only the start and end of the trials are averaged (25 trials at the beginning and 25 trials at the end of the block).

	Estimate	SE	df	t	p
Gain Experiment 5					
γ_{00}	0.962	0.01	38.29	69.53	**<0.001**
VS	-0.02	0.01	1040.05	-1-23	0.21731
Post-Test 1	-0.09	0.02	1040.05	-4.85	**<0.001**
Post-Test 2	-0.1	0.02	1041.4	-5.68	**<0.001**
VS x Post-Test 1	0.043	0.02	1041.57	1.99	0.04633
VS x Post-Test 2	0.06	0.02	1042.9	2.68	0.00737

Table 12. Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

2. 2. 3. 3 Transfer Analysis

As described in the previous sections, while we observed a stable reduction of saccadic gain in the Post-Tests for reflexive saccades, we noticed quite a wide range of saccadic gain reduction for voluntary saccades. To better understand the origin of these differences we analysed the transfer rate across experiments.

We first calculated the effect of adaptation on both types of saccades separately, as the mean difference between Test 2 and Pre-Test divided by Pre-Test. We then calculated the transfer rate between voluntary and reflexive saccades by dividing the effect of adaptation on voluntary and reflexive saccades (See Methods for formulas). As shown in Figure 15 and Table 13, the transfer rates between experiments amply varied. A decrease in transfer rate between experiments was observed, from experiment 1 to 5 (detailed values in Table 13).

To understand what factors contributed to those differences, we ran a linear mixed growth analysis on the transfer rate between voluntary and reflexive saccades. As shown in Table 14, the analysis confirmed a statistical significant main effect of the overlapping of the fixation, specifically finding a difference between experiments in the Overlap condition ($p < 0.05$), while no effect of Instruction was found significant.

We also ran a second linear mixed model analysis on the transfer rate depending on experiment number (see Methods). Experiment 5 was taken as the baseline. Interestingly we found a significant difference only for Experiment 1 ($p < 0.0.5$), and a trend for Experiment 2 ($p = 0.09$), while Experiments 3 and 4 showed no significant difference. (All values are shown in Table 14).

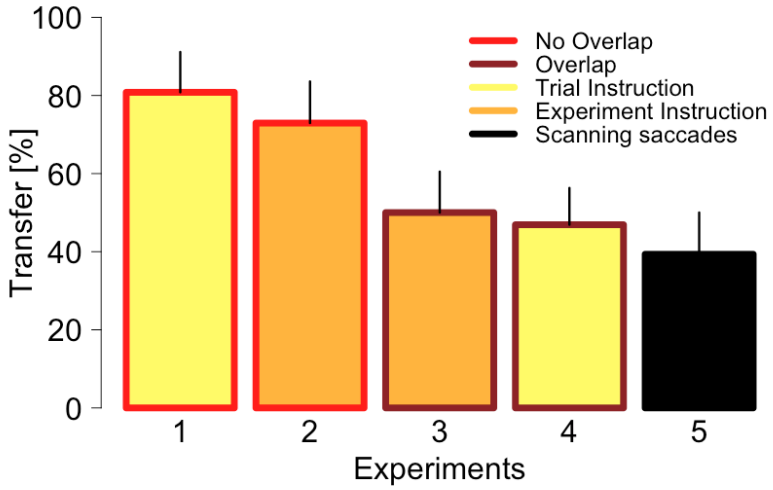


Figure 15. Mean (± MES) Transfer percentages between RT and VT in the five experiments.
Overlap is depicted through border colors: red for No-Overlap conditions (Exp 1 and 2), brown for Overlap condition (Exp 3 and 4). Instruction is depicted through the color of the bar filling: yellow for Trial Instruction conditions (Exp 1 and 4), orange for Experiment Instruction condition (Exp 2 and 3). Experiment 5, the scanning saccade experiment, is depicted with black borders and no filling. This experiment served as a baseline.

Experiment	**1**	**2**	**3**	**4**	**5**
Design	**Overlap** **Trial Instruction**	**Overlap** **Experiment Instruction**	**No overlap** **Experiment Instruction**	**No overlap** **Trial Instruction**	**Control**
			Transfer		
Mean	80.81	72.94	50.02	46.90	39.34
SEM	10.32	10.65	10.47	9.42	10.68

Table 13. Mean and SEM Transfer percentages in the five experiments.

	Estimate	SE	df	t	p
Transfer Analysis					
Effect of Overlap					
γ_{00}	37.21	14.05	23.25	2.65	**0.0143**
No Overlap	11.29	16.19	16.86	0.7	0.4951
Overlap	39.87	17.15	24.29	2.32	**0.0288**
Effect of Instruction					
γ_{00}	39.44	15.16	24.34	2.6	**0.0156**
Trial- instruction	16.51	18.22	24.8	0.91	0.3736
Experiment- Instruction	27.84	17.71	20.54	1.57	0.1312
Effect of Experiment					
γ_{00}	37.14	14.51	20.5	2.56	**0.0184**
Exp 1	42.53	19.68	20.92	2.16	**0.0424**
Exp 2	36.76	20.20	16.02	1.82	0.0875
Exp 3	18.21	19.03	7.6	0.96	0.37
Exp 4	6.31	19.05	21.25	0.33	0.74

Table 14. Quantitative results of the linear mixed growth analysis of the saccadic gain change during the adaptation paradigm.
Estimate= estimate parameter value. SE= standard error of the parameter estimate. df= degrees of freedom. t= t-value. p= probability of committing a Type-I-error. γ_{00}= intercept of the linear regression. In bold statistically significant results.

2. 2. 4 Discussion

The present study introduces a new way of investigating gain adaptation transfer between reflexive and voluntary saccades. In order to draw conclusions about the parameters that define voluntary saccades, we used a standard paradigm to elicit voluntary saccades in all experiments and decided to manipulate only the instruction given to the participants and the

timing of target appearance, instead of using different types of voluntary saccades as previously done (for a review see Hopp & Fuchs, 2004; Pélisson et al., 2010).

We were mainly interested in two types of analysis: (1) the amount of transfer between RS and VS within each experiment and (2) the comparison across the observed transfer rates in each experiment. The analysis of each experiment confirmed that the adaptation paradigm worked well in all experiments: after adapting reflexive saccades we observed in all five experiments a reduction in saccadic gain affecting mainly reflexive saccades and, to a smaller degree, voluntary saccades. These results are in line with previous literature (Alahyane et al., 2007; Alahyane et al. 2008; Deubel, 1995; Deubel, 1999; Fujita et al., 2002; Gaveau et al., 2005). As discussed in the Introduction Section these previous studies showed different profile patterns in the amount of adaptation transfer, varying from no/little transfer (Deubel, 1995; Deubel, 1999), to a more consistent one (Fujita et al., 2002). Resolving this apparent contradiction was one of the focuses of this study.

One of our hypotheses relied on the idea that it is probably too naive to consider reflexive and voluntary saccades as two completely different movements. A large amount of literature supports the idea that these types of saccade rely on both common and separate cerebral pathways: a faster lower-level pathway for both reflexive and voluntary saccades, and two specialised pathways in higher cortical areas, mainly involving parietal regions for reflexive saccades and frontal ones for voluntary saccades (Pierrot-Deseilligny et al., 1991; Leigh & Zee, 2015). It is therefore possible that within the voluntary saccade category, some parameters can be identified as more or less voluntary, possibly involving differently higher cortex areas, suggesting the need to upgrade the old dichotomy between voluntary and reflexive saccades into a more continuous frame of reference, based both on behavioural parameters and involvement of different brain areas.

Interestingly we first noticed a difference between the five experiments when considering one condition, namely Overlap, the timing of appearance of the target(s). In addition to the abovementioned effect of the adaptation paradigm, we observed a significant interaction between the final post-test and the saccade type when the fixation cross and the

target were simultaneously present on the screen. This result indicates that only in the Overlap condition adaptation had a differential role depending on whether the elicited saccade was voluntary or reflexive. Interestingly the same pattern of results was shown in the scanning saccade experiment.

We therefore compared the results between all five experiments to find out (1) whether the target appearance timing did play a role, and (2) where the observed differences in transfer rate might originate. We observed, as expected, a low transfer rate in the case of the scanning saccade experiment (our baseline) and an increase in the other experiments. Statistically the Overlap factor (the timing of appearance of fixation and target(s)) did have a significant effect, while the Instruction factor (the instructions given to the participants) did not. This is interesting in defining which parameters can define a voluntary saccade in contrast to a reflexive one. The lower amount of transfer in experiments in which the target and the fixation were present simultaneously on the screen indicates that this can be a parameter worth using to define this difference. On the opposite end the varying of instructions between trials do not seem to make a difference between experiments.

We therefore think this line of research should be continued in trying to identify better experimental definitions when researching voluntary saccades and this study should be seen as a first step in that direction. We are aware about the need to find more parameters to discriminate between voluntary and reflexive saccades.

The study of saccadic transfer between different saccade types has been a useful tool for investigating the possible site(s) of adaptation in the brain, as mentioned in the Introduction. Our data supports the idea of a complex interaction between reflexive and voluntary saccade systems in the brain. If on one hand our findings that show a substantial difference in transfer between reflexive and voluntary saccades is in line with the generally accepted idea of separate mechanisms of saccadic metrical recalibration in the brain (Alahyane et al. 2007; Deubel, 1995; Deubel, 1999; Péllisson et al., 2010; Straube et al., 1995), they also suggest that this mechanism may not be as independent as often described and that voluntary and reflexive saccades might best be described as a continuum rather than as a dichotomy.

Early studies on monkeys identified the cerebellum, specifically the vermis and the fastigial nuclei, as responsible for maintaining saccadic metrical accuracy, in the case of reflexive saccades (Optican & Robinson, 1980; Soetedjo et al, 2019, Shadmehr, 2017; Vilis et al., 1983). The same cerebellar involvement has been found in human studies (Barash et al., 1999; Colnaghi et al., 201; Desmurget et al., 1998; Jenkinson & Miall, 2010; Straube et al., 2001; Takagi et al., 1998). Human studies also showed a role of the parietal cortex in adaptation of voluntary saccades (Cotti et al. 2007, Cotti et al., 2009; Gerardin et al. 2012; Panouillères et al., 2014), and an involvement of the lateral cerebellum was also found (Alahyane et al. 2008; Panouillères et al., 2012; Panouillères et al., 2013). Even though our behavioural data cannot directly argue for any specific neural area involved in saccadic adaptation, it is in line with those findings, by showing a modulating influence of the transfer rate between different amounts of "voluntariness" of the task. We therefore might assume a higher or lower involvement of different neural areas depending on the task itself. However, in order to draw stronger conclusions, it would be necessary to run similar experiments in the opposite direction, i.e. analysing the transfer of adaptation between our manipulated voluntary saccades on reflexive saccades. This would give us a better idea about the level of (a)symmetry in the adaptation pattern.

We need however to also note that a more controlled design would be advantageous in running this set of experiments. Even though we were able, thanks to our statistical analysis, to account for participant variability, in the ideal case we should run these five experiments using the same participants in all of them. It is also to be noted that more data would be necessary in order to analyse the interaction effects that we could not compute.

Altogether, we believe this study is particularly interesting in opening a new way of investigating the definition of different saccade types. Instead of only extremising their differences it would be very helpful to consider them as lying on a continuous frame, by updating this old naive dichotomy. We believe this interpretation can prove to be very intriguing especially when looking for cerebral sites of adaptation in the brain.

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3. General Discussion

This thesis investigates the oculomotor mechanisms that mediate our ability to properly move our eyes and thus perceive the visual world around us. One of the most astonishing abilities of the oculomotor system is its capability of repairing itself in the face of consistent behavioural mistakes arising from physiological or pathological changes in the oculomotor system itself. Adaptive mechanisms are in charge of detecting systematic motor performance errors and updating the motor commands to (1) precisely foveate intended visual targets, referred to as metricity, and (2) keep the targets on the fovea for the necessary time to collect visual information, referred to as dynamics.

Dynamical and metrical adaptive mechanisms have been separately investigated in Chapter 2. 1 *"Adaptation of Post-Saccadic Drift in Reflexive Saccades Transfers Only Partially to Voluntary Saccades"* and in Chapter 2. 2 "*Updating the Dichotomy of Reflexive and Voluntary Saccades",* but these mechanisms are far from being separate and independent. In this chapter we will discuss their commonalities and address their specificities.

3. 1 Inducing PSD and Gain Adaptation in Humans

As discussed in Chapter 1. 4, two inputs need to be sent to the oculomotor muscles in order to produce accurate and precise saccades. One input - the pulse of innervation - serves to move the eyes as far as intended, the other - the step of innervation - is able to hold the eye still in fixation. The production of the pulse-step of innervation happens in the brainstem, at the level of the paramedian pontine reticular formation (PPRF) for horizontal saccades, and of the rostral interstitial nucleus of medial longitudinal fasciculus (RIMLF) for vertical saccades (for reviews see Krauzlis, 2008; Sparks, 2002). Furthermore, a mismatch between the pulse and step components of innervation produces dysmetric saccades and/or post-saccadic drifts (Bahill et al. 1975; Bahill et al. 1978). Given the existence of these mechanisms, it was consequential to first investigate whether the adaptive mechanisms able to correct such mismatches could be found in humans (especially for PSD where less research on humans has been done) and secondly whether they could reside at the level of the brainstem as a simple mismatch of the pulse-step innervation.

Our studies showed how a proper adaptation paradigm could induce PSD and gain adaptation in humans. In the first study (Chapter 2. 1) we induced PSD by mimicking its retinal consequences through a consistent outward shift of the target at the end of each saccade. Participants were able to detect this error and to compensate for it. Before the adaptation blocks we observed PSD values very close to zero. This is consistent with the ability to abruptly end saccades and hold them in position, minimising retinal slip. The effects of the PSD adaptation started to emerge already after 80 trials, after which participants developed a compensatory exponential drift, shown by higher PSD drift values during the first and consequent open loop test phases. This behaviour was necessary in order to minimise the retinal slip induced by the drift and keep the target on the fovea. Previous work established the possibility to induce PSD adaptation in humans (Deubel, 1991; Kapoula et al., 1989). However, our study confirmed that a single target drift at the end of the saccade is a better stimulus for inducing this type of adaptation. In line with Deubel (1991), who used the same type of stimulus, we were able to induce adaptation within 800 trials, while in the experiment by Kapoula (1989), using full-field shifts, around 10000-20000 trials were necessary.

The same pattern of results described above for PSD was evident with respect to gain adaptation (Chapter 2. 2). We induced metrical adaptation with the use of the double step paradigm *(*Deubel et al., 1986; McLaughlin, 1967; Miller et al., 1981*),* by displacing the target inward during the execution of a saccade. Similar to what described for PSD, before the adaptation we observed orthometric saccades, and only after the adaptation manipulation we detected a reduction in saccadic gain in all experiments, reflecting the participants' ability to correct what is perceived to be a saccadic error and to recalibrate the oculomotor system in order to produce the desired saccadic amplitude. These findings are in line with many studies, for reviews see Hopp & Fuchs (2002), Pélisson et al. (2010), Soetedjo et al., (2019).

It is important to consider whether the same mechanisms are in play when inducing PSD and gain adaptation (for reviews on gain adaptation see Hopp & Fuchs (2002), Pélisson et al. (2010), Soetedjo et al., (2019), for PSD adaptation Optican & Miles, 1985; Leigh & Zee, 2015), and the adaptive processes involved after lesion studies (Optican & Robinson, 1980; Zee et al., 1981; Optican et al., 1986). The main difference between these processes lies in the time

needed for adaptation to be complete. Induced adaptation (via the double step paradigm or the consistent exponential shift of the target) is very fast (20-30 minutes), while adaptation to peripheral muscle ablation takes considerably longer (hours or days). Scudder et al., 1998 checked whether this difference could arise from the fact that testing after lesions has historically been done while performing saccades of different amplitudes in different directions (adapting many vectors simultaneously). This was indeed the case, as the authors found very similar time courses of gain adaptation when they exposed monkeys to the same number of saccadic vectors in both paradigms. This is the main evidence for using adaptation inducing paradigms to study adaptive mechanisms in humans.

Taken together, these results indicate that healthy humans are unsurprisingly able to produce precise and accurate saccades. Moreover, Munoz et al. (1998) showed how the saccadic system remains relatively stable in its metrics and dynamics over the lifespan, testing 168 subjects between 5 and 79 years of age. Interestingly, however, for both PSD and saccadic gain we observed a very fast adaptation to the shifting (PSD), and the stepping of the visual target stimulus (gain adaptation). In both cases participants produce a different saccadic behaviour within a few trials, showing a flexible and responsive reaction of the oculomotor system. Its priority seems to be producing saccades that are utilitaristically helpful in collecting visual information, which in these specific cases means lowering the saccadic gain to land on the final target position (Chapter 2. 2) and to produce PSD in order to keep the moving target foveated (Chapter 2. 1).

3. 2 Adaptive Mechanisms, Reflexive and Voluntary Saccades

For the purposes of this chapter it is important to mention again the distinction between reflexive saccades and voluntary saccades. These types of saccades have historically been distinguished by the way they are elicited and by their latencies: reflexive saccades occur spontaneously in response to a sudden appearing visual stimulus and have latencies of about 150 - 200 ms, while voluntary saccades are elicited by internal goals and motivations and their latencies range around 200 - 250 ms (Deubel, 1999; Gaymard et al., 1998; Hopp & Fuchs, 2004; Pélisson et al., 2010; Tusa et al., 1986). The neural pathways underlying the production of

RS and VS share some degree of commonalities and specialisation, with the general finding of higher cortical areas being more specific to a single saccade class, while subcortical areas being involved in the production of all saccade types (see Section 1. 5). With this in mind two possibilities seem feasible: the existence of separate adaptation mechanisms involved in the recalibration of each saccade type at a different stage in the neural processing of saccades or a common adaptation mechanism acting at a single locus on the final common pathway of saccadic generation. Inducing adaptation on one saccade type and testing its effect on the other saccade type, called transfer of adaptation, is a useful tool to determine which hypothesis is closer to the real functioning of adaptive mechanisms. A complete and symmetrical transfer between different saccade types (after only one of them underwent the adaptation procedure) would indicate the adaptation locus being after the convergence of all neural pathways, while a partial or null transfer of adaptation would argue for the involvement of saccade type specific sites in the brain.

While no previous research has been done on the transfer of adaptation between different saccade types for PSD, the topic has been widely investigated in the case of gain adaptation. Our study, described in Chapter 2. 1, was indeed the first one to tackle the question whether PSD adaptation on RS would also transfer to VS. As discussed, this question is particularly relevant in trying to understand the properties of dynamic adaptation and its neural substrates. To this end we adapted RS and tested both RS and VS in an open loop test condition at the end of the experiment. While we observed a full adaptation effect for RS (reflected by a 94% transfer between RS post-test and RS pre-test), the transfer from RS to VS amounted to 68%. Furthermore, the statistical analysis gave us an important insight: there was no significant difference between saccade types when not taking the effect of the adaptation paradigm into account. This important result leads us to conclude that only the learning effect of adaptation differentiates between saccade types, meaning that we have no reason to conclude that the different types of saccades have any real behavioural difference in our experiment besides from how they are affected by the PSD adaptation.

As mentioned, in contrast to PSD, many studies investigated the transfer between RS and VS concerning gain adaptation. However, previous literature describes somewhat

conflicting results on the amount of transfer between RS and VS (for a review see Hopp & Fuchs, 2002, in particular Table 1). We were interested in disambiguating these results and understanding why they might have originated. To this end we induced adaptation through the double step paradigm in RS and tested VS in five different experiments. What differentiated each experiment and our work from previous studies, was the way we manipulated VS. Instead of using different types of voluntary saccades like previously done (Alahyane et al., 2008; Deubel, 1995; Deubel, 1999; Fujita et al., 2002; Hopp & Fuchs, 2010), we used a more comparable manipulation of VS that can be described by two axes: experimental instructions to the participants (Instruction) and the timing of appearance of fixation and target(s) (Overlap). This allowed us to uncover different rates of adaptation transfers between RS and VS depending on the degree of "voluntariness" of the saccade type. We observed different degrees of adaptation transfer from RS to VS in our experiments, ranging from 39% transfer in the case of scanning saccades (considered as our baseline for VS), to 80% transfer in our less voluntary definition of VS, passing by 47%, 50% and 72% in the other experiments. In trying to understand these differences we discovered that the instructions given to the participants did not play any role in defining the differences between transfer rates of adaptation. However, we found an important effect of the timing of target(s) appearance, as the simultaneous presence of visual fixation and targets lead to lower amount of transfer adaptation. Overall we observed a lower transfer rate in more "voluntary" conditions, which might be due to varying degrees of involvement of specific saccade type brain regions depending on the experiment. We therefore propose a revision of the differential definition of VS and RS, by switching from the old used dichotomy to a continuous frame of reference. We also propose to further this way of investigating what defines a voluntary saccade by testing more quantifiable factors. This method would lead to a better understanding of the saccade system and could help quantify the difference between different saccade types.

3. 3 Neural Mechanisms of Saccadic Adaptation

Which cerebral mechanism could be involved in the dynamical and metrical adaptive mechanisms, in particular, could this system recalibration be exclusively accounted for by a simple mechanism in the brainstem? Our results showed that RS and VS were not affected

equally by our adaptation manipulation, arguing against an exclusive role of the brainstem both for PSD and metrical adaptation. Previous work on primates had already pointed away from the brainstem by showing a role of the cerebellum in this mechanism, more specifically indicating the oculomotor vermis for the metrical control, and the flocculus for the dynamical control of saccades (Optican & Robinson, 1980; Shadmehr, 2017). PSD was also shown to be induced outside the brainstem regions in one previous study on humans (Deubel, 1991). The brainstem is known to be the final stage in saccade production, and it is known to have the same mechanisms and involvement in the programming of all saccade types (for a review see Sparks, 2002). If adaptive mechanisms were limited to the level of the brainstem, with a simple mismatch of the pulse-step innervation we would observe the same level of adaptation in the open loop post-test conditions both for RS and VS. The fact that in both PSD and gain adaptation the percentage of adaptation in VS is lower than in RS is further evidence of a mechanism that resides upstream from the brainstem, where the neural pathways for VS and RS separate.

It is important to note that our studies are behavioural and it is therefore only possible to argue on a theoretical level about the brain structures involved in adaptive mechanisms for PSD and metricity. They nevertheless revealed some important insights that may be helpful for future work to further investigate this topic at the neurophysiological level. Our data on both PSD and gain adaptation shows different rates of adaptation in different saccade classes after the adaptation procedure, which is in line with different hypotheses based on the idea of different loci of adaptation being involved.

One possibility is to imagine a specific locus of adaptation for each saccade type at a different neural computational stage, i.e. a specific locus of adaptation at a neural level that is not shared by the other saccade type. This type of model has been proposed by Deubel (1999) in the context of saccadic gain adaptation. The model assumes the existence of three loci of adaptation, one for reflexive saccades in the collicular pathway (downstream from the SC), one for memory-guided saccades at the output of the PFC and one for voluntary saccades modifying the strength of the connections between FEF and the reticular formation. Recent studies on saccadic gain adaptation seem to confirm this hypothesis by discovering loci of

adaptation within the cortex through PET, fMRI and TMS studies (Gerardin et al., 2012; Panouillères et al., 2014, Blurton et al., 2012; Guillaume et al., 2018). This recent evidence points toward an involvement of the parietal cortex (IPS specifically) in the gain adaptation of voluntary saccades. This of course raises a natural question: how is an involvement of IPS in voluntary saccade adaptation compatible with the fact that the parietal cortex is mainly responsible for the generation of reflexive saccade? Panouillères et al., 2014 propose a model in which reflexive saccades gain adaptation is mediated via the fastigial nucleus in the cerebellum while voluntary saccades via the parietal cortex. The authors reconcile the abovementioned contradiction by citing studies that show how parietal areas seem to be more involved in the processing of attention mechanisms than saccadic initiation in monkeys (Wardak et al., 2002) and humans (Rafal, 2006).

A further possibility is a specific locus of adaptation for each saccade type at a different computational stage in the cerebellum. This type of model has been proposed by Alahyane et. al (2007). It is known that two distinct neural circuits within the cerebellum control the dynamic and metrical precision of saccades, one residing in the flocculus, the other in the vermis and fastigial nucleus (for a review see Shadmehr, 2017). However we can also speculate that different loci in the cerebellum could be responsible for different saccadic adaptive mechanisms specific to voluntary or reflexive saccades. This idea is supported by some lesion studies. Straube et al. (1995) analysed the eye movements of a patient with a bilateral lesion of the fastigial nuclei, discovering an interesting double dissociation. While the patient was not able to produce orthometric RS, VS resulted and was unaffected by the lesion. Furthermore, data from Alahyane et. al (2008) tested a gain adaptation paradigm in cerebellar patients, also finding a double dissociation. The authors observed a gain adaptation impairment in RS for the patient with a medio-posterior lesion, and impairment in VS for the patient with a lateral-anterior lesion.

These hypotheses assume the involvement of the thalamus as a relay station between the cerebellum and the cortex. Gaymard et al. (2001) did indeed find that patients with a lesion involving the cerebellar areas of the thalamus could not adapt their saccadic gain, while this was not true for thalamus lesions that did not involve cerebellar pathways.

3.4 Practical Consequences

The present work not only sheds light and proposes some likely neural mechanisms involved in the functioning of the saccadic adaptation system for saccadic gain and PSD, but also opens some considerations about clinical work in the field of neurology.

Saccadic performance is a helpful diagnostic tool for identifying underlying neurological diseases (Leigh & Zee, 2015). The clinical investigation and the patients behavioural difficulties can be directly attributed to specific neurological pathologies. To this extent it is important to note that assuming adaptive mechanisms rely on one neural locus in the brain or are spread across the cortex and mediated by different loci in the cerebellum, as we propose, has direct implications for clinical diagnostic investigation.

The physician has two main methods to test saccades at the patient's bedside, instructing the patient to fix alternatively two stationary targets (like the tip of a pencil and the doctor's nose) for voluntary saccades, and checking the ability of the patient to saccade a suddenly appearing stimulus (like wiggling one's finger) for testing reflexive saccades. An experienced physician is able through this simple investigation to assess saccadic initiation, accuracy and conjugacy. If more precise measures are needed the physician will use eye movements recordings as used in the research laboratories.

The patient studies and the double dissociations studies mentioned in this thesis, seen together with the cited experimental work, are building a more reliable picture of adaptive mechanisms. Currently, we can better identify their location, and understand how the oculomotor system achieves the impressive task of repairing its own metrical and dynamical saccadic parameters. The existence of multiple adaptation mechanisms spread on different neural pathways, as proposed in this thesis, is an important insight in thinking of better instruments to properly diagnose neurological pathologies. A deeper knowledge may therefore prove helpful to add useful tools in addition to the ones already at a physician's disposal in the diagnostic procedure. Moreover, a good understanding of saccade type-specific adaptive

mechanisms can help develop new protocols for rehabilitation, not only based on the training of reflexive saccades, but aimed specifically at the patient's behavioural difficulties and therefore the impacted neural pathway.

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List of Author Contributions

- *Adaptation of Post-Saccadic Drift in Reflexive Saccades Transfers Only Partially to Voluntary Saccades*

Giulia Manca designed the study, collected, analyzed, interpreted, and visualized the data, and wrote the manuscript.

Heiner Deubel designed the study, participated in interpreting the results, and commented on the manuscript.

- *Updating the Dichotomy of Reflexive and Voluntary Saccades*

Giulia Manca designed the study, collected, analyzed, interpreted, and visualized the data, and wrote the manuscript.

Heiner Deubel designed the study, participated in interpreting the results, and commented on the manuscript.

Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation “Dynamical and Metrical Adaptation of Saccadic Eye Movements in Humans” selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “Dynamical and Metrical Adaptation of Saccadic Eye Movements in Humans” is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 7.3.2021

Munich, 7.3.2021 Unterschrift/ Signature

Giulia Manca