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Integration processes of oculomotor memory in the normal and pathological brain

Nicolas Deravet

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Jury:

Prof.	Lefèvre, Philippe (Advisor)	UCLouvain
Prof.	Blohm, Gunnar	Queen's University
Prof.	Ivanoiu, Adrian	UCLouvain
Dr.	Montagnini, Anna	Aix-Marseille Université
Prof.	Orban de Xivry, Jean-Jacques	KU Leuven
Prof.	Yüksel, Demet	UCLouvain
Prof.	Keunings, Roland (Chairman)	UCLouvain

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In some aspects, doing a PhD resembles climbing. From the bottom of a wall of knowledge, you begin your ascension. At some point, however, you may meander, hesitate, and tire out. It is then that having a belayer to guide you to the next grip or allow you some rest is invaluable. Here, I would like to thank the people that have helped me up there.

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Contents

Scope and outcomes of the thesis

Vision is an extremely important sense, and the eye movements that allow us to make use of it involve neural pathways across most major areas of our brain. The wide distribution of these pathways has made the study of eye movements a valuable window into the inner workings of our brains.

In this thesis, we investigate the eye movements of healthy and pathological participants, first to validate and challenge a current theoretical and computational model of these movements, then to further our understanding of complex disorders that can affect the brain.

In particular, we first investigate model-driven predictions by presenting participants with noisy visual information, in the form of a moving target having a Gaussian distribution of luminosity, and with variable levels of prior information about target motion. Through this, we validate a prediction of our reference model by showing reliability-weighted integration of visual and memory inputs in the control of eye movements.

Then, we expand our investigation to pathological participants pre-

senting one of two disorders thought to compromise brain areas involved in this process: either a developmental disorder that affects visual processing, amblyopia, or a degenerative disorder affecting the control of behavior and speech, fronto-temporal dementia. Using healthy participants as a reference, we discuss their performance in eye-movements tasks, highlight specific deficits, then draw parallels with the brain areas involved and our reference model.

Outcomes of the thesis

Journal articles

- ◇ Deravet, N., Blohm, G., Orban de Xivry, J.-J., & Lefèvre, P. (2018). Weighted integration of short-term memory and sensory signals in the oculomotor system. Journal of Vision, 18(5), 16. https://doi.org/10.1167/18.5.16
- ◇ Deravet, N., Yüksel, D., Orban de Xivry, J.-J., & Lefèvre, P. (2019). Integration of past and current visual information during eye movements in amblyopia. Progress in Brain Research, Elsevier, Vol. 248, pp. 45–63.

Articles in preparation

- ◇ Deravet, N., Yüksel, D., Ivanoiu, A., Orban de Xivry, J.-J., & Lefèvre, P., Frontotemporal dementia patients exhibit a deficit in predictive saccades.

Conference communications

- ◇ Deravet, N., Orban de Xivry, J.-J., Blohm, G., & Lefèvre, P. (2014) Prior experience biases the oculomotor response to a

moving target. *PhD student day IoNS*, Woluwe, Belgium

- ◇ Deravet, N., Orban de Xivry, J.-J., Blohm, G., & Lefèvre, P. (2014) Prior experience biases the oculomotor response to a moving target. *13th Belgian Day on Biomedical Engineering*, Brussels, Belgium
- ◇ Deravet, N., Orban de Xivry, J.-J., Blohm, G., & Lefèvre, P. (2014) Prior experience biases visually-guided smooth pursuit response. *PAI / DYSCO Study Day*, Namur, Belgium
- ◇ Deravet, N., Orban de Xivry, J.-J., Blohm, G., & Lefèvre, P. (2014) Prior experience biases visually-guided smooth pursuit response. *Young Researcher Day - ICTEAM*, Belgium
- ◇ Deravet, N., Orban de Xivry, J.-J., Blohm, G., & Lefèvre, P. (2014) Prior experience biases visually-guided smooth pursuit response. *Annual meeting of the Society for the Neural Control of Movement*, Amsterdam, Netherlands
- ◇ Deravet, N., Blohm, G., Orban de Xivry, J.-J. & Lefèvre, P. (2014) Prior experience biases the oculomotor response to a moving target. *Annual meeting of the Society for Neuroscience*, Washington, USA
- ◇ Deravet, N., Yüksel, D., Orban de Xivry, J.-J. & Lefèvre, P. (2016) Integration of past and current visual information during eye movements in Amblyopia. *Annual meeting of the Society for Neuroscience*, San Diego, USA
- ◇ Deravet, N., Yüksel, D., Orban de Xivry, J.-J. & Lefèvre, P. (2017) Integration of past and current visual information during eye movements in Amblyopia. *Annual meeting of the Society for the Neural Control of Movement*, Dublin, Ireland

Chapter 1

Introduction

Vision is one of our most important senses, providing us with information about the world outside of our reach along with smell and hearing. However, provided there is light, vision has more range, precision and versatility than hearing or smell: it allows us to perceive static and moving objects, their color, their shape, and much more. From that information, we can then apply dozens of heuristics to guess their texture, weight, material, direction, velocity, danger, and more.

Of course, there are limitations on the overall amount of visual information we can receive from the world. Light needs to enter our eyes through our pupils and strike our retinas for us to perceive it, but only the fovea - a small area in the center of the retina - can provide maximal acuity and color perception. Further away from the center, both acuity and color perception fall off, along with the variety and density of photoreceptors.

Because of this, we rely on eye movements to keep what interests us projected unto our foveas. These movements are typi-

cally called gaze shifting movements, and are composed of saccades, smooth pursuit, and vergence. Another type, called gaze-stabilizing movements, include the opto-kinetic reflex (OKR, or optokinetic nystagmus) and the vestibulo ocular reflex (VOR). Finally, fixation and its associated fixational eye movements typically occur in-between the other movements to keep our gaze on a stationary target.

In this chapter, I will describe different means by which we keep our gaze on a target, focusing on fixation, saccades and pursuit eye movements, before discussing the attempts that have been made to model them. Afterwards, I will describe the neural basis controlling eye movements, and finally I will outline how some developmental or degenerative disorders can affect these movements.

1.1 Means of keeping our gaze on a target

When tracking a moving visual target, we make extensive use of saccades and pursuit eye movements. Saccades are very fast (up to 700°/s) and brief (in the dozens of ms) eye movements shifting our gaze unto a target, while smooth pursuit eye movements are slower (typically less than 100°/s) and continuous movements that stabilize moving targets unto our foveas. When the target stops moving, fixation maintains our gaze on it, with small movements, rapid or slow, on and around it.

Because pursuit and saccades exhibit very different dynamics, it motivated their study as independent processes: saccades to correct for position error, and pursuit to correct for velocity error (or *retinal slip*). In the last 15 years, this view has been increasingly

challenged, following mounting evidence of shared sensory inputs and brain structures. Furthermore, fixation should not be discounted when discussing saccades and pursuit, as it can influence both of them.

For simplicity, I will describe key features of fixation, saccadic and pursuit eye movements independently before further discussing the interaction of the latter two.

1.1.1 Fixation

Once thought as simply an absence of eye movements, fixation is now recognized as an active and dynamic process that requires the inhibition of intrusive movements to maintain the gaze on a specific target (Krauzlis, Goffart, & Hafed, 2017). As such, fixation also interacts with saccades and pursuit, typically by increasing their latency. Indeed, turning off a currently fixated target shortly before the onset of a moving target will reduce the latency of the ensuing eye movement, which is known as the "gap effect" (Krauzlis et al., 2017; Saslow, 1967). Furthermore, this gap effect can extend to other spatially oriented responses such as finger pointing (Pratt, Bekkering, Abrams, & Adam, 1999).

Despite its name, fixation does contain tiny movements around the target, either slow – the ocular drifts –, or fast – the ocular tremors –. From time to time, typically several times per second (Martinez-Conde, Macknik, & Hubel, 2004), micro-saccades are also produced. These saccades are small, below 1°, do follow the main sequence known in bigger saccades (Bahill, Clark, & Stark, 1975; Zuber, Stark, & Cook, 1965), and exhibit saccadic suppression (Hafed, Chen, & Tian, 2015). While they appear to be involuntary, it is possible to exert some amount of control on them to reduce

their rate, for example during difficult tasks (Hafed, Lovejoy, & Krauzlis, 2011; Pastukhov & Braun, 2010), or to orient their endpoints, for example while treading a needle (Ko, Poletti, & Rucci, 2010). In addition, the orientation of micro-saccades can reveal the direction of covert attention (Engbert & Kliegl, 2003).

1.1.2 Saccades - key features

Saccades (ex. in Fig. 1.1) can reach angular velocities of several hundred degrees per second, and are short in duration, rarely lasting more than a few dozens of milliseconds (Bonnet et al., 2013). Their trajectories tend to be very stereotyped, which is directly related to the systematic increase of their peak velocity and duration with amplitude, a relationship that has been called 'main sequence' (Bahill et al., 1975; Harris & Wolpert, 2006).

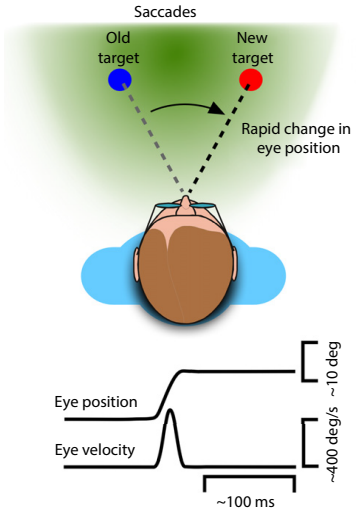

Figure 1.1: Saccadic eye movements: simplified principle as well as typical position and velocity traces of a saccade elicited by a $\approx 10°$ target step. From: Krauzlis, R.J. (2013)

Although saccades can be reflexive, typically towards unexpected stimuli, we can also initiate them voluntarily based on a range of sensory or memory inputs (Brignani, Bortoletto, Miniussi,

& Maioli, 2010; Groh & Sparks, 1996; Hughes, Nelson, & Aronchick, 1998; Yao & Peck, 1997). Perhaps counter-intuitively to their velocity, the initiation of reflexive saccades is rather slow, with latencies around 200ms (Gaymard, 2012; Irving, Steinbach, Lillakas, Babu, & Hutchings, 2006). However, this latency can be drastically reduced depending on the context. For example, extinguishing a fixation target before showing the saccadic target (gap paradigm) can allow for 'express' saccades, with latencies down to 80ms (Kingstone & Klein, 1993). Futhermore, when both position and time of target appearance are predictable, latencies can lower again to 0ms or below, in what is typically known as 'predictive saccades' (Shelhamer & Joiner, 2003).

Another important property of saccades is saccadic suppression: a strong (but not complete) inhibition of visual information before, during and right after the saccade execution. This inhibition selectively targets motion and space information (dorsal pathway), and does not, for example, impair shape or color recognition (Bremmer, Kubischik, Hoffmann, & Krekelberg, 2009; Wurtz, 2008). Recently, this mechanism has been suggested to be more than an attempt to ignore irrelevant sensory inputs, but rather the natural outcome of a sensorimotor process weighting its inputs based on reliability (Crevecoeur & Kording, 2017). In this context, the intense motor command necessary to produce the saccade induces uncertainty in the eye position estimate, which then affects the measure of position error, i.e. a sensory input. Then, taking into account sensorimotor delays, an optimal estimator attributes lower weight to visual inputs with a timing similar to saccadic suppression.

Finally, the saccadic system is tightly coupled with the mechanisms of attention (Wilder, Kowler, Schnitzer, Gersch, & Dosher, 2009), and has been shown to share attentional resources with the

pursuit system (Jin, Reeves, Watamaniuk, & Heinen, 2013).

1.1.3 Pursuit - key features

Smooth pursuit eye movements (Fig. 1.2) are slower than saccades and allow us to track and stabilize a moving target unto our foveas. Because of this, they are mostly driven by velocity error signals due to velocity differences between a target and the eye, i.e. the retinal slip (Lisberger, 2010; Westheimer, 1954). Still, there are also position inputs to the pursuit system, as shown by the smooth eye movement that is evoked towards a target briefly flashed during ongoing pursuit (Blohm, Missal, & Lefèvre, 2005). Contrarily to saccades, they cannot be voluntarily initiated and require either a moving visual stimulus, or the expectation of one (Hafed, Goffart, & Krauzlis, 2008; Lisberger, 2010). Conversely, smooth pursuit movements cannot be inhibited when the visual scene is only composed of moving elements (Keller & Heinen, 1991).

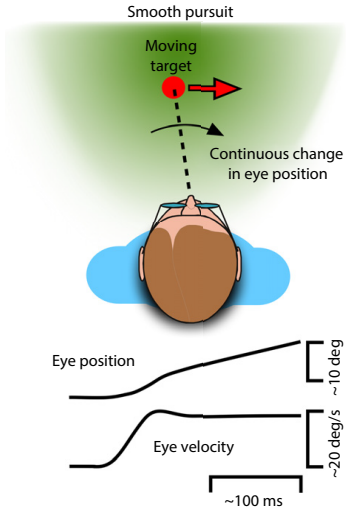

Figure 1.2: Smooth pursuit eye movements: simplified principle, and typical position and velocity traces elicited by the onset of a pursuit target moving at a constant 20°/s. From: Krauzlis, R.J. (2013)

The latency of smooth pursuit towards a visual target is in the

range of 100 to 150ms (Tychsen & Lisberger, 1986), after which the eye accelerates until it reaches target velocity between 100 and 200ms later, usually overshooting it by 5 to 20% (Mrotek, Flanders, & Soechting, 2006). At this point, it may oscillate for a couple of cycles at a frequency of 3-4Hz (D. A. Robinson, Gordon, & Gordon, 1986), although this appears to vary between individuals and contexts (Orban de Xivry, Bennett, Lefèvre, & Barnes, 2006; Wyatt & Pola, 1987).

The first 100ms-interval after the eye starts moving is called "open-loop", as sensory delays prevent new visual information from affecting the eye movements. However, the term 'open-loop' is to be nuanced because, since there is no inhibition of visual feedback, visual stimuli such as flashes can still affect eye movements with latencies below 100ms (Buonocore, Skinner, & Hafed, 2019).

Once target velocity has been reached, steady-state pursuit takes place. In this phase, the eye velocity closely matches target velocity, with gains that are typically within 0.9-1.0 for velocities below 30°/s (Lencer & Trillenberg, 2008), with some accounts of high gains up to 100 °/s (Meyer, Lasker, & Robinson, 1985).

1.1.4 Cooperation between pursuit and saccades

Saccades and smooth pursuit eye movements have different strengths, weaknesses and purposes. We have strong incentives to maintain the accuracy of pursuit high to allow us to discriminate target features. In turn, this can enhance our ability to predict target motion (Spering, Schütz, Braun, & Gegenfurtner, 2011), and to intercept it (Fooken, Yeo, Pai, & Spering, 2016), which is quite useful when we need to hit a ball. However, in some cases,

smooth pursuit accuracy cannot be maintained, and cooperation with saccades is necessary.

Such a case routinely occurs when target motion exceeds pursuit limits, or when its direction or velocity changes unpredictably. By triggering a so-called catch-up saccade, the accrued position error can be corrected and the pursuit can resume. In addition to the position error, the catch-up saccade takes into account the retinal slip 100ms before its initiation to adapt its amplitude (Daye, Blohm, & Lefèvre, 2014). However, this process takes more time and may still be ongoing after the saccade initiation, which can lead to curved saccades (de Brouwer, Missal, & Lefèvre, 2001; Schreiber, Missal, & Lefèvre, 2006).

The exact parameters of the trigger of these catch-up saccades are still investigated, but among current hypotheses are the time to foveation - i.e. the time necessary for the eye to reach the target without saccade - (de Brouwer, Yüksel, Blohm, Missal, & Lefèvre, 2002), or the level of confidence that a saccade will be needed given a probabilistic prediction of position error that accounts for retinal slip and uncertainties (Coutinho, Lefèvre, & Blohm, under revision).

Overall, such an interaction is a balancing act between rapidly stabilizing the fovea on the target to improve vision and reducing visual feedback due to saccadic suppression.

To summarize, these behaviors are evidence that saccade and pursuit systems are working together to track targets, by sharing inputs and internal representations (Krauzlis, 2004; Orban de Xivry & Lefèvre, 2007).

1.2 Memory, prediction and internal representation of a target

By most accounts, the time necessary for a human to elicit an eye movement based on visual inputs is 80ms at best (Gaymard, 2012), and often around 100ms (K. Fukushima, Fukushima, Warabi, & Barnes, 2013; Tychsen & Lisberger, 1986). Such a delay has important consequences, notably on smooth pursuit, because it induces a lag between our eyes movements and target motion, degrading our perception (Fooken et al., 2016).

Therefore, the brain takes advantage of a range of cues and prior information to predict future target motion and minimize this lag (Kowler, Aitkin, Ross, Santos, & Zhao, 2014). Among those are physical laws, like gravity or collisions (Angelaki, Shaikh, Green, & Dickman, 2004), the history of target motion (Kowler, Martins, & Pavel, 1984; Kowler & Steinman, 1979b) and the periodicity of the motion (Dodge, Travis, & Fox, 1930).

In smooth pursuit tasks, expectation of target motion can elicit anticipatory smooth pursuit before the actual target onset, producing an anticipatory increase of eye velocity proportional to the expected target velocity (Kowler et al., 1984). This typically occurs after a few repetitions of the motion, when target onset is preceded by a fixation of constant duration, and tends to be magnified in the gap paradigm (Kowler, 1989; Kowler et al., 1984). In addition, active pursuit is not required to elicit this behavior (Barnes, Grealy, & Collins, 1997), although passive viewing elicits lower anticipatory velocity (Burke & Barnes, 2008). Conversely, expecting the termination of target motion elicits anticipatory slowing of the pursuit (Boman & Hotson, 1988; De Hemptinne, Barnes, & Missal, 2010). In saccades, expectations about a target jump can elicit predictive

saccades with latencies lower than 80ms (Findlay, 1981).

Periodic target motion, in which the target position varies from side to side according to a periodic function, is another condition that allows anticipation. Typically, sensory delays induce a lag of smooth pursuit eye movements behind the target when it changes direction. However, after a few repetitions of the movement, smooth pursuit eye movements anticipatorily slow down and reverse direction in time with the target, leading to a lag close to zero (Barnes, Barnes, & Chakraborti, 2000; Dallos & Jones, 1963; Dodge et al., 1930).

Furthermore, if during the steady-state phase of smooth pursuit the target is suddenly blanked (extinguished), smooth pursuit gain will gradually fall to zero. If the target reappears unexpectedly, pursuit will then be initiated again. However, this changes if the target is expected to re-appear: instead of falling to zero when the target is blanked, the eye velocity will decrease to a plateau, then reaccelerate when the target reappears. Furthermore, if the duration of the blanking is known beforehand, this reacceleration can even occur before target reappearance (Bennett & Barnes, 2003). Although smooth pursuit eye velocity gain is reduced during the blank, catch-up saccades are still made towards the hidden target to compensate, which reveals that an accurate representation of the target remains and that this representation is shared between both pursuit and saccadic systems (Orban de Xivry et al., 2006; Orban de Xivry & Lefèvre, 2007).

Most of these processes require the oculomotor system to retain a representation of the target motion within a short-term memory. Indeed, behavioral experiments have shown that subjects can retain velocity and timing-related information for several seconds (at least 4s), although the information deteriorates over time (Barnes &

Donelan, 1999; Wells & Barnes, 1998; Y. Yang & Lisberger, 2010). We will therefore define "short-term memory" as a memory able to store target-related information for a few seconds. In addition, the oculomotor system needs to have a way to extrapolate stored information to cope with delays, such as an internal model. In the next section, I will discuss how such a system might work, on the basis of models of smooth pursuit.

1.3 Models of eye movements

In the study of sensorimotor processes, models have helped to summarize current knowledge and highlight new investigation targets. Despite ever-growing knowledge about it, the oculomotor system remains complex and replete with unknowns. As such, models either zoom-in on the role of small neural sub-systems in specific tasks (Quaia, Lefèvre, & Optican, 1999), or abstract part of the complexity by characterizing whole processes, such as visually-guided pursuit, with simple functional models (as described below). For the purposes of this work, we will focus on functional models of (predictive) smooth pursuit.

Early models of smooth pursuit attempted to reproduce the dynamics of visually guided smooth-pursuit, such as its delayed initiation, its acceleration and overshoot of target velocity, and the oscillations during steady-state (Krauzlis & Miles, 1996; D. A. Robinson et al., 1986; Young, Forster, & Van Houtte, 1968). Briefly, they used a combination of a negative feedback model and an internal positive feedback to reproduce the initial pursuit response and the pursuit maintenance, respectively. However, these models could not reproduce zero-lag pursuit of sinusoidal motion, since they lacked a predictive component.

Some authors solved this problem by adding to the models a predictor extrapolating future target motion (Shibata, Tabata, Schaal, & Kawato, 2005). While this allowed zero-lag sinusoidal motion pursuit, it did not reproduce the dynamics of blanked target pursuit. Indeed, no visual input is available during blanking, which mandates the existence of an internal representation of the target/eye velocity to maintain pursuit.

By combining a predictor component with a memory holding target velocity, Barnes and Asselman (1991) obtained a model that, across several versions (Barnes, 2008; Bennett & Barnes, 2004) was shown to reproduce both zero-lag sinusoidal pursuit and blanked target pursuit. To do that, however, the model relied on a switch between predictive and reactive behaviors, and on the arbitrary adjustment of specific gains, which made it difficult to generalize and to draw comparisons with actual neural processes.

At this point, there was a need for a more principled integration of predictive (extraretinal) and reactive (retinal) components of pursuit. In parallel, Bayesian and reliability-based integration rapidly grew in popularity in sensorimotor studies (Kording & Wolpert, 2004), and several authors turned towards it as a possible solution for sensory motion integration (Bogadhi, Montagnini, Mamassian, Perrinet, & Masson, 2011; Dimova & Denham, 2009; Freeman, Champion, & Warren, 2010; Montagnini, Mamassian, Perrinet, Castet, & Masson, 2007).

Shortly thereafter, two models of smooth pursuit using reliability-based integration to combine retinal and extra-retinal information were proposed (Bogadhi, Montagnini, & Masson, 2013; Orban de Xivry, Coppe, Blohm, & Lefèvre, 2013). The crucial novelty of these models was their ability to process noise and learn through the integration of memory and visual information. Up to

that point, eye-movement models were deterministic, having direct access to the true values of visual and memory information, and ignoring the noisy nature of those signals (Kording & Wolpert, 2004; Osborne, Hohl, Bialek, & Lisberger, 2007; Osborne, Lisberger, & Bialek, 2005).

Both models used two recursive Bayesian estimation processes: one to estimate the sensory/retinal input, and one to build the memory/extra-retinal input. These two inputs were then optimally integrated according to the inverse of their variance, i.e. their reliability, to generate the signal driving pursuit. They differed on a couple of aspects, notably in the nature of the memory: in Orban de Xivry et al. (2013), the memory was a dynamical representation of the target, updated over time and across trials, while in Bogadhi et al. (2013) it was a static memory of target velocity.

Here, I will describe more thoroughly the model of Orban de Xivry et al. (2013) because its approach to memory allowed the reproduction of a wider range of anticipative pursuit behaviors, such as predictive re-acceleration during blanking.

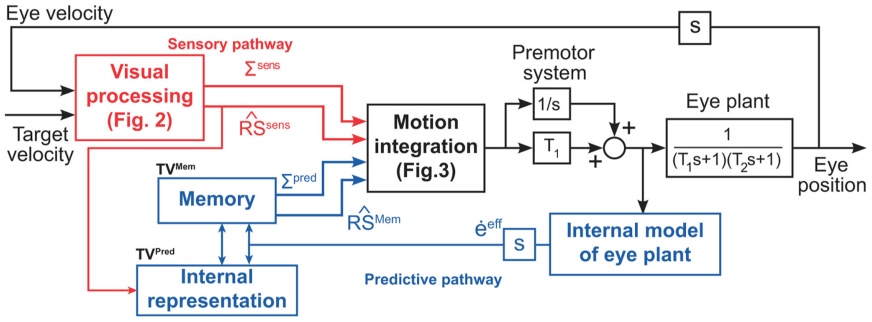

Figure 1.3: Model of smooth pursuit. From: Orban de Xivry, Coppe, Blohm and Lefèvre (2012)

In this model (cf. Fig. 1.3), two Kalman filters (Visual processing and Memory/Internal representation boxes) provide estimates

of the retinal (RS^{Sens}) and extraretinal (RS^{Mem}) inputs, as well as estimates of their uncertainty (Σ^{Sens} and Σ^{Pred}). These estimates are then optimally combined according to their reliability (cf. formula 1.1) into a weighted estimation of the retinal slip that is processed by the motion pathway to produce the motor command (Motion integration box).

$$\widehat{RS}_k = \frac{\Sigma^{Pred}}{\Sigma^{Pred} + \Sigma^{Sens}} \widehat{RS}_k^{Sens} + \frac{\Sigma^{Sens}}{\Sigma^{Pred} + \Sigma^{Sens}} \widehat{RS}_k^{Mem} \qquad (1.1)$$

Furthermore, the output of the predictive pathway (RS^{Mem}), is obtained from TV^{Mem} (the target velocity), which is a time-shifted version of TV^{Pred} 150ms in the future. This means that TV^{Mem} approximates target motion 150ms in the future, on the basis of the dynamical representation (TV^{Pred}) obtained during previous trials. Accounting for sensorimotor delays, this gives the predictive pathway a lead of around 70ms over the actual target motion.

With this model, it is possible to simulate anticipatory pursuit, zero-lag sinusoidal target tracking and blanking behavior, including accelerating targets, using a single mechanism. Furthermore, it also predicted that in cases of conflict between the predictive and sensory inputs, such as a new target at a higher velocity, the response would be more strongly influenced by the most reliable input. Testing this prediction is the topic of the second chapter of this work.

As discussed previously, saccades and pursuit share inputs and representations of the target motion/position, and the saccadic system would therefore be expected to share the relevant parts of the pursuit model. Furthermore, the saccadic system also performs some form of weighted integration of its retinal and extraretinals

inputs (Byrne & Crawford, 2010; Niemeier, Crawford, & Tweed, 2003; Ostendorf & Dolan, 2015).

Still, saccades remain mostly driven by position signals, therefore extending these models to handle position inputs would be a first step in a full model of gaze control. This could also improve the model by allowing it to simulate the effect of position inputs on pursuit (Blohm et al., 2005; Buonocore et al., 2019). Currently, we know of one such attempt by Coutinho et al. (under revision), which was applied to better understand the trigger of catch-up saccades.

1.4 Neural basis of eye movements

This section will describe the main pathways and areas involved in the control of eye movements. Its objective is not to give an in depth description of all brain areas involved in the control of eye movements, but rather to give an overview of the most important areas.

The first requirement for eye movements is to be able to perceive a visual target. The projections of the retina most relevant for eye movements are to the Superior Colliculus (SC), and to the primary visual area (V1), in the occipital lobe, through the lateral geniculate nucleus (LGN) (Reid & Usrey, 2013). After processing in V1, signals can take two routes: the ventral stream, involved in object recognition ('what' pathway), and the dorsal stream that controls movement (the 'where', or 'how' pathway), which is the one that interests us here (de Haan, Jackson, & Schenk, 2018; Goodale & Milner, 2018).

1.4.1 Fixation

The neural basis of fixation is still investigated, but is thought to involve the superior colliculus (SC), the medio-posterior cerebellum (MPC), and possibly the omnipause neurons (OPNs).

While OPNs are well known for their role in inhibiting saccades, their role in pursuit is more complex (Missal & Keller, 2002), and there is no direct evidence that their inactivation leads to problems with fixation (Kaneko, 1996). The MPC is an important structure for the control of gaze accuracy, and altering the activity of its caudal fastigial nuclei introduces slight position offsets into the fixation (Goffart, Chen, & Sparks, 2004; F. R. Robinson, Straube, & Fuchs, 1993).

Finally, the SC receives input from several visual cortical areas, and provides output to the OPNs, among others. A defining feature of this multi-layered structure is its retinotopic mapping, exhibited from its most superficial layers involved in sensory processing (Klier, Wang, & Crawford, 2001), to its deepest layers involved in motor control. The rostral end of this retinotopic map corresponds to the fovea, and its intermediate layers are active during fixation. This has been interpreted as a defining feature, leading to the name of 'fixation cells'. In that interpretation, fixation cells inhibit the activity of peripheral cells that can trigger saccades, in a winner-takes-all manner (Krauzlis et al., 2017; White & Munoz, 2011).

However, an alternative hypothesis is that of the 'equilibrium', in which target-related activity is balanced across the SC, with imbalances leading to saccades (Goffart, Hafed, & Krauzlis, 2012; Hafed et al., 2008). Supporting evidence comes from chemical inactivation of the rostral part of the SC, which did not impair fixation and even decreased micro-saccades (Goffart et al., 2012) in the ab-

sence of peripheral stimulus. Another source of evidence against the 'fixation-cell' theory is that it implies the existence of some border between fixation and saccade cells. Therefore, there should be a lower limit to the amplitude of saccades, which cannot explain the existence of micro-saccades. In the equilibrium hypothesis, activity across the SC represents a measure of saliency or interest towards a target position, which scales across all saccades amplitude, including micro-saccades that are made towards a quasi-foveated target (Krauzlis et al., 2017).

1.4.2 Saccades

For saccades, the most important projections of V1 are to the parietal cortex, in particular to the parietal eye field (PEF – lateral intraparietal area, or LIP, in monkeys), and to the Frontal Eye Field (FEF) in the frontal cortex (Foxe & Simpson, 2002; Scudder, Kaneko, & Fuchs, 2002). The PEF and the FEF are bilaterally and reciprocally connected, and both are connected to the Superior Colliculus, either directly (PEF and FEF), or indirectly (FEF through the basal ganglia) (Gaymard, 2012; Krauzlis, 2004). See Fig. 1.4.

Saccades may be triggered by both PEF and FEF areas. However, there appears to be a gradient between reflexive (and prompter) saccades mainly triggered by the PEF (Pierrot-Deseilligny, Rivaud, Gaymard B., & Agid, 1991), and volitional saccades mainly involving the FEF (Keating, 1991; Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994).

Higher order saccades, such as memory-guided, predictive and anti saccades, may recruit more areas of the frontal cortex such as the Supplementary Eye Field (SEF) and the dorsolateral prefrontal

cortex (DLPFC), also called pre-frontal eye field (pre-FEF). The involvement of the SEF has been shown in the timing of sequences of saccades, conditional activations, and during predictive saccades (Lee et al., 2016; Leigh & Kennard, 2004; Lukasova et al., 2018). The DLPFC has been shown to perform functions related to the inhibition of unwanted saccades, notably during anti-saccades, in maintaining attention, and processing oculomotor memory (Barbey, Koenigs, & Grafman, 2013; Rowe, 2000). Furthermore, some areas within the basal ganglia, such as the striatum, have also been associated with predictive saccades (Coslett, Wiener, & Chatterjee, 2010).

Situated at the top of the brainstem and connected to both the FEF and PEF, the superior colliculus is crucial for orienting behaviors and saccade planning. Its most superficial layer encodes a form of sensory position error signal in retinal coordinates (Klier et al., 2001), while its deeper layers are mostly devoted to motor command computation (Krauzlis, Liston, & Carello, 2004). These motor commands are sent through descending outputs to the brainstem saccade generator, either directly or through the cerebellum (Gaymard, 2012; Krauzlis, 2004). While the brainstem saccade generator produces the final commands sent to the extra-ocular muscles, the cerebellum, notably the oculomotor vermis, plays an important role in the adjustment of saccades metrics (Keller & Missal, 2003).

1.4.3 Pursuit

Receiving inputs from the primary visual area, the motion processing pathway, composed of the middle temporal area (MT) and the medial superior temporal area (MST), provides the main input to smooth pursuit by determining speed and direction of the retinal

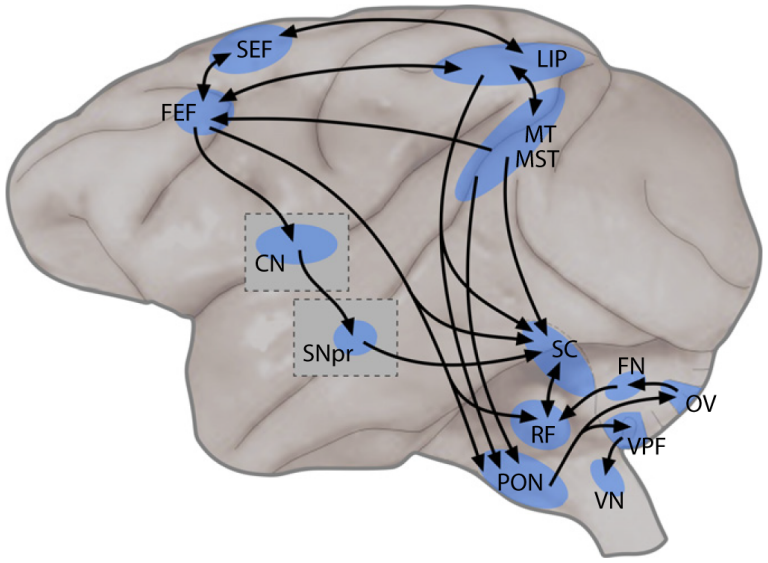

Figure 1.4: Descending and inter-cortical pathways involved in the control of gaze movements on a view of the monkey brain, LIP: lateral intraparietal area (PEF in humans) CN: caudate Nucleus, SNpr: substantia nigra pars reticulata, RF: reticular formation, PN: pontine nuclei, FN: fastigial nucleus, VN: vestibular nuclei, VPF: ventral paraflocculus, OV: oculomotor vermis (lobules VI and VII of the vermis). From Krauzlis (2013)

motion (Jogan & Stocker, 2015; Stone & Krauzlis, 2003). See Fig. 1.4. While MT contains neurons with small receptive fields that only respond to retinal motion, MST neurons have larger receptive fields and respond to more complex motion, with some neurons exhibiting extra-retinal activity (Ilg & Thier, 2003; Krauzlis, 2013; Newsome, Wurtz, & Komatsu, 1988). This has led to the broad association of MT with pursuit initiation and MST with pursuit maintenance (Krauzlis, 2004).

Both MT and MST project to the pursuit-related neurons in the FEF (FEFsem), which is hypothesized to control the gain of the transformation between motion inputs and pursuit eye movements (Darlington, Beck, & Lisberger, 2018; Tanaka & Lisberger, 2001).

This is supported by studies showing that lesions to this area impair the gain of visually-guided pursuit for target motion towards the same side as the lesion, as well as predictive pursuit (Keating, 1991). In addition, despite earlier hypotheses (Srihasam, Bullock, & Grossberg, 2009; Tanaka & Lisberger, 2001), it was shown by (Mahaffy & Krauzlis, 2011) that FEFsem does not contribute to target selection, although its activity can reflect this selection.

Another important cortical area is the supplementary eye field (SEF), bilaterally and reciprocally connected to the FEF (Huerta, Krubitzer, & Kaas, 1987). It has connections with the motion processing pathway, but only with the dorsomedial part of the MST, the MSTd, which itself does not project to the FEF (Huerta & Kaas, 1990). In addition, the SEF has been linked to functions of visual memory and anticipation of target motion (J. Fukushima et al., 2011; Nyffeler, Rivaud-Péchoux, Wattiez, & Gaymard, 2008). Altogether, this has led to the conclusion that the SEF is mainly involved in planning, rather than generating, smooth pursuit (K. Fukushima et al., 2013; Krauzlis, 2005).

Furthermore, stimulation of the parietal eye field (PEF) can also elicit pursuit (Kurylo & Skavenski, 1991). It is connected to both FEF and SEF, and contains a representation of the position of the eye in its orbit (Ilg & Thier, 2008). The main consensus regarding its role is that it differentiates between self and external retinal motion (Missal & Heinen, 2017).

All these cortical areas (MT/MST, FEF, SEF, PEF) project to the pontine nuclei (PON), in particular the dorsolateral pontine nuclei (DLPN), which relays oculomotor signals to the flocullus and ventral paraflocullus (VPF) in the cerebellum. In addition, the FEF and SEF have a second pathway towards the cerebellum, through the PON and the nucleus reticularis tegmenti pontis (NRTP), to

reach the posterior cerebellar vermis (lobules VI and VII), also known as the oculomotor vermis (Keller & Heinen, 1991; Krauzlis, 2004; Thier & Ilg, 2005). Activity in the flocullus/paraflocullus has been linked to eye velocity, smooth pursuit, and the cancellation of the vestibulo-ocular reflex, but not to the retinal slip (K. Fukushima et al., 2013; Kheradmand & Zee, 2011). As for the cerebellar vermis, lesions/inactivations have been shown to disrupt the initial acceleration of pursuit movements (F. R. Robinson, Straube, & Fuchs, 1997; Takagi, Zee, & Tamargo, 2000), suggesting a role in eye acceleration and pursuit initiation (Krauzlis, 2004). Finally, the outputs of the VPF and posterior cerebellar vermis are sent to the vestibular nuclei and the brainstem reticular formation, respectively, were they shape the commands sent to motor neurons.

1.4.4 Shared neural structures of saccades and pursuit

As documented in the section on interaction, behavioral studies proved that saccades and pursuit interact and share sensory inputs and internal representation of the target. Correspondingly, there is significant overlap between their neural pathways, as reviewed by (Krauzlis, 2004; Lynch & Tian, 2006; Orban de Xivry & Lefèvre, 2007).

Cortically, aside from the area MT/MST, the main oculomotor areas PEF (Andersen, Essick, & Siegel, 1987; Kurylo & Skavenski, 1991; Lynch & McLaren, 1982), FEF (Tian & Lynch, 1996a, 1996b) and SEF (Schlag & Schlag-Rey, 1985; Tian & Lynch, 1995) all contribute to both pursuit and saccades through inter-connected sub-regions specialized for each type of movement. As such, they constitute two parallel cortical pathways with similar architecture

(Krauzlis, 2005; Orban de Xivry & Lefèvre, 2007).

Sub-cortically, saccadic and pursuit pathways are also intertwined. Some subcortical neurons exhibit both pursuit and saccade-related activity, and can be sensitive to both velocity and position.

For example, pursuit-related neurons in the dorsolateral pontine nuclei (DLPN) also exhibit saccade-related activity, and are sensitive to both position and velocity (Dicke, Barash, Ilg, & Thier, 2004). Furthermore, the DLPN receives inputs from the superior colliculus (SC), predominantly associated to the saccade pathway. Indeed, the SC has been documented to provide smooth pursuit with a position input and to influence target selection. It is currently hypothesized that it encodes broad motor goals and orientation (Krauzlis, 2003; White & Munoz, 2011).

The SC also receives inputs from the FEF through the basal ganglia, which is known for its role in the control of volitional saccades through its (dis)inhibitory effects on the SC (Hikosaka, Takikawa, & Kawagoe, 2000). However, both saccade and pursuit subregions of the FEF project to the basal ganglia, wherein several studies have confirmed the presence of pursuit-related activity consistent with the (dis)inhibition of directions (Basso, Pokorny, & Liu, 2005; Yoshida & Tanaka, 2009).

Within the cerebellum, the oculomotor vermis also exhibits saccadic and pursuit activity, affecting both saccade metrics and pursuit initiation (Krauzlis & Miles, 1998; Manto et al., 2012; Takagi et al., 2000).

Further overlaps are found in the premotor nuclei, which receive afferences from the SC as well as from both pursuit and saccades subregions of the FEF, and contain neurons activated by both pursuit and saccades. Among those, burst neurons, responsi-

ble for the initial burst of activity required by saccades, have subpopulation that are also modulated during pursuit. OPNs, which stop firing at the start of a saccade, acting like a release mechanism, are also modulated during smooth pursuit eye movements (Missal & Keller, 2002; Yan, Cui, & Lynch, 2001).

Finally, both saccadic and pursuit systems include an ascending pathway from the cerebellum through the thalamus, providing valuable feedback for the control of eye movements (Sommer & Wurtz, 2002, 2004; Tanaka, 2005, 2007; Tian & Lynch, 1997).

1.4.5 Oculomotor memory and prediction

Mounting evidence points to the frontal lobes having a crucial role for prediction and memory in oculomotor processes.

Both the FEF (K. Fukushima, Yamanobe, Shinmei, & Fukushima, 2002; MacAvoy, Gottlieb, & Bruce, 1991) and SEF (de Hemptinne, Lefèvre, & Missal, 2008; Nyffeler et al., 2008) have been shown to exhibit prediction-related signals for smooth pursuit. In particular, the SEF has been linked to memory, cueing and anticipation, both of saccades and pursuit (Shichinohe et al., 2009). Furthermore, stimulation of the SEF facilitates anticipatory pursuit (Missal & Heinen, 2004).

In further studies, single-unit neurons were recorded during a memory-oriented pursuit task to separate the memory and movement preparation components of these signals (J. Fukushima et al., 2011; K. Fukushima et al., 2011, 2013; Shichinohe et al., 2009). These studies showed that memory of target direction and go/no-go signals are predominantly found in the SEF rather than in the FEF. Chemical inactivation produced congruent results: it negatively affected pursuit initiation in both areas, while only FEF

inactivation impaired pursuit maintenance, and only SEF inactivation significantly impaired direction and go/no-go errors. Studies of lesions show a similar pattern. Lesions to the FEF affect the gain of visually-guided and predictive pursuit (Keating, 1991), while lesions to the SEF raise the rate of cued direction errors but do not inhibit visually-guided pursuit gain (J. Fukushima et al., 2011). In summary, the FEF sets the gain of visuomotor transformations (Tanaka & Lisberger, 2001), while the SEF is involved in the selection of responses on the basis of context-dependent rules, possibly by assigning different values to them (Stuphorn, 2015).

Other frontal areas, like the dorso-lateral prefrontal cortex (DLPFC) have also been shown to be active during predictive tasks. The DLPFC has been implicated in inhibition mechanisms that directly influence the SC through prefronto-corticular tracts (Pierrot-Deseilligny et al., 2003). It has also been shown in lesions studies to be necessary for manipulating spatial knowledge in working memory, for example during anti or predictive saccades (Barbey et al., 2013). In addition, it is more activated during blanking periods than during visually-guided pursuit (Ding, Powell, & Jiang, 2009). Overall, this suggests that the role of the DLPFC is to compute and select responses from working memory, rather than to maintain and store them (Rowe, 2000).

Further extra-retinal signals are found in the parietal cortex, in particular in the MST area. While the MT area quickly stops firing when a target is blanked, the MST area sustains its activity (Kawano, Shidara, Watanabe, & Yamane, 1994; Nagel et al., 2006). The MST area is also active during anticipatory pursuit (Ilg & Thier, 2003). Through its connections to the FEF and SEF, this area could take part in the generation of predictive movements, for example by extrapolating motion (Masson, Montagnini, & Ilg,

2009), or by computing the perceived target motion, with predictive processes handled in the prefrontal areas (K. Fukushima et al., 2013).

Aside from cortical areas, extra-retinal signals have also been shown in the cerebellum. Some purkinje cells are active during sinusoidal or circular pursuit (Leung, Suh, & Kettner, 2000). In monkeys, (K. Fukushima et al., 2011) showed that purkinje cells in the flocullar regions were associated to pursuit execution, while cells in the dorsal vermis and caudal fastigial nucleus were related to memory and no/go decisions. However, the same authors suggest that the monkeys training might have played a part in the cerebellar involvement in working memory (K. Fukushima et al., 2013). Still, the strong connections between the cerebellar vermis and motor-related frontal cortical areas (Coffman, Dum, & Strick, 2011), support the hypothesis of functional links between them.

In an fMRI study, predictive saccades have been shown to recruit sub-cortical areas and the cerebellum, with little involvement of prefrontal areas SEF and DLPFC (Lee et al., 2016), possibly by relying on extracortical rhythmic mechanisms. However, these areas might initially be necessary, as lack of maturity (Lukasova et al., 2018) or lesions (Pierrot-Deseilligny et al., 2003) both impair performance in predictive saccades.

Drawing a few parallels between our reference (pursuit) model and neural structures, one could expect to find the visual processing branch of the model, including a form of kalman filtering, within the V1+MT/MST areas. Interestingly, a recent study found indications of an encoding of precision (inverse variance) in the synaptic gain of the pyramidal cells in V1 (Adams, Bauer, Pinotsis, & Friston, 2016).

The predictive branch of the model could reasonably be handled by the prefrontal cortex. While its storage is difficult to pinpoint to an area or mechanism, the oculomotor memory could be created and updated through the SEF, thanks to its connections to both MST and prefrontal areas.

The FEF would then perform the weighted integration between oculomotor memory and sensory inputs, and produce the motor signal, which was also suggested in (Darlington et al., 2018). In addition, behavioral results from (Bogadhi et al., 2013) indicate the persistence of the aperture problem right after a blanking period during steady-state pursuit, when the memory of the target motion has already been acquired. This suggests that visual processing is difficult to override with prediction, either because of direct projections to the brainstem or privileged access to the FEF, which might be a strategy to preserve the ability to react fast to unexpected visual changes.

1.5 Pathologies affecting the neural basis of EM

Eye movements can be measured rapidly and non-invasively, and their neural pathways are extensively studied (Barnes, 2008; K. Fukushima et al., 2013; Kowler, 2011; Kowler, Anderson, Dosher, & Blaser, 1995; Leigh & Kennard, 2004; Lisberger, 2015). Because their execution involves many brain areas (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Krauzlis, 2004; Krauzlis et al., 2017; Lynch & Tian, 2006), they can be a useful tool to study brain function and identify abnormalities (Hannula et al., 2010; Leigh & Kennard, 2004). Reciprocally, brain

disorders with known targets can also help us to better understand eye movements. In this context, this section describes two pathologies that can affect eye movements: unilateral amblyopia and frontotemporal dementia. Then, their study is put in the context of this work.

1.5.1 Unilateral amblyopia: a developmental pathology

Description

Amblyopia (lit. *blunt eye*) is a developmental disorder of vision, with an incidence of at least 1.6% globally, and closer to 3% in Europe (Hashemi et al., 2018). Both bilateral and unilateral amblyopia exist, but in this work we will only study the latter, and further mentions to amblyopia will also refer to it.

Unilateral amblyopia is primarily defined by a reduction of the best-corrected acuity in one eye that cannot be exclusively attributed to a physical abnormality of the eye, but the underlying deficit is much more complicated (Daw, 2014). Indeed, amblyopia is also associated with reduced contrast sensitivity at high spatial frequencies (Gstadler & Green, 1971; Hess & Howell, 1977; Levi & Harwerth, 1977) and spatial distortions (Hess, Campbell, & Greenhalgh, 1978; Lagrèze & Sireteanu, 1991).

Amblyopia results from degradations of the retinal image during a sensitive period of visual development, typically thought to take place until 7 to 8 years of age. The degradations known to cause amblyopia are: anisometropia (differences of the 2 eyes refractive errors), strabismus (misaligned eyes), and deprivation/organic (mostly physical obstruction of the retina, for example by a cataract), although it is not uncommon to find

patients exhibiting both anisometropia and strabismus. While anisometropia and deprivation are optical deficits and strabismus a motor deficit, all reduce the quality of the correlation between the two retinal images.

The standard and evidence-based treatment for amblyopia is to first provide refractive correction then follow up with occlusion therapy (patching the fellow eye) or atropine drops, with the intention of improving the performance of the amblyopic eye (Writing Committee for the Pediatric Eye Disease Investigator Group et al., 2012). While such therapies have proved their efficacy in the recovery of visual acuity, other deficits linked to binocular vision tend to remain (Birch, 2013). In addition, around 50% of children do not achieve normal vision in their amblyopic eye (Holmes et al., 2003; Woodruff, Hiscox, Thompson, & Smith, 1994), and 25% of children show recurrence of amblyopia after the cessation of occlusion/penalization therapy (Joly & Franko, 2014). One possible reason for that is that these treatments only work on a monocular level (Jia et al., 2018). As such, in recent years, the binocular nature of amblyopia has gained in attention, and new therapies are being investigated.

Neural consequences

The neural consequences of amblyopia are still debated, but it is now accepted that the deficits must extend beyond V1 (Barnes, Hess, Dumoulin, Achtman, & Pike, 2001; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998; Kiorpes & McKee, 1999) and contrast coding (Tao et al., 2014). Indeed, monkeys with anisometropic amblyopia have been shown to exhibit mapping irregularities between V1 and V2, such that the subunits in extra-striate receptive fields are disordered (Tao et al., 2014). In humans with ani-

sometropic amblyopia, distortion of the retinotopy of V1 has been shown for the amblyopic eye compared to the fellow eye inputs (Li, Dumoulin, Mansouri, & Hess, 2007), which has been linked to a dislocation of the position of population receptive fields associated to the amblyopic input (Clavagnier, Dumoulin, & Hess, 2015). Another fMRI study showed an overall reduced BOLD response, and an increase in the deviation of the response locus of V1, V2 and V3 of the amblyopic eye's cortical representation, compared to the fellow eye (Farivar et al., 2017). Furthermore, this same study found that the severity of acuity loss was positively correlated with the level of reduction of the BOLD response, for most eccentricities.

The effect that these reduced activation and distortions of cortical representations have on higher visual areas are still not well understood. However, since extrastriate areas are downstream from V1, their development (and feedback) is likely to be affected by these deficits (Kiorpes & Daw, 2018). Indeed, the fact that deficits related to contrast or motion perception (Kiorpes, Tang, & Movshon, 2006; McKee, Levi, & Movshon, 2003; Simmers, Ledgeway, Hess, & McGraw, 2003) can also be found in the fellow eye (Ho et al., 2005; Meier & Giaschi, 2017; Varadharajan & Hussaindeen, 2012) is further proof that amblyopia affects the oculomotor system beyond the monocular level, possibly including higher visual areas.

Oculomotor consequences

In monocular, amblyopic eye viewing conditions, eye movements deficits have indeed be found, such as unstable fixation (Ciuffreda, Kenyon, & Stark, 1979b; González, Wong, Niechwiej-Szwedo, Tarita-Nistor, & Steinbach, 2012), as well as higher latencies and more variable gain in saccades (McKee, Levi, Schor, & Movshon, 2016; Raashid, Wong, Chandrakumar, Blakeman, &

Goltz, 2013). Visually guided smooth pursuit has received more limited attention, but studies have found lower pursuit gains with more catch-up saccades, as well as asymmetry in the pursuit performance (Ciuffreda, Kenyon, & Stark, 1979a; Schor, 1975; Von Noorden & Mackensen, 1962a). One recent study by Raashid, Liu, Blakeman, Goltz, and Wong (2016) investigated smooth pursuit in anisometropic amblyopia and found delayed pursuit onset, with no steady-state gain difference. In most studies including different amblyopic types, strabismic amblyopia tended to induce more pronounced deficits than anisometropic amblyopia.

In monocular, dominant (fellow) eye viewing, eye movements deficits have also be found, such as unstable fixation (Shaikh, Otero-Millan, Kumar, & Ghasia, 2016), fixational eccentricity (Bedell & Flom, 1985) and abnormal pursuit movements (Fukai, Tsutsui, & Nakamura, 1976). This, once again, suggest that unilateral amblyopia affects the oculomotor system beyond the monocular level (Meier & Giaschi, 2017; Perdziak, Witkowska, Gryncewicz, & Ober, 2016).

In this context, the 3rd chapter of this thesis investigates whether the smooth pursuit performance of amblyopic patients reveals a different way of weighting the visual and memory inputs to their oculomotor system.

1.5.2 FTD: a degenerative pathology

Description

Frontotemporal Dementia (FTD) is an umbrella clinical term that designates a heterogeneous and complex group of neurodegenerative disorders (Bang, Spina, & Miller, 2015; Bigio, 2013; Laforce, 2013), typically encompassing two broad categories according to

the clinical presentation: behavioral variant FTD (bvFTD; Laforce (2013); Rascovsky et al. (2011)) presenting with a frontal syndrome, and primary progressive aphasia (PPA) presenting with a language impairment, itself divided into three variants (Gorno-Tempini et al., 2011) : semantic (svPPA, also known as semantic dementia), nonfluent/agrammatic (naPPA, also known as progressive nonfluent aphasia) and logopenic (lvPPA).

These variants are classified based on clinical symptoms and brain imagery, but are only the manifestation of underlying molecular pathologies. These pathologies are mainly split into three subtypes (Goedert, Ghetti, & Spillantini, 2012; Laforce, 2013; MacKenzie et al., 2010) characterized by insoluble deposits of proteins: tau protein (FTLD-tau), TAR-DNA Binding element Protein 43kDa (FTLD-TDP or TDP-43), or fused in sarcoma (FTLD-fus). Despite the better knowledge of the underlying neuropathologies acquired in recent years, there are currently no curative treatments for FTD. Still, these proteins might offer a promising target for future treatments.

However, early diagnosis of FTD will be paramount in the success of future treatments (for example disease-modifying drugs targeting its molecular causes), in order to intervene before irreversible neuronal loss has occurred (Logroscino et al., 2019; Warren, Rohrer, & Rossor, 2013). Despite the improvement of diagnostic criteria (Bertoux et al., 2012; Rascovsky et al., 2011), there still remain a need to determine early, pre-symptomatic features (Chare et al., 2014). This has motivated research into potential biomarkers, including biological, neuroimaging or neurophysiological markers (Hu, Trojanowski, & Shaw, 2011; Rohrer et al., 2015; Rohrer & Zetterberg, 2014).

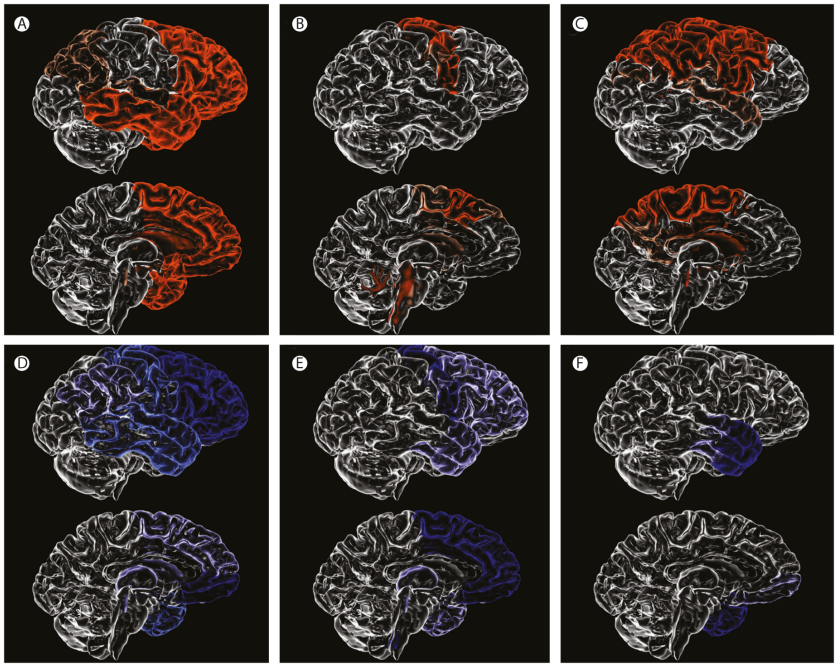

Figure 1.5: Patterns of brain atrophy in main FTLD pathologies. First row: FTLD-tau pathologies (Pick's disease, progressive supranuclear palsy, corticobasal degeneration). Second row : FTLD-TDP pathologies (TDP type A, TDP type B, TDP type C). From Bang, Spina & Miller (2015)

Neural consequences

FTD mainly affects the frontal and anterior temporal lobes, but can also affect some subcortical structures, the brainstem and the cerebellum (Bang et al., 2015; Garibotto et al., 2011; Grinberg, Rueb, & Heinsen, 2011; Laforce, 2013; Landin-Romero et al., 2017; Zhang et al., 2013). Nevertheless, the pattern of atrophy progression tend to differ between the underlying molecular pathologies (as can be seen in Fig. 1.5). Although significant progress has been made in recent years, unknowns remain regarding the variability of the rate of progression and the presymptomatic phases of the disease (Chare et al., 2014; Rohrer & Zetterberg, 2014).

Oculomotor consequences

There is a wide overlap between brain areas typically affected by FTD and cortical areas responsible for the control of voluntary and predictive eye movements, such as the frontal eye fields (FEF), supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (DLPC) (Anderson & MacAskill, 2013; Antoniades & Kennard, 2015; Gaymard, 2012; Leigh & Kennard, 2004). Therefore, several studies have investigated the eye movements of FTD patients (Henley et al., 2014; Meyniel, Rivaud-Péchoux, Damier, & Gaymard, 2005), and highlighted abnormalities among several FTDs, including Progressive Supranuclear Palsy (PSP), Cortico Basal Degeneration (CBD) and FTDtau. However, the overall picture is complex to interpret, reflecting the wide variety of profiles that can fall under the FTD classification.

In the context of saccades, one study showed longer latencies of reflexive saccades with an increase in the tendency for early saccades in bvFTD (Burrell, Hornberger, Carpenter, Kiernan, & Hodges, 2012), as well as poor performance on an anti-saccade task. This was also found in Douglass, Walterfang, Velakoulis, and Abel (2018), who also showed a deficit in the number of self-paced saccades, but no significant deficit in predictive and memory-guided saccades. In contrast, Boxer, Garbutt, and Seeley (2012) only found higher latencies in AD patients, showing instead that FTDtau patients (FTDP-17, PSP) had decreased horizontal velocity and gain in reflexive saccades. However, they also showed impaired anti-saccades performance in all FTD patients but those with CBD.

Studies of the oculomotor pursuit showed reduced gain and initial acceleration in several types of FTD, but especially in PSP (Boxer et al., 2006; Garbutt et al., 2008). On the contrary, a study

with patients in earlier phases of FTD found normal gains and acceleration, but a specific impairment in predictive reacceleration during the blanking of a pursuit target (Coppe, Orban de Xivry, Yüksel, Ivanoiu, & Lefèvre, 2012). In this study, this impairment was suggested to be linked to a time estimation deficit, which has been documented in other types of tasks in FTD (Henley et al., 2014).

Higher-order saccades such as memory-guided or predictive saccades were only investigated once in bvFTD (Douglass et al., 2018). These saccades involve more brain areas (notably the SEF) and pathways than reflexive saccades, and these pathways overlap with those of predictive smooth pursuit and timing (K. Fukushima et al., 2013; Lee et al., 2016; Lukasova et al., 2018). In particular, predictive saccades require the estimation of timing and might therefore offer a way to reproduce the results of (Coppe et al., 2012), which is the topic of 4th chapter of this thesis.

1.6 Outline of the thesis

Chapter 1

In the current chapter, the context within which this work takes place has been reviewed. First, a short review of the different eye movements contributing to oculomotor target tracking was presented. Then, prediction processes in eye movements were explored, followed by a description of current models for oculomotor pursuit. This was followed by a presentation of the main neural substrates contributing to eye movements. Finally, amblyopia and frontotemporal dementia (FTD) were described, along with their potential effect on eye movements.

Chapter 2

In the second chapter, we explore a core hypothesis of smooth pursuit models based on Bayesian integration (discussed in Chapter 1); namely that short-term memory and visual information about target motion are integrated based on their reliability. To do so, we use a smooth-pursuit task in which the reliability of visual information (the target) and memory information (the number of repetitions) are independently manipulated.

Chapter 3

In the second chapter of this work, we showed evidence for reliability-based integration of visual and memory inputs by the oculomotor system. However, unknowns remained, such as how reliability is estimated, and how prolonged exposure to noisy inputs might affect it. In this third chapter, we investigate reliability estimation by reproducing the experiment of the 2nd chapter with patients exhibiting unilateral amblyopia, for whom visual reliability (from the amblyopic eye) should intrinsically be lower. Thus, we compared amblyopic patients, whose amblyopic eye outputs noisy information, to control participants confronted with a noisy visual input (a noisy target). However, while the visual system of amblyopic patients has developed in the presence of a noisy visual input (the amblyopic eye), this isn't the case for the controls. Our hypothesis was that a different development of the visual system would affect the relative weights of memory and visual information.

Chapter 4

While anticipating the velocity or the position of a target only requires a short-term memory, to anticipate its onset requires the ability to process time. It is known that the frontal lobe plays an important role in timing, and that it is among the main areas affected by FTD. In a previous study, Coppe et al. (2012) highlighted a specific impairment of predictive pursuit during a 800ms blanking in FTD patients, postulating that timing impairments might be at play. Therefore, in chapter 4 we investigate a similar population of FTD patients with a predictive saccade task designed to probe their timing capabilities. Saccades were preferred to pursuit as they are easier to process, which would be valuable in a clinical setting. Our initial hypothesis was that the performance of FTD patients would deteriorate along with the increase of the time between predictive saccades.

Chapter 5

Finally, the main findings of this work are summarized and discussed, and future works are outlined.

Chapter 2

Weighted integration of short-term memory and visual signals in the oculomotor system

Abstract

Oculomotor behaviors integrate sensory and prior information to overcome sensory-motor delays and noise. After much debate about this process, reliability-based integration has recently been proposed and several models of smooth pursuit now include recurrent Bayesian integration or Kalman filtering. However, there is a lack of behavioral evidence in humans supporting these theoretical predictions. Here, we independently manipulated the reliability of visual and prior information in a smooth pursuit task. Our results show that both smooth pursuit eye velocity and catch-up saccade

amplitude were modulated by visual and prior information reliability. We interpret these findings as the continuous reliability-based integration of a short-term memory of target motion with visual information, which support modeling work. Furthermore, we suggest that saccadic and pursuit systems share this short-term memory. We propose that this short-term memory of target motion is quickly built and continuously updated, and constitutes a general building block present in all sensorimotor systems.

2.1 Introduction

Over the last two decades, Bayesian integration of different signals (i.e., the weighted summation based on the respective reliability of each signal) has been widely applied to the study of cognitive processes. Its intrinsic ability to handle the uncertainty of different signals and combine them makes it a particularly useful tool to model how the brain handles the imperfect sensory representations of the external world. Indeed, be it relative to movement (Tassinari, Hudson, & Landy, 2006; J. Yang, Lee, & Lisberger, 2012), learning (Nassar, Wilson, Heasly, & Gold, 2010), or estimation (Stocker & Simoncelli, 2006), numerous studies have highlighted behaviors that exhibit reliability-based integration. Furthermore, when several senses give information about the same event or object, reliability-based integration allows their (near) optimal combination (Ernst & Banks, 2002; Jacobs & Fine, 1999; Landy, Banks, & Knill, 2011). It has recently been suggested (Bogadhi et al., 2013; Orban de Xivry et al., 2013) that internal predictive and sensory afferent information is combined in a Bayes-optimal fashion during smooth pursuit eye movements; this prediction has not been tested explicitly in humans.

The oculomotor system is well studied and offers many typical examples of sensorimotor processes relying on both noisy sensory inputs (Bogadhi et al., 2013; Osborne et al., 2005; Spering, Kerzel, Braun, Hawken, & Gegenfurtner, 2005) and prior experience (Kowler et al., 1984; Madelain & Krauzlis, 2003; J. Yang et al., 2012) to produce accurate movements. For example, visual tracking has to cope with sensory delays (Osborne, Bialek, & Lisberger, 2004) and internal noise (Osborne et al., 2005). By integrating visual inputs with past experience and cues, the oculomotor system can overcome sensory delays and noise to produce eye movements matching current target movement. In the pursuit system, this allows, for example, anticipatory smooth eye movements (Dodge et al., 1930; Hayhoe, McKinney, Chajka, & Pelz, 2012; Kowler et al., 2014; Westheimer, 1954) or zero-lag smooth pursuit tracking of a sinusoidal target motion (Dodge et al., 1930; Orban de Xivry et al., 2013). In the saccadic system, predictive saccades can be observed when tracking a target jumping at a fixed frequency (Shelhamer & Joiner, 2003), or a bouncing ball (Diaz, Cooper, Rothkopf, & Hayhoe, 2013). Thus predictive and sensory information interact to drive oculomotor behavior.

The process of integration of sensory and predictive signals is still up to debate. Several models have been proposed to explain how sensory inputs and predictive signals might be integrated during smooth pursuit: Some have used a switching mechanism between predictive and sensory-feedback processes (Barnes, 2008; Bennett & Barnes, 2004), but in recent years several authors turned to reliability-based integration (Bogadhi et al., 2011; Dimova & Denham, 2009; Freeman et al., 2010; Montagnini et al., 2007).

In 2013, Orban de Xivry et al. proposed a model that, for the first time, was able to simulate the integration of a continuous

flow of sensory information with past experience to drive motor behavior. This model used reliability-based integration (Kalman filtering) both to predict target movement and to simultaneously build a dynamic memory of it. Specifically, the model predicts that the estimated target movement is the reliability-weighted (reliability 1/variance) average of visual and predictive target motion signals, in agreement with Bayes-optimal cue integration. This model managed to reproduce a large repertoire of pursuit behaviors. The same year, Bogadhi et al. (2013) proposed a similar model that used a static memory of target velocity and two recurrent Bayesian networks for sensory and predictive signal integration. However, while there are several studies on the influence of prior information on oculomotor tracking (Kowler, 2011; Kowler et al., 2014; Wende, Theunissen, & Missal, 2013; J. Yang et al., 2012), few if any investigated the mechanisms of integration of such prior information with sensory information, and how the reliability of the memory and the sensory inputs can influence this integration, until very recently, when this was done with monkeys by Darlington, Tokiyama, and Lisberger (2017).

Here, we present two target eye-tracking experiments, with 13 human participants, in which we independently manipulated the uncertainties of visual information and short-term memory. As predicted by the model of Orban de Xivry et al. (2013), we observe reliability-based integration of a short-term memory of target motion with visual information during movement. Furthermore, we extend the results of Darlington et al. (2017) by showing that, in addition to smooth pursuit, catch-up saccades also exhibit features of this reliability-based integration. Given the similarities of smooth pursuit with other cortical sensorimotor systems (Lisberger, 2015; Lynch & Tian, 2006) and recent studies of memory updating

(Gershman, Radulescu, Norman, & Niv, 2014; Nassar et al., 2010), we believe that our results validate an important prediction; continuous reliability-based integration of current sensory information with working memory signals is a general principle that is likely to be part of all sensorimotor processes.

2.2 Methods

2.2.1 Participants

Because of the absence of previous literature on the topic, a power analysis could not be used beforehand to determine the number of participants. We therefore decided to refer to what is typically done in eye movement research and targeted a pool of more than 10 participants per experiment. Twenty participants between 18 and 30 years old were recruited to participate in our experiments. Thirteen participants (four female) participated in the first experiment and 13 (six from the first) in the second experiment (five female).

Participants had normal or corrected-to-normal vision. After being given a full description of the experiment, informed consent was given by the participants. The procedures were approved by the Université catholique de Louvain Ethics Committee and were in accordance with the Declaration of Helsinki.

2.2.2 Protocol

Participants were seated in a dark room, and looked at a 197 $\times$ 150 cm screen at 151 cm in front of them, spanning 64° of their visual field. Head movements were restrained with chin and forehead rests. The stimuli were projected onto the screen with a cine8 Barco projector (Barco Inc., Kortrijk, Belgium) at a refresh rate of

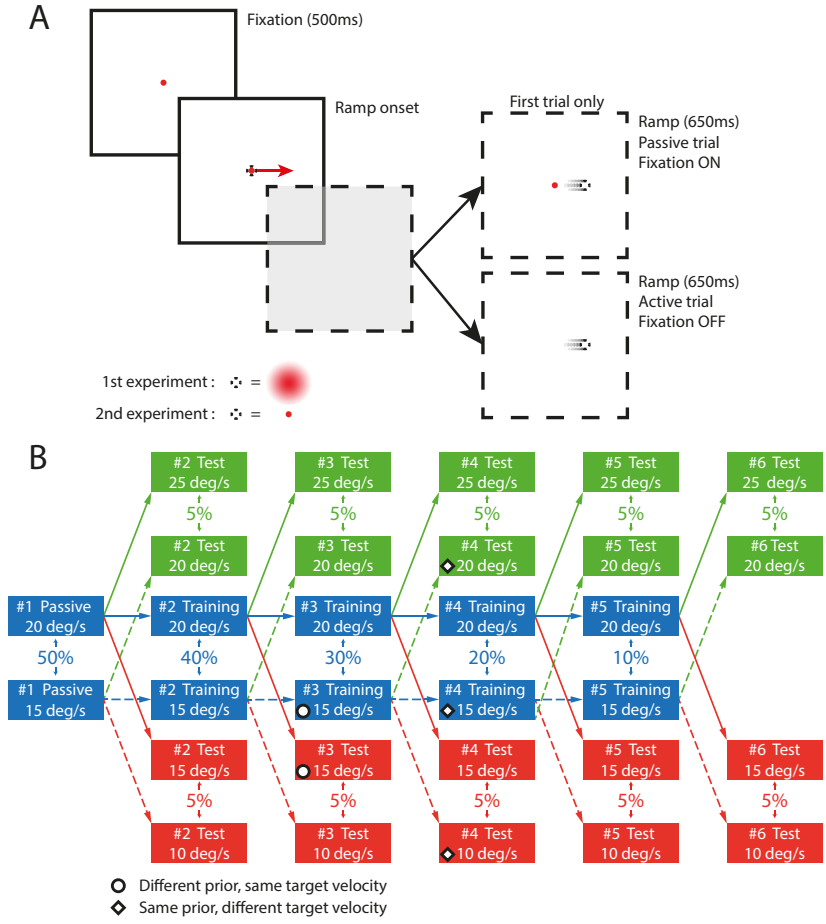

Figure 2.1: Experimental protocol. **A.** Time course of trials (in one of the six possible directions).**B.** Template of blocks (regardless of direction). Each block starts with a passive trial and ends with a test trial (red/green), and direction remains constant within a block. Percentages indicate the % of blocks containing trials of the same type (color) and number (#) at one of the two available velocities (ex: 100% of the blocks have one passive trial). Black rings give an example of two trials that can be compared to highlight the effect of previous trials. Black diamonds give an example of trials comparisons highlighting visual effect. Dashed arrows indicate a 15°/s prior target velocity. Solid arrows indicate a 20°/s prior target velocity. Note that the noisy target shown here has been made more salient in panel A to ensure that it is visible on the figure. Its actual appearance is shown in suppl. Figure 2.11, with suppl. Figure 2.12 showing the standard target as reference.

100 Hz, and the eye movements were recorded at 1,000 Hz using an Eyelink 1000 (SR Research, Ottawa, Ontario, Canada). The display of visual stimuli was handled by an in-house toolbox, while interactions with the Eyelink were handled by the Psychtoolbox (Kleiner et al., 2007). Calibrations trials were first performed at the start of the experiments, then every 30 trials (62 min). Breaks were allowed before every calibration (every 2 min), and the total duration of an experiment was around 30 min.

In the design of the protocol, we wanted to make sure that behaviors could only be related to the current block-that is, that there was no transfer of information between blocks. As such, block duration and features were randomized, direction changed after each block, and each of them started with a passive trial meant to wash out previous block-related memories.

Two types of stimuli were used: a red fixation target (uniform disk, diameter 0.8°) and a red pursuit target. The protocol was identical for both experiments except for the pursuit target. In Experiment 1, the pursuit target was a two-dimensional (2-D) Gaussian spot ($\sigma = 1.278$; hereafter the noisy target, cf. Supplementary Figure 2.11). In Experiment 2, the pursuit target was a uniform disk (0.8° of diameter; hereafter the standard target, cf. Supplementary Figure 2.12). The overall luminance of the stimuli was the same for all stimuli; however, given the difference in the distribution (the pixel at the center of the noisy target has 5% of the luminance of any pixel of the standard target), the noisy target was harder to perceive.

For both experiments, there were three types of trial: passive, training, and test. All trials started with the display of the fixation target at the center of the screen. After 500 ms, the pursuit target appeared at the center and immediately moved in one out of six

possible directions (20°, 0°, 20°, 160°, 180°, or 200°) at a constant velocity (15°/s or 20°/s for training trials) during 650 ms. In passive trials, the fixation target remained on for the whole trial, and participants were instructed to keep looking at the fixation target while inhibiting movements toward the pursuit target. In the other trials, the fixation target disappeared at the onset of the pursuit target and participants were instructed to follow the pursuit target with their eyes (see Figure 2.1).

The trials were presented in blocks: Each block consisted of one passive trial followed by one to five trials with 850 ms between trials. To warn participants of the start of a new block, an auditory cue (440 Hz, 80 ms) was given 200 ms before the appearance of the fixation target. Target direction and velocity remained constant throughout a block, except for the last trial, hereafter named test trial, for which velocity was reduced or increased by 5°/s with respect to previous trials of the same block. Training trials are the trials displayed between the passive trial and the test trial. To summarize, each block started with one passive trial and ended with one test trial, with up to four training trials in between (Figure 2.1B).

As examples of two possible blocks, we will describe the three-trial block ending at the black-ring marked (red) test trial, and the six-trial block ending with the (green) test Trial 6 at 20°/s (cf. Figure 2.1B). The three trial block begins at Trial 1 with a passive trial with a target at 20°/s. It is followed by one training trial (Trial 2), also at 20°/s. The last trial (Trial 3) is a test trial that, in this case, has a lower (red arrow) target velocity of 15°/s. The six-trial block also begins with a passive trial (Trial 1), this time at 15°/s. Knowing that, we can then follow the dashed arrows (indicating a prior target velocity of 15°/s) and identify the ensuing four training

trials (Trials 2-5) that have the same target velocity of 15°/s. The final trial is the test trial (Trial 6) that has a higher (green arrow) target velocity of 20°/s and concludes the block. There were 120 conditions in total (6 Directions x 2 Training Velocities x 5 Block Lengths x 2 Test Velocities). The average number of trials per condition was four, yielding 480 trials per participant.

In this protocol, we expected the noisy target to elicit less reliable visual information, and the repetition of training trials to elicit more reliable short-term memory of target motion. Within the framework of the model (Orban de Xivry et al., 2013), the reliability of each of these inputs directly affects its weight in the integration of target motion (according to Bayesian or more generally reliability-based integration). As a consequence, the mismatch in target velocity created by test trials will lead to different eye velocity outcomes depending on the relative reliabilities of short-term memory and visual information.

2.2.3 Comparisons between trials

To observe the influence of previous trials on the oculomotor response, we compared trials that had the same current target velocity, but different past target velocities (different prior trials). For example, we compared test trials having a target velocity of 15°/s (thus preceded by training trials at 20°/s) with training trials having a target velocity of 15°/s (thus preceded by training trials at 15°/s). In this situation, visual information (target motion) is the same for both test and training trials, but prior information is different, effectively highlighting its effect (cf. black rings in Figure 2.1B).

In a similar way, the impact of visual information was esti-

mated by comparing test trials to training trials that had the same past target velocity, but different current target velocities. (cf. black diamonds in Figure 2.1B). We always made comparisons between trials with the same trial number (in the same column on Figure 2.1B).

2.2.4 Data processing

Data were processed using the MATLAB software (RRID: SCR_001622; MathWorks, Natick, MA). Blinks were detected based on missing values in the Eyelink output (when the pupil cannot be detected) and subsequently removed from the data, including a safety margin before and after the blink, up to the first local minimum in the y-coordinate. Eye position signals were low-pass filtered at 40 Hz. Eye velocity and acceleration were obtained from position signals using a central difference algorithm on a ±10-ms interval. For the analyses, we pooled data across all directions.

Saccade onset and offset were detected using a $500°/s^2$ threshold on the acceleration data. Saccades were thereafter removed from smooth eye velocity data and replaced by linear interpolation.

In order to remove abnormal trials from the data set while limiting visual inspection of the data, we set a few criteria: (a) during the last 100 ms of fixation, eye position within 3° of the fixation target, (b) no missing data (blinks) in the first 450 ms of pursuit, (c) lower limit on eye displacement of at least 40% of target displacement, (d) no eye velocity over 40°/s during pursuit epochs. Based on these criteria, we set aside less than 3% of the trials. When analyzing eye velocity during pursuit epochs, we included only trials for which steady state pursuit velocity reached 33.33%

of target velocity (98% of trials).

Measures of pursuit features

In this protocol, we took no step to reduce the occurrence of catch-up saccades in the early phases of pursuit, as we wanted to guarantee continuous target display (no gap) and coherent target direction within a block (no step-ramp paradigm; Rashbass 1961). As a consequence of this approach, most trials contain saccades during the early phase of pursuit. This, combined with the lower eye velocity (in particular for the noisy target) makes measures of pursuit features more difficult during this phase. Looking at the very start of the initiation, around 100 ms, would avoid most saccades; however, our interest is in the integration process of visual information with prior information, the former of which is barely accessible at that time.

Therefore, we concentrated our analyses on the steady-state phase of smooth pursuit, during which eye velocity is higher, eye acceleration is lower, and saccades are more uniformly distributed, which allows us to make more robust measures of eye velocity. In parallel, we were able to study the integration of visual and prior information in the early pursuit through the analysis of catch-up saccades.

Fitting algorithm:
Pursuit onset and eye movement velocity during steady-state were obtained for each trial by fitting a piece-wise linear regression on the eye velocity data (least square regression, using the *lsqcurvefit* function of the MATLAB Optimization Toolbox), as follows (Figure

2.2, Equation 2.2.4):

$$f(t) = \begin{cases} P1 \; if \; t \leqslant T1 \\ P1 + B \times (t - T1) \; if \; T1 < t \leqslant T2 \\ P2 \; if \; T2 < t \end{cases} \tag{2.1}$$

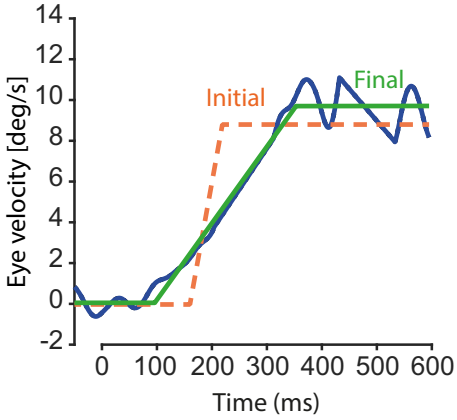

Figure 2.2: Typical fit and its initial parameters. The dashed line illustrates the initial parameters for the fit. The continuous line shows the resulting fit of the eye velocity data.

Where t is time in seconds, P1 and P2 are velocity plateaus (representing initial and steady-state velocities, in degrees per second), T1 and T2 are the reaction time and the pursuit steady-state onset time (seconds), and B is the initial acceleration, connecting the plateaus between times T1 and T2 (degrees per second squared). P1, P2, T1, and B were the free parameters of this fit. The fitted interval spanned 650 ms, from 50 ms before target onset up to 600 ms after.

Initial parameters for P1, P2, T1, and B were determined as follows: P1 was set to the average velocity in the first 100 ms of the interval, T1 to the time after which the eye velocity exceeded 20% of the target velocity. The variable T2 was defined as the start of the subinterval during which eye velocity exceeded 33% of the target

velocity for at least 125 ms. P2 was then set to the average value of the eye velocity during the interval. Finally, B was determined from the previous parameters, such that it didn't exceed $150°/s^2$. If any of the conditions couldn't be met, or if a suitable interval (33% of target velocity for 125 ms) couldn't be found, the initial parameters were set to default values: T1 to 150 ms, T2 to 350 ms, and P2 to 80% of the target velocity.

Since we wanted the fitting algorithm to measure smooth pursuit eye velocity, we gave less weight to the eye velocity data interpolated during catch-up saccades, setting it to 0.3 (compared to 1 for pursuit data). After applying the fitting algorithm, trials whose steady-state velocity plateau (P2) duration was under 50 ms were analyzed again. They went through a second step of fitting, using the same function, but with T2 as a free parameter instead of B. This allowed the use of a different set of initial values, with a steady-state velocity plateau lasting at least 50 ms. After the second fitting, any trial whose fitted steady-state plateau (P2) was still less than 50 ms long was rejected (6% of trials), as it meant that the algorithm could not find the steady-state of the smooth pursuit.

Computation of smooth pursuit eye velocity gain:
The eye velocity gain of training trials was computed simply by dividing the eye velocity during steady state by the target velocity. Test trials, by definition, always have a target velocity that differs from the previous trial. To be able to compare them with training trials, we computed the eye velocity gains of test trials by dividing the eye velocity during steady state by the target velocity of training trials with the same trial number. The training trials used were the ones the test trials were being compared to, and therefore depended on the type of comparison (prior or visual, as defined below).

When studying the influence of prior information, the eye velocity gains were computed with respect to the training trials having the same target velocity as the test trials (cf. black rings in Figure 2.1B). For example, the data in the red error bar of Figure 2.4B correspond to test trials having a prior target velocity of 20°/s and a current target velocity of 15°/s. Since these test trials are compared to training trials with a target velocity of 15°/s, the eye velocity is divided by 15 and the mean of training gains is subtracted from it. The result is bigger than zero, revealing an effect of prior information. In a similar way, the data in the green error bar of Figure 2.4B corresponds to test trials with a prior velocity of 15°/s and a current target velocity of 20°/s, whose gain is therefore computed by dividing eye velocity by 20, and from which the average gain of training trials at 20°/s is also subtracted.

When studying the influence of visual information, the eye velocity gains were computed with respect to the training trials having the same prior target velocity as the test trials (cf. black diamonds in Figure 2.1B). For example, the data in the green and red dashed error bars of Figure 2.5B correspond to test trials having a prior target velocity of 15°/s (indicated by the dashes) and either 20°/s (green) or 10°/s (red) of current target velocity. We compare them to training trials having the same prior target velocity, 15°/s, and therefore divide the eye velocity by 15 before subtracting the mean gain of training trials, highlighting the effect of the change in target velocity.

Normalization of gains across the two training target velocities: Our protocol is such that test trials target velocities matched training trials target velocities at 15°/s and 20°/s. As such, the sign of the prior effect on eye velocity was positive at 15°/s (prior at 20°/s) and negative at 20°/s (prior at 15°/s). To be able to compare across

the two training target velocity conditions, we normalized, for each participant, the difference of eye velocity between training and test trials by the difference between their prior target velocities according to the following Equation 2.2 :

$$NormEffect_{prior} = \frac{\begin{array}{r} mean(Eye\ Velocity\ of\ Training) \\ -\ Eye\ Velocity\ of\ Test \end{array}}{\begin{array}{r} Prior\ Target\ Velocity\ of\ Training \\ -\ Prior\ Target\ Velocity\ of\ Test \end{array}} \tag{2.2}$$

When the comparison across velocities had to be made for the effect of visual information, we normalized, for each participant, the difference of eye velocity between training and test trials by the difference of their target velocities using the following Equation 2.3:

$$NormEffect_{visual} = \frac{\begin{array}{r} mean(Eye\ Velocity\ of\ Training) \\ -\ Eye\ Velocity\ of\ Test \end{array}}{\begin{array}{r} Target\ Velocity\ of\ Training \\ -\ Target\ Velocity\ of\ Test \end{array}} \tag{2.3}$$

Both equations allowed us to report the effects of visual or prior information on eye velocity as a percentage of the change in target velocity (5°/s).

Saccade metrics

We also studied the amplitude of the first (catch-up) saccade occurring between 100 and 400 ms after target onset (94% of first saccades made after target onset). The amplitude of the catch-up saccades made during training trials was used as a reference to build a linear model of the saccadic behavior of each participant (cf. Figure 2.3).

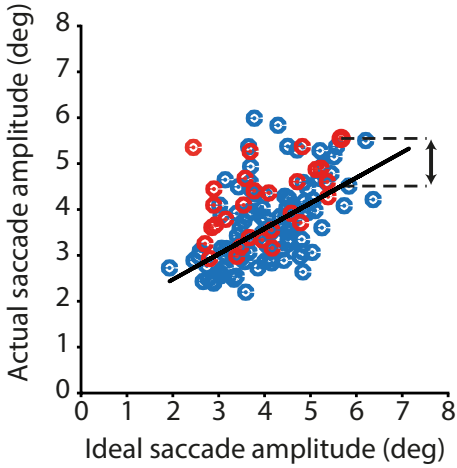

Figure 2.3: Computation of saccade residuals. Blue dots correspond to saccades made during training trials, red dots to saccades made during test trials with the same target velocity, but whose prior trials had a higher target velocity. The fit made on the training data is shown by the black line. Dashed lines and arrows show the measure of the residual of one of the test trials.

For each of the participants, we computed the ideal amplitude of each saccade (difference between eye position at the onset and target position at the offset), and its actual amplitude. Then, the baseline relationship between those two parameters was obtained from training trials by fitting a linear regression (robustfit function, Statistics Toolbox, MATLAB) on the saccades data. Finally, saccades made during test trials were compared to this regression line by computing the mean of the residuals (vertical distances between test saccades data points and the regression line). Given this method, a mean value greater than zero implied that saccades made during test trials had larger amplitudes than those made during training trials.

To compare saccades made during test trials across experiments (standard and noisy targets), we had to take into account differences of saccade latency between the two experiments. On average, the first catch-up saccade elicited in the noisy target experiment was made 50 ms later than in the standard target one. To keep our analysis clear and limit the number of parameters to ac-

count for, we decided to only compare saccades of similar latencies, for which participants had the same exposure to the visual stimuli.

Therefore, we used a bootstrap procedure to create $N = 10,000$ samples of saccades from the two experiments, such that, for each sample, the latency distributions of the two experiments would be the same. This was done for each training target velocity. For each participant, the average residuals (one per training velocity) for each experiment were then obtained by averaging the average residuals (R_i) obtained for each of the 10,000 bootstrapped samples ($R = \frac{1}{N}\sum \overline{R}_i$). For example, considering the saccades depicted in Figure 2.3, the bootstrap procedure might give several subsets of the red dots (test trials), which will then be compared to the regression model built from all blue dots (training trials) to obtain one average residual per subset.

2.2.5 Data analysis

The effect of prior information (see previous section) on eye velocity or saccade amplitude was analyzed by comparing trials with the same target velocity but different priors of target velocity. For each training target velocity there was only one corresponding test target velocity condition (test at $20°/s - 5°/s$ for a training at $15°/s$, $15°/s + 5°/s$ for a training at $20°/s$). For each of those two conditions separately, we compared eye movement measures using a repeated measures analysis of variance (rANOVA), using the trial number (four levels) and the type of trial (training or test) as within-subjects factors.

The effect of visual information on eye velocity or saccades was analyzed by comparing trials with the same target velocity during the previous trials ($15°/s$ or $20°/s$) but with different target velocities

in the current trial (three levels: 5°/s, 0°/s, 5°/s with respect to target velocity during the previous trials, which correspond to three types of trial: test: 5°/s, training, and test 5°/s). Eye movement measures were compared using repeated measures ANOVA with the following within-subject factors: target velocity in previous trials (two levels), type of trial (three levels), and trial number (four levels).

When comparing data across the two types of target to examine differences in the magnitudes of the effects, we used a mixed-design ANOVA with the type of target as between-subjects factor. Comparisons on the effect of the prior were made for the two velocity conditions (after normalization with training data), and included the trial number as within-subject factor. The comparison was also made with the velocity condition as an additional within-subject factor. Comparisons on the effect of visual information were made with target velocity in previous trials, type of trial and trial number as within-subject factors.

We analyzed the influence of the number of trials on the magnitude of the effects using linear regressions on the means per participant and per trial number. ANOVAs and linear regressions were performed with the R software (R Core team 2016, RRID:SCR_001905; ez package 2015). Sphericity assumptions were verified through Mauchly's Test for Sphericity. If sphericity assumptions were violated, we only reported results that were significant after Huynh-Feldt sphericity correction. When appropriate, we also reported the generalized eta-squared (ges) as a measure of effect size (Bakeman, 2005).

2.3 Results

In this study, we varied the reliability of sensory and prior information independently in order to see how each of these information channels can influence the oculomotor response.

Our first hypothesis was that the noisy (Gaussian) target would be harder to track for the participants. This was confirmed by measures of the pursuit onset (respectively to target onset) in the second trial (mean of 145.5 ms for the noisy target, 87.4 ms for the standard target; $F(1, 24) = 18.37$, $p = 0.0003$, $ges = 0.38$), and lower visual smooth pursuit gains overall (0.75 for the noisy target, 0.89 for the standard target; $F(1, 24) = 11.98$, $p = 0.0026$, $ges = 0.31$). These overall differences are not expected to affect further results, which are always relative to training trials done with the same target.

From this, we expected to observe a hallmark of Bayesian integration on measures of eye movements: dynamic weighting of the effects of prior and sensory information as a function of their reliability. More precisely, we expected to see stronger effects of prior information-and weaker effects of visual information- with the noisy target, thus highlighting a weighting dependent on visual reliability. At the same time, we also expected a gradual increase of the effect of prior information with each trial repetition, highlighting the increase of the reliability of prior information.

2.3.1 Prior information about the target velocity biases smooth pursuit eye velocity

We measured the effect of prior information on smooth pursuit by comparing eye velocity for a selection of test and training trials

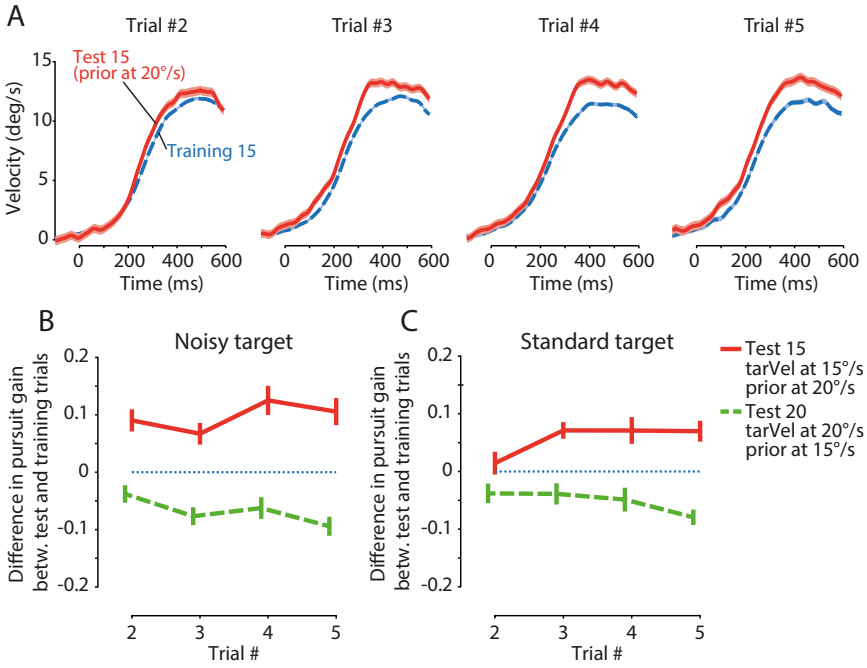

Figure 2.4: Prior information effect on eye velocity gain. **A** Averaged eye velocity traces of Training15 and Test15, for all participants (of the first experiment, noisy target), for all trials allowing direct comparison between a test and a training condition with a current target at 15°/s. Blue traces are the average eye velocity of training trials, while red traces are those of the test trials. The surrounding hue indicates the standard error of the mean. **B** Averages of participant's average differential gains of the smooth pursuit eye velocity response to a noisy target moving at 15°/s (full red line) or 20°/s (dashed green line) that was preceded by trials with the same target either at a higher (20°/s, full red line) velocity or a lower (15°/s, dashed green) velocity (test trials). The error bars indicate the standard error of the mean. **C** Same as panel (B), but for the second experiment with a standard target. Dashed lines indicate a 15°/s prior target velocity.

(Figure 2.1B). The selected trials had identical target velocities (for example 15°/s) during the current trial but different target velocities during the previous ones (for example 15°/s for training and 20°/s for test trials). In addition, these trials were matched by trial number. Therefore, any difference in behavior between these test and training trials has to be attributed to the influence of prior information on the oculomotor response. This comparison is illustrated on Figure 2.4A, which shows average eye velocity profiles (noisy target) for training and test trials for different trial numbers. On this figure, a clear and long-lasting bias (up to 500 ms after the target motion onset) can be seen. Furthermore, this bias appears to increase with the number of previous trials, which is further discussed in the last part of the results section.

To evaluate the influence of the prior information on the smooth pursuit response, we computed the steadystate smooth pursuit gain for each trial (see Methods) and subtracted the gain of the training trial from the gain of the corresponding test trial (Figure 2.4B and C). For example, the test data from Panel A corresponds to the solid red error bar in Panel B. For all types of test trials, the smooth pursuit response was biased towards the velocity of the preceding trials (main effect of trial type; noisy target, test15: $F(1, 12) = 51.81$, $p < 0.0001$, $ges = 0.17$, test20: $F(1, 12) = 53.11$, $p < 0.0001$, $ges = 0.1$; standard target, test15: $F(1, 12) = 21.38$, $p = 0.0006$, $ges = 0.07$, test20: $F(1, 12) = 24.95$, $p = 0.0031$, $ges = 0.06$). That is, on a given trial, the steady state smooth pursuit gain was higher (respectively lower) if this trial was preceded by trials with higher (respectively lower) target velocity. This demonstrates the effect of prior information on smooth pursuit eye velocity. This effect was true for both target types.

2.3.2 Visual information about the target velocity affects smooth pursuit eye velocity

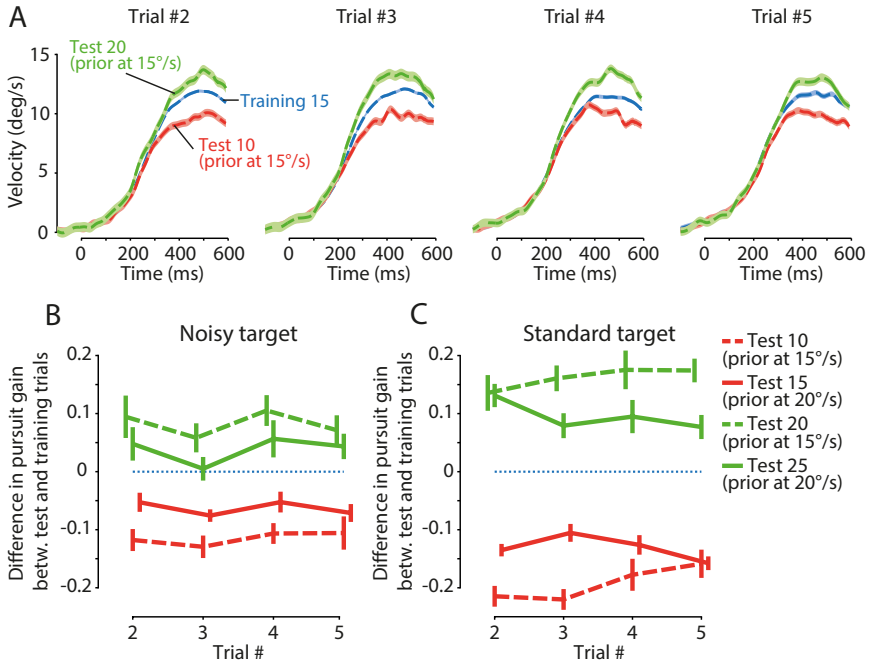

Figure 2.5: Visual information effect on eye velocity gain. **A.** Averaged velocity traces of all participants (noisy target), for all trials with the same target velocity prior—15°/s— and all comparable trial numbers (all but the first and the last). The conditions Training15 (blue trace), Test10 (decrease of velocity, red trace) and Test20 (increase in velocity, green trace) have the same prior at 15°/s. The hue around each trace is the standard error of the mean. **B.** Averages of participant's average differential gains of the smooth pursuit eye velocity response to trials of a noisy target moving at 10°/s or 20°/s (respectively red and green dashed lines) or at 15°/s or 25°/s (respectively red and green solid lines) that were preceded by trials with the same target either at a higher velocity (all red lines) or a lower velocity (all green lines). The x-axis indicates the trial number and the error bars the standard error of the mean. **C.** Same as Panel (B), but for the second experiment with a standard target.

The impact of visual information on the smooth pursuit eye movements was measured by comparing test and training trials that

had the same prior information (same number of previous trials with the same target velocity), but different target velocities (see Figure 2.1B).

Looking at eye velocity, this comparison (see Figure 2.5A) showed that visual information had a clear effect: Conditions having a higher target velocity showed, when compared to training conditions, a bias towards higher eye velocities and conditions having a lower target velocity showed a bias towards lower eye velocities. This effect was already present during the first active trial (Trial 2), persisted during later trials, and could be observed as late as 500 ms after the target onset.

To highlight the effect of visual information on smooth pursuit eye velocity, we computed the difference of pursuit gains (see Methods) to obtain the change in pursuit gain between test and training trials. The differential gains show that the visual information modulated the smooth pursuit gain for all conditions of each experiment (Figure 2.5B and C), which was confirmed by statistical analyses.

We found that the steady state eye velocity gains of test trials were significantly different from those of training trials, both for the noisy target (main effect of trial type: $F(2, 24) = 37.03$, $p < 0.0001$ Huynh-Feldt corrected, $ges = 0.23$) and the standard target (main effect of trial type: $F(2, 24) = 124.29, p < 0.0001$ Huynh-Feldt corrected, $ges = 0.53$). Note that the interaction with the trial number is discussed in the last section of the Results.

For both types of target, the magnitudes of the biases were higher for the conditions for which prior target velocity was at 15°/s (interaction effect between trial type and prior target velocity; noisy target: $F(2, 24) = 29.34, p < 0.0001$ Huynh-Feldt corrected, $ges =$

0.03; standard target: $F(2, 24) = 30.08, p < 0.0001$ Huynh-Feldt corrected, $ges = 0.05$). Thus overall, visual information affected pursuit gain.

2.3.3 Saccade amplitude is biased by prior information about the target velocity

It is known that saccade and pursuit share many inputs. In particular, catch-up saccade amplitude is dependent on the difference between target and eye velocity (de Brouwer, Missal, Barnes, & Lefèvre, 2002). Therefore, if the internal representation of target velocity is biased by prior information, we would expect that this bias also results in alterations of catchup saccade amplitude. Thus, we tested if the prior information about the target motion would also influence the catch-up saccades. To do so, we compared the amplitude of saccades in test and training trials by computing the difference between the amplitude of saccades made during test trials and the amplitude of saccades made during training trials of the same target velocity (see Methods and Figure 2.3).

We found that saccades were biased by prior information about target velocity; the amplitude of saccades made during test trials was more likely to be larger than during training trials if the previous trials had a higher target velocity and to be smaller if the previous trial target was slower (main effect of trial type; noisy target, test15: $F(1, 12) = 34.47$, $p < 0.0001$, $ges = 0.28$, test20: $F(1, 12) = 18.62$, $p = 0.001$, $ges = 0.18$). When the standard target was presented on the screen, we found a similar effect of the prior on saccade amplitude (standard target, test15: $F(1, 12) = 6.82$, $p = 0.023$, $ges = 0.02$, test20: $F(1, 12) = 17.1$, $p = 0.0014$, $ges = 0.16$). Figure 2.6A illustrates this effect on some representa-

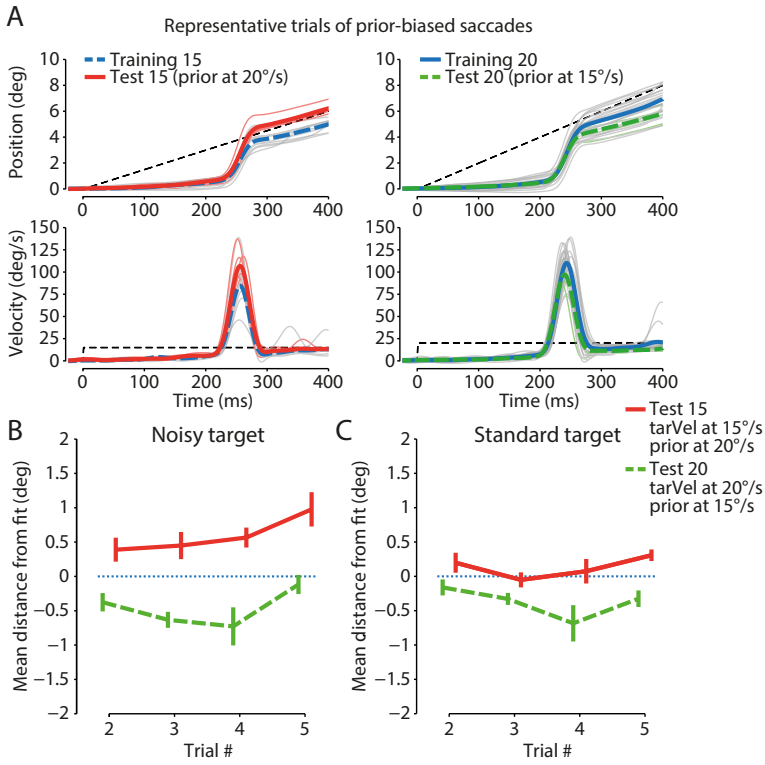

Figure 2.6: (A) Effect of prior information on concomitant saccades. Position and velocity profiles of saccades made at the same time (15-ms window) in representative training and test trials. Left panel: Saccades made around 220 ms after the onset of the target, during training trials with a prior of target velocity at 15°/s (blue traces) and test trials with a prior of target velocity at 20°/s (red traces). Right panel: Saccades made around 220 ms after the onset of the target, during training trials with a prior of 20°/s (blue traces) and test trials with a prior of 15°/s (green traces). (B) Effect of prior information on saccades (noisy target). Averages of participant's average residuals (vertical distance from fit on training data) of the amplitude of saccades made during test trials, with respect to the trial number. The blue dotted line indicates the training reference (that has been subtracted from all data), red/green traces show residuals of saccades made during test trials. The error bars indicate the standard error of the mean. (C) Same as Panel (B), but for the second experiment with a standard target.

tive trials from one participant. Another way to look at this effect is presented in Figure 2.3, where it can be observed that the data

points from test trials - the red dots-tend to be located above the regression line, indicating a bias towards larger saccades coherent with an effect of a higher target velocity prior.

Because saccades can sometimes be adjusted online via internal feedback, we also studied the peak velocity of the saccades, as it is a good marker of saccade planning (Chen-Harris, Joiner, Ethier, Zee, & Shadmehr, 2008). Similarly to saccade amplitude, we also found peak velocity to be biased towards prior target velocity. Peak velocity tended to be higher, compared to training trials, during test trials with higher prior target velocity, while it tended to be lower when prior target velocity was lower (main effect of trial type; noisy target, test15: $F(1, 12) = 24.05$, $p = 0.0004$, $ges = 0.26$, test20: $F(1, 12) = 12.95$, $p = 0.0037$, $ges = 0.10$; standard target, test15: $F(1, 12) = 5.36$, $p = 0.04$, $ges = 0.05$, test20: $F(1, 12) = 14.5$, $p = 0.0025$, $ges = 0.17$).

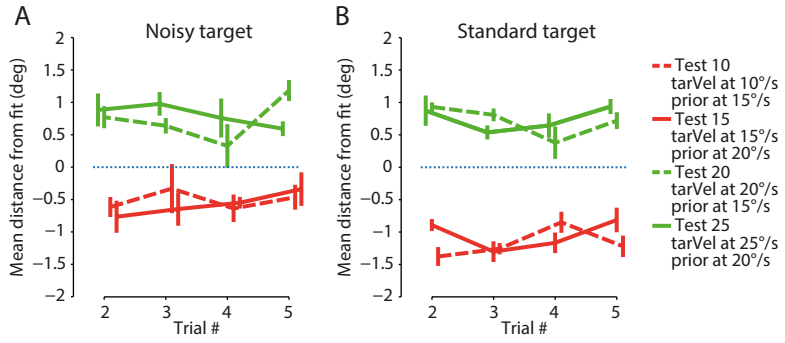

Figure 2.7: (A) Effect of visual information on saccades. Averages of participant's mean residuals (vertical distance from fit on training data) of the amplitude of saccades made during test and training trials, with respect to their trial number. Red/green traces show residuals of saccades made during test trials (the training residuals have been subtracted from all data). The x-axis indicates the trial number and the error bars the standard error of the mean. (B) Same as Panel (A), but for the second experiment with a standard target.

2.3.4 Saccade amplitude is also biased by visual information about the target velocity

As a sanity check for our analysis of saccades, we compared saccades made within conditions having the same prior information and different visual information about the target velocity. As expected, saccade amplitude was also influenced by visual information (Figure 2.7), meaning that catch-up saccades accounted for the velocity change. Test trials with a higher target velocity than training trials (green traces) had larger saccade amplitude, and conversely, test trials having a lower target velocity (red traces) than training trials exhibited smaller saccades. Once more, this effect was present for all velocities, and in both experiments (main effect of trial type, noisy target: $F(2, 24) = 69.39, p < 0.0001$ Huynh-Feldt corrected, $ges = 0.4$; standard target: $F(2, 24) = 211.96, p < 0.0001$ Huynh-Feldt corrected, $ges = 0.7$). We found no influence of the training (previous) target velocities (15°/s and 20°/s) on the magnitude of the effect (cf. dashed lines vs. full lines in Figure 2.7).

2.3.5 Lower visual information reliability induces stronger prior information effect

By comparing the normalized effect of prior information across the two types of target (Figure 2.8), we found that the influence of the prior was significantly stronger for the noisy target than for the standard target. As such, the magnitude of the effect on eye velocity was significantly different between the two targets (main effect of target type: $F(1, 24) = 4.43$, $p = 0.046$, $ges = 0.08$). Furthermore, we observed significant differences of the modulation of saccade amplitudes by prior information (main effect of target type: $F(1, 24) = 7.17$, $p = 0.0132$, $ges = 0.08$). In other words,

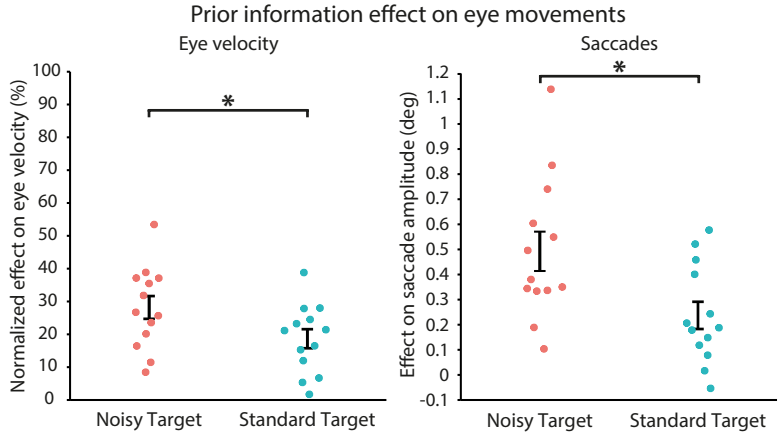

Figure 2.8: Magnitude of the effect of prior information on eye velocity (left panel, % is relative to the target velocity change: 5°/s, cf. Equation 1) and on saccade amplitudes (right panel). Dots are participant's averages across velocities. Error bars are centered on the averages of participant's averages across both comparable velocities and indicate standard errors of the mean. Significance (* indicates p , 0.05) refers to a mixed design ANOVA with within-factors "target velocity" and "trial#" and between-factors "type of target".

when confronted to a noisy, less reliable target, participants gave more weight to prior information than when confronted to the standard target. This effect of prior information also appeared to vary depending on the participants, as shown by the vertical spread of the individual averages of the effects.

2.3.6 Higher visual information reliability induces stronger visual information effect

As a complement to the previous analysis, comparing the two types of target (Figure 2.9), we found that the standard target elicited a stronger effect of the visual information on both smooth pursuit and saccadic eye movements. Indeed, the effect on eye velocity was stronger (main effect of target type; $F(1, 24) = 20.77$, $p < 0.0001$,

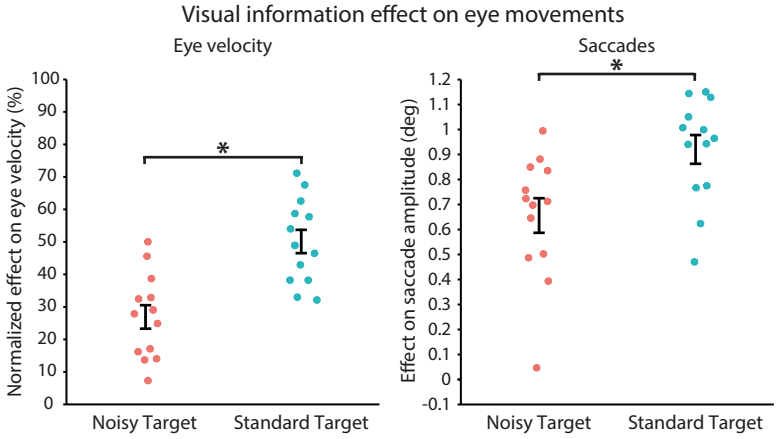

Figure 2.9: Magnitude of the effect of visual information on the eye velocity (left panel, % is relative to the target velocity change: 5°/s, cf. Equation 2), and on saccade amplitude (right panel). Dots are participant's averages across comparable velocities. Error bars are centered on averages of participant's averages across velocities and indicate standard errors of the mean. Significance (* indicates p , 0.05) refers to a mixed design ANOVA with within-factors "training target velocity" and "trial#", and between-factors "type of target".

$ges = 0.26$), and saccade amplitude was more strongly modulated (main effect of target type; $F(1, 24) = 8.64$, $p = 0.007$, $ges = 0.1$) when the target was standard rather than noisy. This behavior, opposite to that of prior information, is coherent with the hypothesis that the reliability of visual information is higher for the standard target than for the noisy target, which would give more weight to visual information when pursuing the standard target. Again, this effect appeared to vary depending on the participants, as can be seen in the spread of the individual averages of the effects.

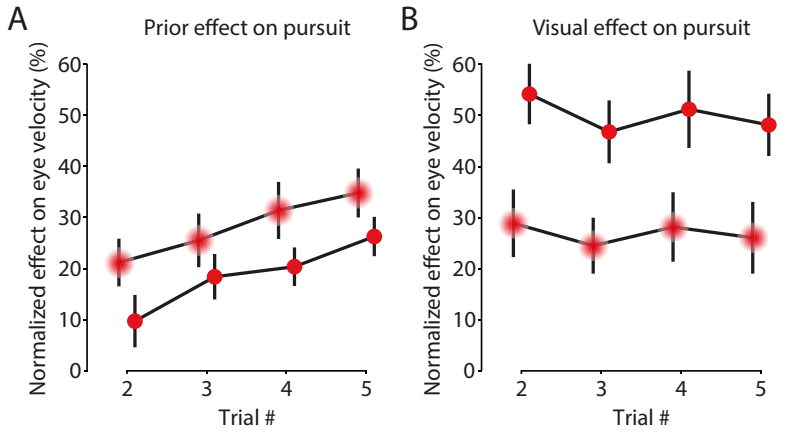

Figure 2.10: Effect of trial number. (A) Influence of trial number on the magnitude of the effect of prior information on eye velocity (averages of participant's averages). (B) Influence of trial number on the magnitude of the effect of visual information on eye velocity (averages of participant's averages). Percentages are relative to the target velocity change (% of 5°/s). Error bars indicate the standard error of the mean.

2.3.7 Higher prior reliability induces stronger effect of the prior, but doesn't seem to affect visual effect

Postulating that the reliability of the prior information increases with the number of repetitions (Orban de Xivry et al., 2013), we analyzed how the effect of prior information evolves with trial number. To do so, we computed a simple linear regression on normalized measures of the smooth pursuit gain (see methods) to predict the effect magnitude based on the trial number.

Across target types, we found that the magnitude of the effect of the prior on the eye velocity gain significantly increased with the trial number (significant regression slope of 4.9%/trial: $F(1, 206) = 11.39$, $p = 0.0009$), supporting the hypothesis that the weighting of prior information is dynamically updated to reflect its reliability

(Figure 2.10A). We also computed the linear regression separately for each target type, and observed that for both targets there was a significant increase of the effect with the trial number (noisy target: slope of 4.7%/trial, $F(1, 102) = 5.1$, $p = 0.026$; standard target: slope of 5.2%/trial, $F(1, 102) = 6.76, p = 0.011$).

In contrast, we found no indication (p . 0.39) of an effect of the number of repetitions on the impact of visual information on eye velocity (Figure 2.10B).

Note that we could not perform the analysis of interaction of the number of repetitions on saccades because, since we had to match saccade latency distributions to compare saccades across targets (experiments), the number of comparable saccades was reduced by almost 50%. Consequently, the number of comparable saccades per (test) trial number was too low for such an analysis.

2.4 Discussion

To investigate the dynamic reliability-based weighting of visual information and memory of target motion during eye movements, we asked participants to visually track either a noisy (Gaussian) target or a standard target for a variable number of identical trials. Then, we tested how the nervous system weighted new sensory information and prior expectations by presenting a trial with a different target velocity. Our results show that previous trials had a greater effect on eye velocity and catch-up saccades amplitude when the target was a Gaussian blob, in a manner consistent with a reliability-weighted integration of visual information with short-term memory. It was also observed that the effects of previous trials on eye movements appeared as early as after one trial and increased with the number of trials, hinting at a short-term memory

of perceived target motion that is dynamically built and updated.

2.4.1 Eye movements use a reliability-based representation of target motion

It has been known for a long time that extraretinal and sensory signals can both drive smooth pursuit (Barnes & Asselman, 1991; Dodge et al., 1930; Kowler & Steinman, 1979a); however, how these two signals are integrated within the pursuit system has remained elusive. The first models including predictive smooth pursuit had a separate predictive pathway, activated by switches (Barnes, 2008). Such models often struggled to explain the transition between predictive and reactive pursuit and why predictive signals are observed despite the randomization of target features (Kao & Morrow, 1994; Kowler & McKee, 1987).

In recent years, new models of smooth pursuit able to combine sensory and extraretinal signals without the need for a switch between pathways have appeared. The models of Orban de Xivry et al. (2013) as well as Bogadhi et al. (2013) both included two separate recursive Bayesian/Kalman filters (one for visual inputs, one for extraretinal inputs) and could reproduce many aspects of smooth pursuit behavior in different contexts of visual information. They differed in a few aspects, including the type of memory of the target and assumptions about the visual reliability of the target. The recent model of Darlington et al. (2017) took a different approach, in which a prior (extraretinal input) directly enhances the gain of the visual-motor transmission of sensory inputs of similar direction and velocity, hinting at a role of the smooth eye movement region of the frontal eye fields (FEF_{sem}) in the representation of the prior.

Here, we mainly refer to the model of Orban de Xivry et al. (2013) because we can compare its predictions of the repeated tracking of a noisy target to our experiments. With a few modifications, we believe that similar predictions could be made by the model of Bogadhi et al. (2013). The model of Darlington et al. (2017) can predict the effect of prior on smooth pursuit without modification. However, its implementation of priors is oriented towards smooth pursuit gain modulation, and would need to be extended to saccades to explain the effect of prior on saccade amplitude that we observed. In contrast, the models of Orban de Xivry et al. (2013) and of Bogadhi et al. (2013) are less specific and could explain this effect through the influence of the prior on their prediction of the retinal slip, which is known to be taken into account by the saccadic system to produce catch-up saccades (Daye et al., 2014; de Brouwer, Missal, et al., 2002).

Compared to the predictions of the model of Orban de Xivry et al. (2013), we found that our results supported them. Indeed, the modulation of the effect of previous trials on eye velocity by both the reliability of visual information (noisy or standard) and the reliability of the memory (number of repetitions) are strong indicators of a reliability-based integration of visual information with a memory of target motion. Furthermore, these results reproduce, with humans, the results of Darlington et al. (2017) regarding eye velocity and highlight the gradual increase of the reliability of prior information. Importantly, our results go further than these studies by showing that similar processes are at work for catchup saccades, which fits well with the fact that saccades and smooth pursuit are influenced by common inputs (Krauzlis, 2004, 2005; Orban de Xivry & Lefèvre, 2007).

While these common inputs have been suggested to be sensory

signals from position and motion pathways (Blohm et al., 2005; de Brouwer, Missal, et al., 2002; Krauzlis, 2004), or outputs from the forward model (Ego, Yüksel, Orban de Xivry, & Lefèvre, 2016; Orban de Xivry et al., 2006), we show here that an internal representation of target motion, stored in short-term memory, is also shared by the two systems. Hence, catch-up saccade amplitude was affected both by the target velocity of previous trials and by the velocity of the ongoing target. Moreover, the magnitude of the effect of previous trials was greater when the visual target was the (less reliable) Gaussian blob, which is fully compatible with reliability- based integration and shows that prior information influences gaze planning upstream from the separation between saccadic and smooth movement pathways.

Therefore, we show in the present study that the whole oculomotor system has access to a single short term memory of target motion, and that reliability-based integration captures well the process by which this memory is combined with sensory signals.

2.4.2 Nature of the representation: Short-term memory or prior

Here, we made the assumption that the extraretinal signals consist of an internal representation of target motion (Orban de Xivry, Missal, & Lefèvre, 2008) and not a prior on target velocity (Bennett & Barnes, 2004; Bogadhi et al., 2013; J. Yang et al., 2012). These two possibilities differ in the sense that an internal representation of target motion is a memory of the target motion paired to a measure of uncertainty while a prior is a Gaussian distribution with a mean and standard deviation (see Tassinari et al. 2006, for a study on the ability of humans to do reliability-based integration).

The rapid change in the weight of the extraretinal signals with trial number (Figure 2.10) first appears to be at odds with a prior on target velocity, which is commonly slowly built and gradually updated. However, while many trials have usually been required to obtain a prior distribution (J. Yang et al. 2012: several days of training in monkeys; Kording and Wolpert 2004: 1,000 trials in humans), there is now more and more literature describing shorter timescales for the building of certain sensorimotor priors-for example of target position: In 2008, Izawa and Shadmehr suggested continuous prior integration with sensory information; in 2011, Verstynen and Sabes reported on "fast adapting priors" built within 10 trials; in 2012, Rao, DeAngelis, and Snyder suggested rapidly varying priors downstream of the sensory representation. Priors of target velocity and timing were also suggested to be continuously integrated with other sensorimotor signals by authors such as Heinen, Badler, and Ting (2005), and it can be argued that this trend has culminated with the rapidly adapting, one-trial priors proposed by Darlington et al. (2017).

At this point, the gap between these two concepts of extraretinal signals is narrowing. Still, an internal representation of target motion can also drive anticipatory pursuit (Orban de Xivry et al., 2013), and there is previous evidence in favor of an internal representation of target motion (Bennett, Orban de Xivry, Lefèvre, & Barnes, 2010; Orban de Xivry et al., 2008).

Although an internal representation of target motion is assumed in this study, it should be noted that the protocol used cannot differentiate between the two, and that our conclusions could be reframed in the context of priors on target velocity.

2.4.3 Reliability-based integration of a short-term memory with new information

In recent years, reliability-based integration of sensory inputs with other signals has provided an elegant framework to explain how the brain can process noisy and changing visual information to produce appropriate movements. Reliability-based integration has already been observed for inputs from different sensory systems (Ernst & Banks, 2002; Landy et al., 2011), for visual position information and ongoing motor commands (Kording & Wolpert, 2004), for visual motion information and a low-velocity prior (Jogan & Stocker, 2015; Stocker & Simoncelli, 2006), and for sensory predictions and sensory feedback (Vaziri, Diedrichsen, & Shadmehr, 2006). However, there have been few studies about the reliability-based integration of a short-term memory with new information in a sensorimotor context (Brouwer & Knill, 2007, 2009; Darlington et al., 2017). Of those, most, including ours, suggest that the brain is continuously integrating and updating this memory with new information. Nevertheless, there is a need for more research to better explain how a memory of target motion can be created and continuously updated in the broad range of contexts encountered in sensorimotor behaviors, including smooth pursuit, saccades and reaching movements.

Outside of the oculomotor context, several authors have studied the dynamics of memory and learning and found processes that relate to reliability-based integration of working memory with new information. They have suggested different models for which a memory is updated on the basis of the outcome of a previous action. The core principle is as follows: The brain maintains states/beliefs about the environment (in our case the target motion), and updates the existing beliefs on the basis of prior information and recent

outcomes for the next trials. In addition, these models particularly focus on whether a new state (a memory) should be formed or the previous one updated, depending on whether a fundamental change in the system is thought to have occurred or not. The states are therefore updated or created depending on the probability of a fundamental change and on the reliability of the signals, namely memory or new sensory information, for example by means of an approximately Bayesian delta-rule model (Nassar et al., 2010; Wilson, Nassar, & Gold, 2013), or a similar optimal filtering model (Gershman et al., 2014). Such belief-updating models have also been applied to the motor adaptation domain (Kording, Tenenbaum, & Shadmehr, 2007; Wei & Kording, 2010).

In all these studies, memory updating is influenced by the reliability of the new incoming information but could entirely take place during the intertrial interval. In contrast, the present study and the study of Darlington et al. (2017) demonstrate that the integration of the memory content and the sensory information takes place during the movement (when visual information about target velocity is available) and directly influences it.

2.4.4 Integration of short-term memory and visual signals in other contexts

Several studies investigated the influence of the memory of a target position on reaching arm movements. Brouwer and Knill (2007, 2009) showed that reaching movements toward a visual target were biased towards its last known position and that the effect was stronger if the contrast of the target was low. Verstynen and Sabes (2011) also showed the presence of a bias toward previous positions of the target during reaching movements despite the fully predica-

ble nature of the next positions. In addition to the position of the target, the spatial structure of the environment itself has also been shown to be memorized during visuomotor tasks (Aivar, Hayhoe, Chizk, & Mruczek, 2005; Hayhoe, Shrivastava, Mruczek, & Pelz, 2003).

Those studies clearly highlight that the reliability of a visual target, and previous information about it, can affect hand movements in a way that is similar to their effect on eye movements (Issen & Knill, 2012). However, these studies mainly focused on the integration of a memory of target position with the visually presented one. Such memories are limited to a position signal and a spatial representation of the scene and do not contain the evolution of the signal over time. Given that we know that the oculomotor system does not restrict this memory to a measure of target velocity but also includes its time course (Bennett et al., 2010; Orban de Xivry et al., 2008), we believe that the content of the working memory used for reliability-based integration during movement is much more complex than the ones previously described (Song & Nakayama, 2009).

Finally, while the integration of the position signals from visual information and memory occurs mostly before movement onset, we observe here a continuous integration of working memory and sensory information during eye movements. Given the similarities between the oculomotor system and other sensorimotor systems (Lisberger, 2015; Lynch & Tian, 2006), we may expect to find a similar process of continuous short-term memory updating in those systems.

2.4.5 Potential for further investigations of this short-term memory

In our protocol, only one test trial is shown per block and always concludes it. While appropriate for our purposes, several variations could answer further questions about the characteristics of the short-term memory. Future studies should explore the effect this change in target velocity has on the memory-for example, through protocols that do not stop at the test trial but show additional trials after. The target velocity of these trials might then go back to training trials velocities, or simply repeat the test trial velocity.

In all those potential protocols, we believe that the relative reliabilities of the short-term memory and the visual information will be paramount. Based on the model of Orban de Xivry et al. (2013), we would expect that the effect a change in target velocity has on subsequent trials will be negatively correlated with the reliability of the short-term memory at the first test trial and positively correlated with the reliability of the visual information. As such, we expect that a single test trial inserted in a sequence of seven training trials will induce stronger perturbations in subsequent trials if it is inserted in Trial 2, rather than in Trial 6 when the reliability of the short-term memory has been strengthened by observing more trials.

Conclusion

In this study, we report experimental evidence in the context of human oculomotor behaviors, in both smooth pursuit and catch-up saccades, that short-term memory can be quickly built, constantly updated, and continuously integrated in a reliability-based manner

with incoming visual information. We believe that this constitutes a general principle of dynamical updating of working memory, one that is consistent with recent studies (Darlington et al., 2017; Gershman et al., 2014; Nassar et al., 2010), and that is likely to be present in other sensorimotor systems (Lisberger, 2015).

Appendix

Supplementary figures

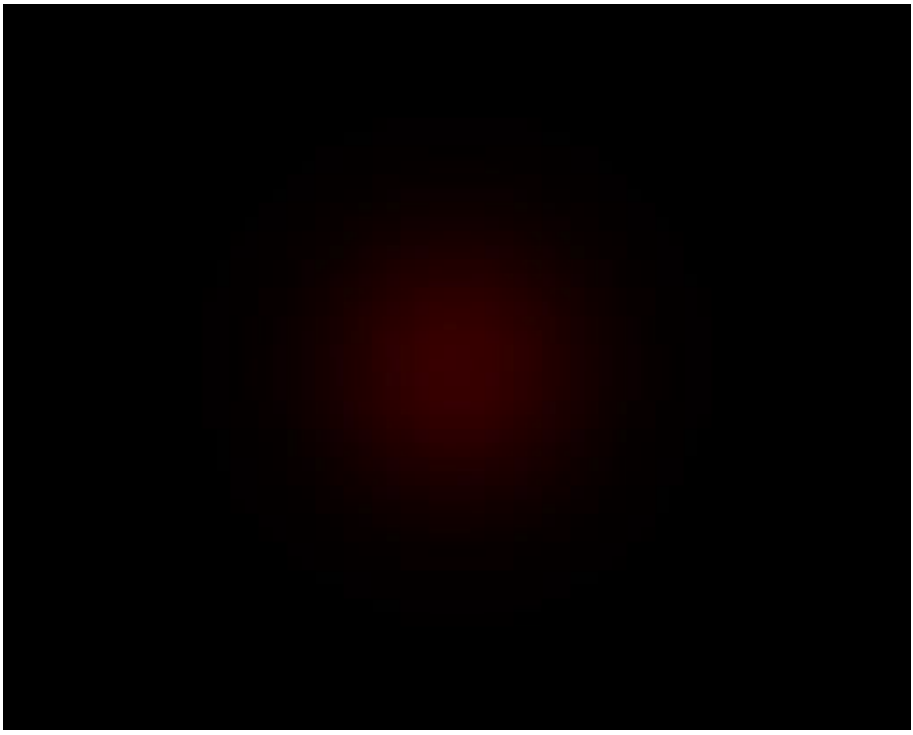

Figure 2.11: Suppl. 1 : Noisy, 2D Gaussian target on a dark background, closer to real experimental conditions. Note that to obtain a correct representation of its luminosity distribution, it is necessary to correct for the non-linearity in RGB color scaling of the display. Also, some computer screens and printers might lack the ability to display the full color gradient or even fail to display it altogether. If the picture is properly scaled so that it is 15cm wide, seeing the target at 50cm should be equivalent to the perspective of the participants.

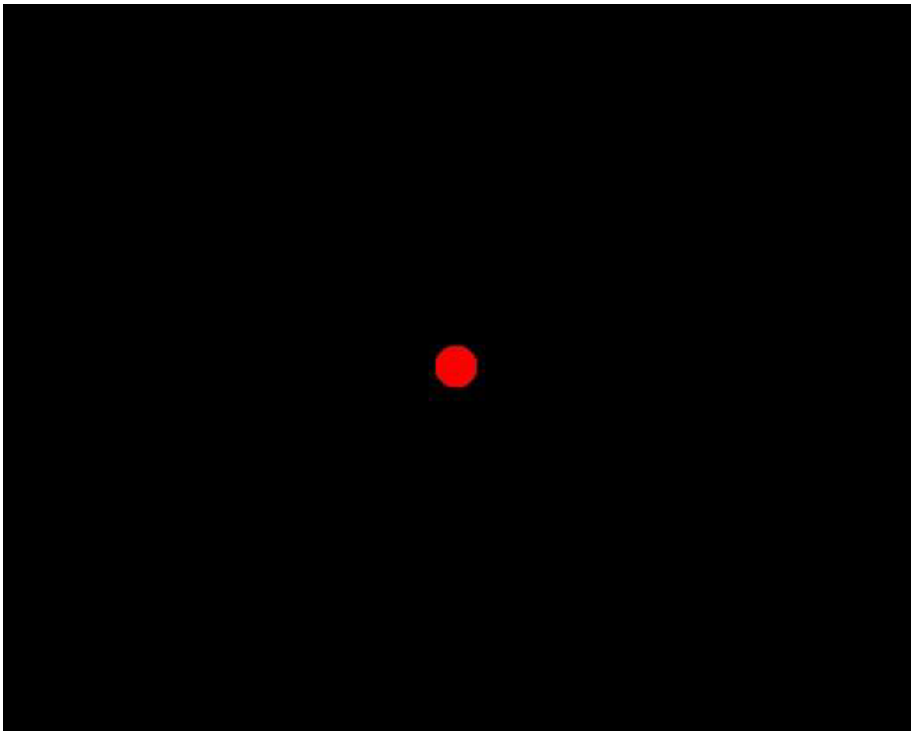

Figure 2.12: Suppl. 2 : Standard target (0.8°of diameter). If the picture is properly scaled so that it is 15cm wide, seeing the target at 50cm should be equivalent to the perspective of the participants.

Chapter 3

Integration of past and current information during eye movements in amblyopia

Abstract

Combination of signals based on their reliability is an increasingly popular model for sensorimotor processing. However, how reliability is estimated, or how such estimation is affected by prolonged exposure to noisy inputs, is still unknown. In this study, we compare patients with unilateral functional amblyopia with control subjects tracking either a reliable target, or a blurry, unreliable target, in a task of repeated, sustained smooth pursuit. We provide evidence that, compared to controls tracking a reliable target, amblyopic and control subjects tracking a blurry target exhibited lower weight of

visual information during smooth pursuit, with no significant difference of prior information weight. In contrast, we found no evidence of lower visual information weight in the catch-up saccades of amblyopic subjects. We conclude that oculomotor performance in unilateral amblyopia mostly lays within the continuum between our control groups, without significant differences in the relative weights of prior and visual information. However, smooth pursuit exhibits additional deficits that might result from abnormal visual development.

3.1 Introduction

There is a growing consensus about the use of reliability-based integration as a model of the processing of noisy, time-delayed or multimodal sensory sources by sensorimotor systems (Berniker & Kording, 2009; Kording & Wolpert, 2004; Rohe & Noppeney, 2018). As a prime example of sensorimotor behaviors, smooth pursuit eye movements have been extensively studied, and several models relying on reliability-based integration have been proposed (Bogadhi et al., 2013; Dimova & Denham, 2009; Montagnini et al., 2007; Orban de Xivry et al., 2013). Most recently, behavioral studies in both monkeys (Darlington et al., 2017) and humans (Deravet, Blohm, Orban de Xivry, & Lefèvre, 2018) have shown evidence of reliability-based integration of noisy visual information with prior information, in line with these models. Numerous unknowns remain, such as the pathways and regions of the brain implicated in the actual integration process (Darlington et al., 2017). One way to explore these questions is to investigate developmental deficits of vision, such as amblyopia.

Unilateral functional amblyopia, while typically characterized

by an acuity loss in one eye for which no physical cause can be found (Daw, 2014; Von Noorden & Campos, 2002), is also associated with other deficits related to contrast or motion perception (Kiorpes et al., 2006; McKee et al., 2003; Simmers et al., 2003). The fact that some of these deficits, in particular deficits of motion perception, can also be found in the fellow, unaffected eye (Ho et al., 2005; Meier & Giaschi, 2017; Varadharajan & Hussaindeen, 2012) shows that amblyopia affects the oculomotor system beyond the monocular level, possibly including pathways responsible for prior integration. Unfortunately, visually guided smooth pursuit in amblyopic patients has received limited attention outside of its potential asymmetry (Ciuffreda et al., 1979a; Schor, 1975; Von Noorden & Mackensen, 1962a), except for a recent study that investigated smooth pursuit latency and steady-state gain (Raashid et al., 2016) in anisometropic amblyopia.

In our study, using a target-tracking task, we compare the sensorimotor behavior of amblyopic patients with controls presented with either reliable or less reliable visual targets. We predicted that, because of their visual acuity deficits, the sensorimotor behavior of amblyopic subjects would be comparable to that of normal subjects presented with a noisy visual target. We also probed the weighting of prior and visual information in patients and controls, which might be expected to be affected by their different history of visual development.

3.2 Methods

3.2.1 Participants

We recruited 20 amblyopic patients, two of which were set aside because of data quality (see data processing). The remaining 18 patients (8 female) were between 12 and 61yo (average=32.56, sd=16.58, cf. Fig. 3.1A). We also recruited 38 control participants, one of which was set aside due to incomplete pupil detection. The remaining 37 controls, between 22 and 56yo (average=32.43, sd=10.72; 21 female, cf. Fig. 3.1A), took part in either one or two versions of the protocol, Standard condition (23) and Noisy condition (25), with 11 participating in both (starting with Noisy condition). While average ages were similar, control were not age-matched to patients (cf. Fig. 3.1A). Control participants had normal/corrected vision, while amblyopic patients had visual acuity between 2/20 to 10/20 Snellen (0.3 to 1 logMAR), and exhibited either anisometropic (n=4), strabismic (n=8) or anisometropic and strabismic (n=6) amblyopia. After full description of the experiment, informed consent was given by the participants. The procedures were approved by the Université catholique de Louvain Ethics Committee and in accordance with the Declaration of Helsinki.

3.2.2 Protocol

Participants sat in a dark room, 151 cm from a 197x150 cm screen placed in front of them, spanning around 65° (horizontal) by 50° (vertical) of their visual field. Head movements were restrained with chin and forehead rests. A cine8 Barco projector (Barco Inc., Kortrijk, Belgium) displayed the stimuli at a refresh rate of 100Hz

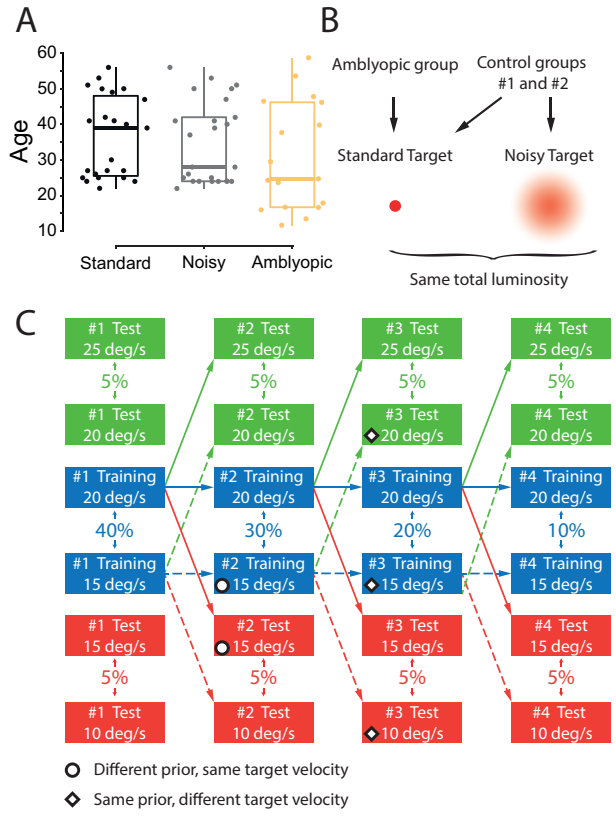

Figure 3.1: A. Age distribution of included participants. Boxplots show medians and quartiles; dots are individual data, with some x-jitter for readability. B. Association between groups and targets. C. Template of blocks (regardless of target direction). Each block starts with a trial of the first column and ends at a trial with no outgoing arrow. Target direction remains constant within a block. Percentages indicate the % of blocks containing trials of the same type (color) and number (#) at one of the two available velocities (ex: 80% of the blocks have at least one Training trial). Black rings give an example of two trials that can be compared to highlight the effect of previous trials (prior). Black diamonds give an example of trials in which the prior is the same but the visual information differs. Dashed arrows indicate a 15°/s prior target velocity. Solid arrows indicate a 20°/s prior target velocity.

while eye movements were recorded at 1000Hz using an *Eyelink*® 1000 (SR Research, Ottawa, Ontario, Canada). The display was handled by a *Matlab*® script through an in-house toolbox, while Eyelink interactions were handled by the Psychtoolbox (Kleiner et al., 2007). Calibration targets were presented at the start and every 30 trials, with breaks allowed before each. The duration of an experiment was around 30 minutes. Importantly, we always recorded the amblyopic or non-dominant eye, masking the other with translucent tape.

In a previous study (Deravet et al., 2018), we established that a blurry Gaussian spot target, with σ=1.27°, is able to significantly deteriorate pursuit performance and induce different relative weights of visual and prior information, which we attributed to the lower reliability of the visual information it provides. Since the primary deficit associated with amblyopia is reduced visual acuity, we expected amblyopic patients to exhibit similar pursuit behavior and considered a protocol allowing us to compare their oculomotor behavior with controls presented with either reliable or less reliable visual information. As such, one (sub)group of controls (Standard condition) and all patients tracked a standard target (uniform disk, diameter 0.8°; cf. Fig. supplement 2.12), while another (sub)group of controls (Noisy condition) tracked a noisy target (Gaussian spot, σ=1.27°; cf. Fig. supplement 2.11). Both targets had the same overall luminance, but different distributions.

This protocol was adapted from Deravet et al. (2018). It consists of blocks (cf. Fig. 3.1) of 1 to 4 Training trials, which build a prior through repeated tracking of a pursuit target with identical velocity (15°/s or 20°/s) and direction (-20°, 0°, 20°, 160°, 180° or 200°). In most blocks (80%), the last trial (Test) changes velocity (±5°/s), thereby creating a mismatch between prior and visual

information and probing their weighting. Each trial began with a 500ms fixation using the same target. Two important differences with the previously published protocol (Deravet et al., 2018) are the absence of passive trial and the use of the same target for both fixation and pursuit.

3.2.3 Data processing

Data were processed using $Matlab^{®}$ ($MathWorks^{®}$). Missing values in the Eyelink output were considered blinks and removed from the data (along with safety margins of up to the first local minimum of vertical eye movement on each side of the blink). Eye position signals were low-pass filtered at 35Hz, and both eye velocity and acceleration were obtained using a central difference algorithm on a ±10-ms interval. Data were pooled across all 6 directions.

We detected saccade onsets and offsets by implementing the algorithm described in (Larsson, Nyström, & Stridh, 2013), slightly altered to handle the noisier data of patients, by detecting over several filtering levels, raising the thresholds for saccades, and checking saccade candidates for consecutive saccades. Once detected, we removed saccades from velocity traces using linear interpolation.

To remove abnormal trials, we set a few criteria: (1) during the last 100ms of fixation, median eye position error $< 5°$, (2) less than 90 missed samples in the first 450ms of pursuit, (3) eye displacement of at least 15% of target displacement, (4) position error during pursuit must not go over 8° for more than 100ms, 5) no saccade made after target onset may be $> 25°$. Finally, we set aside participants whose data were rejected at more than 60% (cf. Participants). From remaining participant's data, the criteria took out $\approx 11\%$ of trials, distributed as: 7% Standard, 9% Noisy, and

19% Amblyopic groups.

When analyzing eye velocity during pursuit epochs, we included only trials for which participants 1) had steady state pursuit gain bigger than 0.2, 2) made forward saccades (or none) and 3) moved at least 5% of target displacement using smooth pursuit ($\approx$ 90% of data). In our analysis of smooth pursuit performance during the first trial, we wanted to compare the visual response of the groups. Therefore, we selected trials during which anticipation was low by requiring pursuit onset to occur later than 50ms ($\approx$ 82% of first training trials).

3.2.4 Data analysis

Pursuit features

Pursuit onset was measured as the intersection of a two-part piecewise linear function (plateau and positive slope) fitted on eye velocity within the interval [-100,300]ms around target onset. The onset time was considered valid if no blink occurred for at least 50ms afterwards, and if the plateau value remained below 4°/s.

Steady-state eye velocity was computed as the slope of a first-order polynomial fitted on the first interval of eye position after the first catch-up saccade that included no saccades, provided that it lasted at least 70ms. If there was no such interval (1.9% of trials), saccadic eye position data were replaced by the integral of their linear interpolation in eye velocity, and included in the fit.

Saccades features

We studied the first catch-up saccade occurring between 100ms and 400ms after target motion onset. We computed position error (PE),

retinal slip (RS) and amplitude (Amp). PE and RS were both assumed to be estimated 100ms before saccade onset (Becker & Jürgens, 1979), and therefore measured at that time. Retinal slip was computed as the difference between target velocity and a 50ms average of eye velocity 100ms before onset.

For each participant and training target velocity, we used data from Training trials #2 to #4 to compute linear models of saccade amplitude vs ideal amplitude (difference between target position at saccade offset and eye position at saccade onset). Data from first trials were fitted in a second model because of their later pursuit onset and bigger saccades. We then computed residuals of the corresponding Test trials to quantify their divergence from Training trials, while accounting for individual differences. The computation of the ideal amplitude depended on the type of comparison (prior vs visual) and is further discussed below.

Comparing trials – prior effect

To assess the effect of prior information, we compared Test and Training trials of matching trial # and visual information, but different experience in prior trials (Test20 vs Train20, Test15 vs Train15, e.g., black circles in Fig. 3.1C), on measures of pursuit gain and saccade amplitude. Given identical visual information, any behavioral difference is attributed to the prior. To estimate the fraction of the prior that is reflected into the behavior across target velocities, we computed a normalized prior effect on the pur-

suit according to Eq. (3.2.4).

$$NormEffect_{prior} = \frac{mean(Eye\ Velocity\ of\ Training) - Eye\ Velocity\ of\ Test}{Prior\ Target\ Velocity\ of\ Training - Prior\ Target\ Velocity\ of\ Test} \tag{3.1}$$

Saccades residuals were computed based on the linear model of saccade amplitude vs the ideal amplitude towards the visible target.

Comparing trials – visual effect

To estimate the effect of visual information, we compared Test and Training trials of matching trial # and prior information, but different target speed (Train15 vs Test10 or Test20, Train20 vs Test15 or Test25, e.g., black diamonds in Fig. 3.1C). Comparisons highlight the effect by considering that participants ignored the change of velocity, so that any difference with Training trials is attributed to it. For pursuit, we achieved this by computing a gain equal to the eye velocity divided by the previous target velocity (15 or 20). To compare the effect on eye velocity across conditions of opposite effects, we also computed a normalized visual effect, as described by Eq. (3.2.4).

$$NormEffect_{visual} = \frac{mean(Eye\ Velocity\ of\ Training) - Eye\ Velocity\ of\ Test}{Target\ Velocity\ of\ Training - Target\ Velocity\ of\ Test} \tag{3.2}$$

For saccades residuals computation, we considered the ideal amplitude to reach, at saccade offset, a predicted target with the same PE at saccade onset, but moving at the previous target's velocity, i.e. that participants relied on previous RS.

Statistical analyses

We compared several measures from the first training trial of each block, provided anticipation was low, as a way to assess the performance of the visual response to target motion. We analyzed subject averages using a linear mixed effects model, with group, target velocity and temporal/nasal direction as fixed effects, participants as random effect, and random slopes for temporal/nasal direction.

Further analyses were always respective to participant's own performance in training trials; therefore, we did not include the temporal/nasal direction factor. To assess the existence of a visual effect, we used a model with fixed effects group, type of target and training target velocity, with a random effect for participants. When comparing the effect of prior or visual information, we used the same analysis method, but with the following fixed effects: group, training Target velocity and Trial # (1st trial/all later ones). We included random intercepts for the participants and random slopes and intercepts for Trial # to account for individual differences. We performed hypothesis tests with type III anova, evaluating denominator degrees of freedom using the Kenward-Roger method.

For these analyses, we relied on the afex (Singmann, Bolker, Westfall, & Aust, 2018), lme4 (Bates, Mächler, Bolker, & Walker, 2015) and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) packages in R (R Core Team, 2018). Post-hocs were pairwise

comparisons using robust independent and dependent t-tests from the WRS2 R package (Mair & Wilcox, 2018), using 20% trimmed means and 2000 bootstrap samples when applicable (Field & Wilcox, 2017).

3.3 Results

In this study, we investigated smooth pursuit in three groups, presented with visual information that was either reliable, noisy, or affected by amblyopia; furthermore, we manipulated the reliability of prior information about target velocity. Here, we first assess how amblyopia and the reliability of visual information affect smooth pursuit latency and gain (cf. Fig. 3.2). Then, we highlight and compare the weights of visual and prior information in pursuit gain and catch-up saccades amplitude.

3.3.1 Performance of smooth pursuit

Pursuit onset is delayed in Amblyopic and Noisy groups

Given previous studies, we expected to observe delayed pursuit onset in the two groups with less reliable visual information. There was indeed a main effect of group ($F(2, 63.11) = 68.79$, $p < 0.0001$): the Noisy (trimmed mean differences in FBQ scores $Mdiff = +38.97ms$, $95\%CI : [34.80, 43.14]$, $Y_t = 18.6$, $p < 0.0001$), and Amblyopic ($M_{diff} = +15.18ms$ $[9.78, 20.57]$, $Y_t = 5.34$, $p < 0.0001$) groups initiated pursuit later than the Standard group. Still, amblyopic patients initiated pursuit faster ($M_{diff} = -23.79ms$, $[-29.44, -18.14]$, $Y_t = 8.1$, $p < 0.0001$) than the Noisy group. In addition, there were main effects of target velocity ($F(1, 124.82) = 10.66$, $p = .001$) and

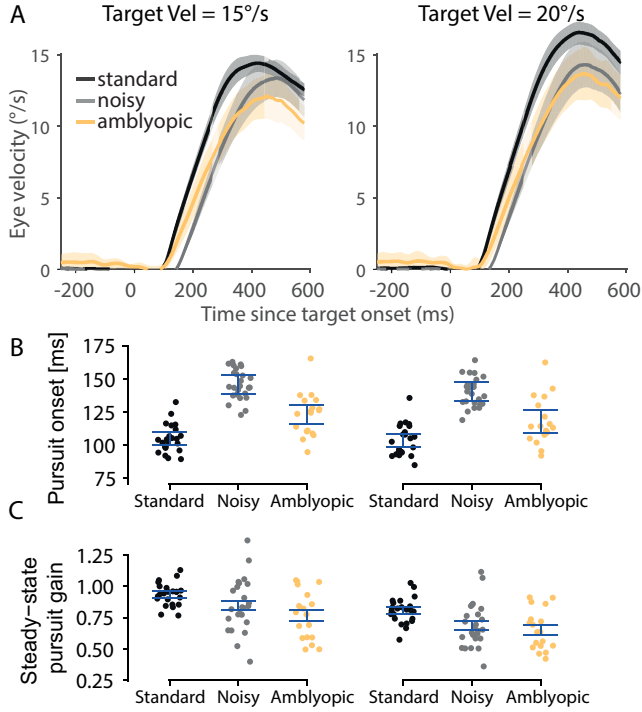

Figure 3.2: Overall pursuit performance during Trial #1. A. Averages, per group, of participant's average eye velocity traces during Training trials at 15°/s and 20°/s. The surrounding shadow indicates 95% CI. B-C. Respectively, Pursuit onset and Steady-state pursuit gain, for Training trials at 15°/s and 20°/s. Dots correspond to individual participants. Error bars are centered on the average of participant's averages and indicate the average of participant's SEM.

temporal/nasal direction ($F(1, 62.8) = 12.16$, $p = 0.0009$).

Steady-state smooth pursuit gain is lower in Amblyopic and Noisy groups

The analysis of smooth pursuit steady-state gain revealed main effects of group ($F(2, 63.08) = 6.22$, $p = 0.003$) and target velocity ($F(1, 124.27) = 325.77$, $p < 0.0001$). There was no main effect of direction ($F(1, 62.35) = 0.7$, $p = .41$), and its inter-

actions with group ($F(2, 62.3) = 2.97,\ p = 0.06$) and velocity ($F(1, 124.27) = 3.75,\ p = 0.05$) were non-significant. Other effects and interactions were also non-significant, with $p > .13$. Overall, the Standard group had higher gain than both Noisy ($M_{diff} = 0.116[0.063, 0.17],\ Y_t = 4.3,\ p < 0.0001$) and Amblyopic ($M_{diff} = 0.183[0.113, 0.253],\ Y_t = 5.2,\ p < 0.0001$) groups, while there was no significant difference between Noisy and Amblyopic groups ($M_{diff} = 0.066[-0.01, 0.145],\ Y_t = 1.7,\ p = 0.09$).

3.3.2 Weighting of prior and visual information in smooth pursuit

To highlight the effect of prior and visual information on eye movements, we compared, respectively, trials with different prior target velocity but the same current velocity, or trials with the same prior target velocity but different current target velocities (cf. methods and Fig. 3.1).

Smooth pursuit: prior information weight does not differ across groups

As can be seen in Fig. 3.3, panels A & B, eye velocity during Test trials was modestly biased towards target velocity in previous trials, being either higher (prior at 20°/s - red traces) or lower (prior at 15°/s - green traces) than the Training trials of matching target velocity. Analyzing the normalized effect of the prior on smooth pursuit (cf. methods, Fig. 3.3C), we confirmed its presence (main effect of Trial # $F(1, 63) = 30.83, p < 0.0001$). We found no significant differences between groups. That is, there was no significant main effect of group ($F(2, 63) = 2.49,\ p = 0.9$), interaction group x Trial # ($F(2, 63) = 0.1,\ p = 0.9$) or group x target velocity x Trial

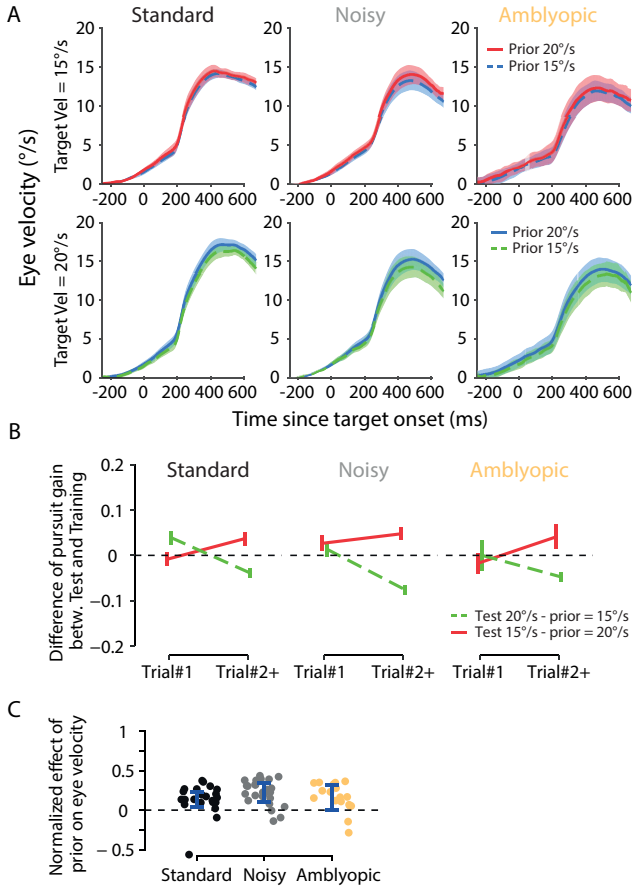

Figure 3.3: A. Averages of participant's average eye velocity traces during Training and Test trials with the same target velocity (1st row: 15°/s; 2nd row: 20°/s), but different priors of target velocity, 1 group per column, for trials #2 to #4. Blue traces correspond to Training trials, red/green traces to Test trials. The surrounding shadows indicate 95% CI. B. Averages of participant's average differential gains of the smooth pursuit eye velocity response to a target moving at 15°/s (full red line) or 20°/s (dashed green line), during the first or later trials, either at a higher (20°/s, full red line) velocity or a lower (15°/s, dashed green) velocity. Error bars indicate the SEM. C. Normalized effect of the prior on eye velocity, with participant's averages as dots, and error bars corresponding to the average of participant's SEM, centered on the average of averages.

$\#\ (F(2, 126) = 1.47,\ p = 0.23).$

There was an interaction target velocity X Trial # ($F(1,126) = 5.89,\ p = 0.02$), corresponding to a smaller effect of the prior for a Test trial at 15°/s (trimmed means difference $M_{diff} = -0.138[-0.219 - 0.057],\ Y_t(39) = -3.43,\ p = 0.001$) compared to a Test trial at 20°/s ($M_{diff} = -0.319\ [-0.434, -0.206]$, $Y_t(39) = -5.66,\ p < 0.0001$). This can be observed in Fig. 3.3, panel B, by comparing red and green traces.

Smooth pursuit: visual information has higher weight in the Standard group

As shown in Fig. 3.4, panels A & B, participant's eye velocity also reflected the higher (green traces) or lower (red traces) target velocity in Test trials, compared to Training trials (blue traces). To analyze the effect of visual information on smooth pursuit, we first established its presence by comparing Training and Test trials, then we compared the groups using the normalized visual effect.

The analysis of the visual gain of smooth pursuit (cf. Methods) revealed main effects of group ($F(2,63) = 8.21,\ p = 0.0007$), training target velocity ($F(1,315) = 452.89),\ p < 0.0001$), and trial type ($F(2,315) = 378.27,\ p < 0.0001$), as well as interactions group X trial type ($F(4,315) = 35.05,\ p < 0.0001$), training target velocity X trial type ($F(2,315) = 48.02,\ p < 0.0001$). The interaction group X training target velocity X trial type wasn't significant ($F(4,315) = 2.33,\ p = 0.06$).

To verify the effect presence in all groups, we explored the interaction group x trial type. Simple effect analysis with robust t-tests showed significant differences between Training trials and Test trials for which target velocity decreased (cf. Fig. 3.4, panel B, red traces) in all groups (Standard, Noisy and Ambly : $p < 0.0001$).

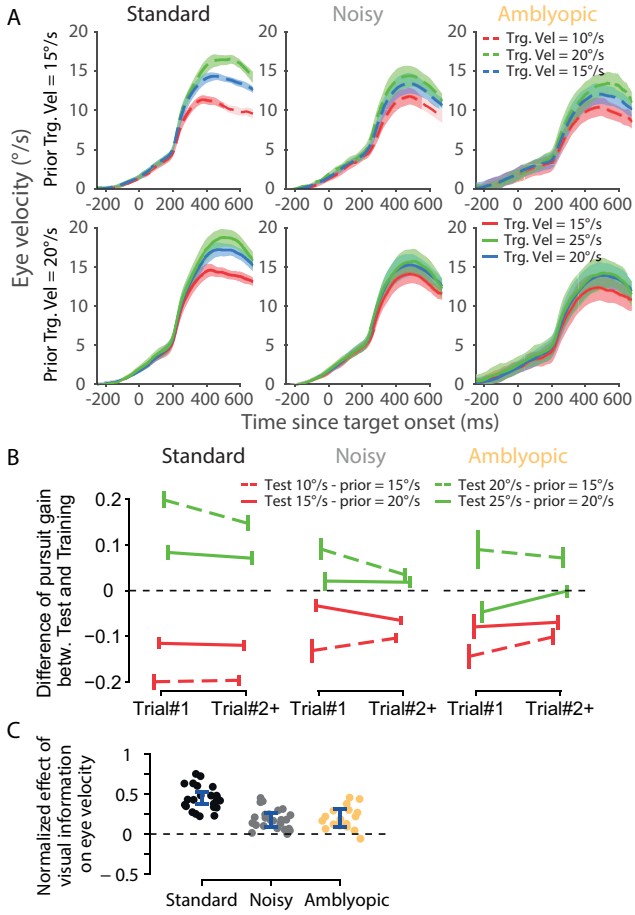

Figure 3.4: A. Averages of participant's average eye velocity traces during Training and Test trials with the same priors of target velocity (1st row: 15°/s; 2nd row: 20°/s), but different target velocity, 1 group per column, for trials #2 to #4. Blue traces correspond to Training trials, red/green traces are Test trials. The surrounding shadows indicate 95% CI. B. Averages of participant's average differential gains of the smooth pursuit eye velocity response to a target moving either at 10°/s or 20°/s (resp. red and green dashed lines) or at 15°/s or 25°/s (resp. red and green solid lines) during the first or later trials, at either a higher (all red lines) or lower (all green lines) velocity. The error bars correspond to the SEM. C. Normalized effect of visual information on eye velocity, with participant's averages as dots, and error bars corresponding to the average of participant's SEM centered on the average of averages.

However, when target velocity increased (cf. Fig. 3.4, panel B, green traces) the difference was significant in the Standard ($p < 0.0001$) and Noisy ($p = 0.006$) groups, but not in the Amblyopic group ($p = 0.202$).

Having confirmed the presence of the effect in all groups, we compared them using the normalized visual effect measure (cf. Fig. 3.4C), and found significant main effects of group ($F(2, 63) = 26.98$, $p < 0.0001$) and training target velocity ($F(1, 126) = 49.62$, $p < 0.0001$). Contrary to the effect of prior information, we found no significant main effect of Trial # ($F(1, 63) = 2.93$, $p = 0.09$), however there was a significant training target velocity x Trial # interaction ($F(1, 126) = 8.72$, $p = 0.004$).

Post-hoc analyses showed the Standard group had the strongest visual effect (Stand vs Noisy: $M_{diff} = 0.293[0.230,\ 0.355]$, $Y_t = 9.2$; Stand vs Ambly: $M_{diff} = 0.263[0.177,\ 0.349], Y_t = 6.16$; both p-values$< 0.0001$), while the Amblyopic and Noisy group did not differ (Noisy vs Ambly: $M_{diff} = -0.03\ [-0.114,\ 0.0545]$, $Y_t = -0.71$, $p = 0.47$).

3.3.3 Weighting of prior and visual information in catch-up saccades

Since saccades share inputs with pursuit (Krauzlis, 2005; Orban de Xivry & Lefèvre, 2007) and based on our previous study, we examined how the mismatch between prior and visual information affected catch-up saccades amplitude.

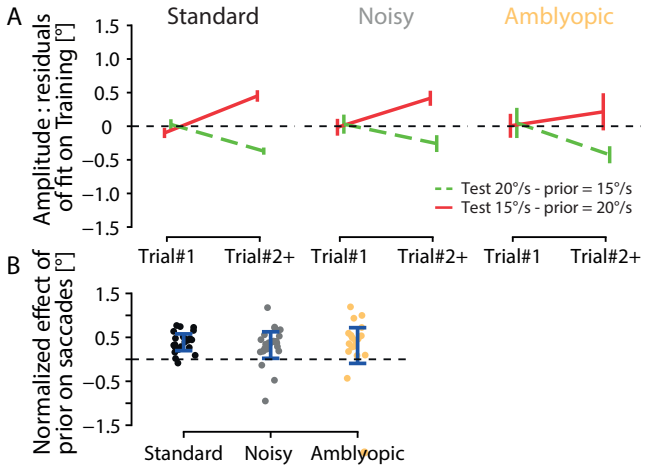

Figure 3.5: A. Effect of prior information on the amplitude of saccades, shown by the averages of each participant's residuals average, for each trial group (1st or later). Red/green traces show data from Test trials. Error bars indicate the SEM. Dashed lines indicate a 15°/s prior target velocity. B. Normalized effect of prior information on saccade amplitude, in later trials. Dots are individual averages of normalized residuals, blue error bars correspond to SEM.

Catch-up saccades: prior information weight does not differ across groups

Similarly to smooth pursuit, all groups exhibited effects of prior (main effect of Trial # $F(1,63) = 27.05,\ p < 0.0001$) on saccade amplitudes. As such, after the first trial, saccade amplitudes made during Test trials were either smaller if the previous target was slower (cf. red traces in Fig. 3.5A), or larger if it was faster (green traces in Fig. 3.5A). Once again, there was no difference between groups (no main effect of group: $F(2,63) = 0.02,\ p = 0.98$, no interaction group x Trial # : $F(2,63) = 0.31,\ p = 0.74$), which is apparent in the Fig.5B comparing the normalized effect of the prior in later trials between groups. All remaining effects and interactions were non-significant ($p > .47$), including the interaction training target velocity x Trial #.

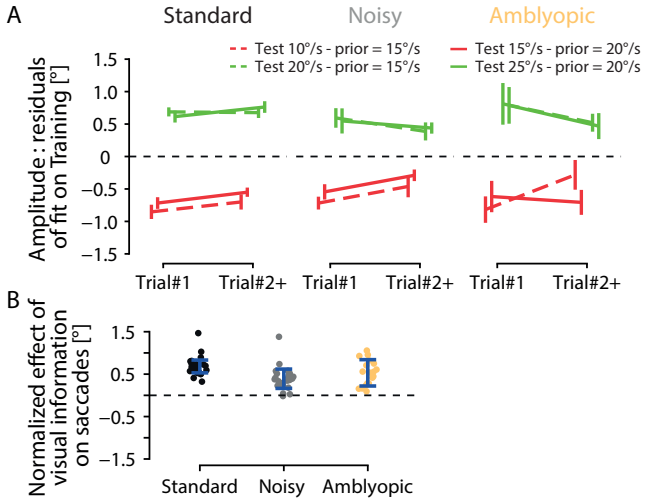

Figure 3.6: A. Effect of visual information on the amplitude of saccades, shown by the averages of each participant's residuals average, for each trial group (1st or later). Red/green traces show data from Test trials. Error bars indicate the SEM. Dashed lines indicate a 15°/s prior target velocity. B. Normalized effect of visual information on saccade amplitude, in later trials. Dots are individual averages of normalized residuals, blue error bars correspond to SEM.

Catch-up saccades: visual information weight is higher in Standard and Amblyopic groups

Of course, saccades were still impacted by visual information. We compared the amplitude of catch-up saccades in Test and Training trials, highlighting significant main effects of group ($F(2,63) = 8.34$, $p = 0.0006$), training target velocity ($F(1,315) = 504.14$, $p < 0.0001$) and type of trial $F(2,315) = 330.86$, $p < 0.0001$), as well as an interaction group x trial type ($F(4,315) = 3.90$, $p = 0.004$). Post-hoc analysis on the interaction group x trial type, showed that all groups exhibited significant effects of visual information ($p < 0.001$) in both types of Test trials. This proved that, in all groups, Test trials induced larger/smaller amplitudes in reaction to faster/slower targets (Fig. 3.6A).

To compare groups, we analyzed the normalized effect of visual information on saccades (cf. methods, Fig. 3.6B), revealing significant group differences (main effect of group $F(2, 63) = 5.45,\ p = 0.007$). Direct comparisons showed that the Noisy group exhibited weaker visual effect on saccades than both the Standard ($M_{diff} = -0.191\ [-0.273,\ -0.108],\ Y_t = -4.49,\ p < 0.0001$) and Amblyopic ($M_{diff} = -0.143[-0.28,\ -0.009],\ Y_t = -2.09,\ p = 0.038$) groups. The Standard and Amblyopic groups did not differ ($M_{diff} = 0.048[-0.078, 0.173],\ Y_t = 0.77, p = 0.459$).

In addition, there was a significant main effect of Trial # ($F(1, 63) = 8.73,\ p = 0.004$), but no significant effect of training target velocity and no significant interaction (all $p > .07$). Post-hocs showed, as seen in Fig. 3.6A, that the effect of visual information on catch-up saccades decreased after the first trial ($M_{diff} = -0.144[-0.218,\ -0.069],\ Y_t = 3.82,\ p < 0.0001$).

3.4 Discussion

In this study, we examined the smooth pursuit performance and the weighting of prior and visual information of patients with unilateral amblyopia, and drew comparisons with two control groups tracking either a reliable uniform target (Standard group) or a noisy Gaussian blob target (Noisy group). Our prediction was that, due to abnormal early visual development (Daw, 2014; Kiorpes & Daw, 2018), the relative weights of visual and prior information in amblyopic patients might differ from both Standard and Noisy groups, despite the fact that the Noisy group is also confronted to less reliable visual information.

Our results show that amblyopic patients exhibited clear deficits of smooth pursuit (latency, gain, reaction to velocity

change) compared to the Standard group, which was similar to the Noisy group and consistent with a lower weight of visual information. Also, despite visual information reliability differences, we found no difference in the weight of prior information across groups. It therefore appears that amblyopia affects smooth pursuit in a way consistent with less reliable visual information, while catch-up saccades and prior information integration are less affected.

To our knowledge, our study is the first to investigate sustained, non-sinusoidal smooth pursuit in amblyopic patients with and without strabismus. While a few studies investigated visually-guided and sustained smooth pursuit in amblyopia (Ciuffreda et al., 1979a; Schor, 1975; Von Noorden & Mackensen, 1962a), all considered sinusoidal motion, and, apart from (Von Noorden & Mackensen, 1962b), low target velocities ($< 10°/s$). Still, we also observed lower pursuit gains in most amblyopic patients. More recently, Raashid et al. (2016) conducted a study of the sustained smooth pursuit of 11 anisometropic amblyopic patients, finding delayed pursuit onset but no difference of steady-state gain.

3.4.1 Lower reliability of visual information in amblyopia differentially affects smooth pursuit and catch-up saccades

As expected based on reliability-based models of smooth pursuit (Bogadhi et al., 2013; Darlington et al., 2017; Orban de Xivry et al., 2013) and on our previous study (Deravet et al., 2018), the noisy target offered less reliable visual information, inducing lower pursuit gain and delayed pursuit onset in the Noisy group. In addition, when presented with an increase or decrease in target velocity, the

Noisy group reacted less than the Standard group, indicating that visual information had lower weight.

Similarly, amblyopic patients showed evidence of lower reliability of visual information compared to the Standard group. However, while smooth pursuit movements showed clear deficits, catch-up saccades remained unaffected. In addition, most amblyopic patients showed no significant oculomotor difference compared to the Noisy group, had shorter pursuit latency and higher weight of visual information in catch-up saccades.

Such differences between saccades and pursuit in amblyopic patients suggest that their saccadic system has access to more reliable visual information than their pursuit system, or that additional deficits affect their smooth pursuit (Bedell, Yap, & Flom, 1990), or a combination of the two, possibly as a result of development in presence of noisy visual inputs.

3.4.2 Prior information integration is not affected by amblyopia

Despite similar protocols, we did not find significant differences of prior information weight between the control groups, therefore not reproducing results of Deravet et al. (2018). While this does not prove that no difference exist, we believe this to be due to the differences between the protocols. In the previous experiment, the fixation target was always a uniform dot, from which disengaging was easier for Standard than for Noisy groups (Krauzlis et al., 2017). Also, while passively viewing target motion can suffice to acquire a prior, its reliability is lower than through active viewing (Barnes & Hill, 1984). We think these differences made the pursuit gain of Noisy controls in Deravet et al. (2018) lower than

in the present study, possibly making the effect of the prior more salient. Alternative explanations could be suggested, such as age differences between the groups, or that our sample of participants did not exhibit this effect, or that the effect is small and could not be separated from noise in this sample.

Our initial hypothesis was that the weight of prior information might be different in amblyopic patients, due to a different development of their visual system (Daw, 2014; Kiorpes & Daw, 2018) or the imbalance in their ocular dominance (Kiorpes et al., 1998). For example, prior information could be given more weight to compensate for the lower reliability of information from the amblyopic eye.

However, we found no significant differences of prior effect between controls and amblyopic patients. It should however be noted that this does not prove the absence of a difference. Still, one hypothesis to explain this result is that, in everyday life, our amblyopic patients have access to more reliable visual information through the fellow eye (Clavagnier et al., 2015), which allows their prior integration pathways to develop similarly to controls. This would likely require prior integration to be processed binocularly, after the integration of visual information coming from both eyes. As such, the integration of visual and prior information about target motion could be done, respectively, in the Area MT (Osborne et al., 2004, 2007), and in the Frontal Eye Fields (Darlington et al., 2017).

3.4.3 Neural basis of smooth pursuit deficits in Amblyopia

Neural deficits within V1, such as losses of sensitivity and acuity, are well documented in amblyopia (Clavagnier et al., 2015; Kiorpes

et al., 1998, 2006), but do not suffice to explain deficits in visuomotor behavior and in extrastriate areas (Kiorpes & Daw, 2018; Kiorpes et al., 1998; Shooner et al., 2015). However, because extrastriate areas are downstream from V1, their development (and feedback) can be affected by these deficits (Kiorpes & Daw, 2018). As such, one explanation for amblyopia is that of an "immature" system in which projections from the amblyopic eye to early visual areas (V1 to V3) are characterized by lower spatial resolution and a disordered topographical map (Clavagnier et al., 2015). The Noisy group, processing noisy visual information through an intact neuroanatomical pathway, would therefore be expected to diverge from acuity-matched Amblyopic patients on behaviors whose development was affected by noisy visual inputs.

Based on behavior differences suggested in our results, we would expect future investigations using similar protocols and visual acuity – matched groups (matching the Gaussian spots of controls to the acuity of amblyopic patients) to outline an even better picture of the specificities of reliability-based integration in Amblyopia. Such acuity matching could be done by incrementally blurring a psychophysical test using software (Dehnert, Bach, & Heinrich, 2011), or through optical degradation (Niechwiej-Szwedo et al., 2012).

3.4.4 Conclusion

In conclusion, oculomotor performance of amblyopic patients mostly lays within the continuum between that of controls tracking a reliable target and tracking a noisy Gaussian target. While their smooth pursuit showed evidence of a lower weight of visual information, their catch-up saccades did not, which suggests that their smooth pursuit pathways incur additional noise, possibly as

a result of developing in presence of noisy visual inputs. Despite these differences, the integration of prior information did not differ between groups, suggesting that the relative weights of prior and visual information are not significantly affected by unilateral amblyopia.

Chapter 4

Frontotemporal dementia patients exhibit deficits in predictive saccades

4.1 Abstract

Prediction and time estimation are all but required for motor function in everyday life. In the context of eye movements, for instance, they allow predictive saccades and eye re-acceleration in anticipation of a target re-appearance. While the neural pathways involved are not fully understood, it is known that the frontal lobe plays an important role. As such, neurological disorders that affect it, such as frontotemporal (FTD) dementia, are likely to induce deficits in such movements. In this work, we study the performance of frontotemporal dementia patients in an oculomotor task designed to elicit predictive saccades at different rates, and compare it to young and older adults. Clear deficits in the production of predic-

tive saccades were found in patients, in particular when the time between saccades was short (∼500ms). Furthermore, a linear classifier trained on FTD and older adults data (> 90% accuracy) segregated 2 asymptomatic participants bearing the C9ORF72 gene in a way consistent with the onset of FTD symptoms within 3 years. Taken together, these results argue in favor of a role of the frontal lobe in predictive movements timing over short timescales, and suggest that predictive saccades in FTD patients warrant further investigation to fully assess their potential as a diagnostic aid.

4.2 Introduction

Frontotemporal Dementia (FTD) is an umbrella clinical term that designates a heterogeneous and complex group of neurodegenerative disorders (Bang et al., 2015; Bigio, 2013; Laforce, 2013), typically encompassing two broad categories according to the clinical presentation: behavioral variant FTD (bvFTD; Laforce 2013; Rascovsky et al. 2011) presenting with a frontal syndrome, and primary progressive aphasia (PPA) presenting with a language impairment, itself divided into three variants (Gorno-Tempini et al., 2011) : semantic (svPPA, also known as semantic dementia), nonfluent/agrammatic (naPPA, also known as progressive nonfluent aphasia) and logopenic (lvPPA). FTD mainly affects the frontal and anterior temporal lobes, as well as some subcortical structures (Garibotto et al., 2011; Laforce, 2013; Landin-Romero et al., 2017; Zhang et al., 2013), and there is wide overlap between these areas and the ones responsible for the control of eye movements (Anderson & MacAskill, 2013; Antoniades & Kennard, 2015; Leigh & Kennard, 2004). As such, several studies investigated the eye movements of FTD patients (Boxer et al., 2006, 2012; Coppe et al., 2012;

Garbutt et al., 2008; Henley et al., 2014; Meyniel et al., 2005), and highlighted abnormalities among several FTDs (including Progressive Supranuclear Palsy, Cortico Basal Degeneration, FTDtau).

In one of these studies (Coppe et al., 2012), FTD patients were asked to track a target moving at a constant velocity. Following a gap period of 300ms, the target started to move at a constant velocity for a few hundred milliseconds, then, on $\approx 75\%$ of the trials, was blanked during 800ms. Blanking typically causes a decrease of smooth pursuit gain, which can be maintained at a plateau if the target is expected to reappear (Madelain & Krauzlis, 2003; Orban de Xivry et al., 2008). In healthy and AD participants, several repetitions of this task elicited predictive reacceleration before the end of the blanking, showing that they had learned the timing of reapparition. On the contrary, FTD patients were shown to make no predictive eye acceleration in the same situation. Still, during the 300ms blank that preceded target onset, they were able to elicit normal predictive acceleration. This prompted the authors to suggest an impairment of time estimation in FTD patients.

In this study, we investigate prediction and implicit time estimation in a varied population of FTD patients using a different type of eye movement, saccades, which are easier to process and analyse in a clinical setting. When the direction, amplitude and timing of the next target step are fully known, a healthy subject typically generates predictive behaviors within few target presentations (i.e. predictive saccades), thereby reducing latencies to 0 or below (Findlay, 1981; Shelhamer & Joiner, 2003).

Because these saccades involve pathways that overlap with predictive smooth pursuit and timing (K. Fukushima et al., 2013; Krauzlis, 2004, 2005; Lee et al., 2016; Lukasova et al., 2018; Orban de Xivry & Lefèvre, 2007), the deficits exhibited by FTD patients

in (Coppe et al., 2012) might transfer to this task. Therefore, we designed a protocol in which the time between two target steps is constant within a trial of several steps, but increases from 500ms to 700ms and to 900ms across several trials. Our initial hypothesis was that FTD patients would exhibit lower performance in trials for which the time between two steps was 900ms, longer than the 800ms of blanking (Coppe et al., 2012), and better performance with 500ms, with 700ms falling somewhere in-between.

4.3 Methods

4.3.1 Participants

Twenty-three patients (12 female) having been diagnosed with a form of FTD at the Memory and Cognition Clinic of the Saint Luc University Hospital accepted to participate in this study. Their eye movements were recorded, and one patient was excluded because of excessive data loss, leaving 22 patients. Their ages ranged from 51yo to 83yo (avg. 68.7yo, sd. 7.36yo). Based on clinical assessment, neuropsychological tests (cf. Coppe et al., 2012), and brain imagery (MRI, F-18 FDG PET scanner, Tc-99m HMPAO or ECD brain scintigraphy), the patients were diagnosed by expert clinicians (AI, JCB, and KS) as presenting either behavioral frontotemporal dementia (bvFTD, 16 patients) or primary progressive aphasia (PPA, 6 patients). For the diagnosis, the revised diagnostic criteria were applied (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).The severity of the symptoms was appreciated by the clinician as mild (11 patients), moderate (6 patients) and severe (3patients). In addition, two participants (47 and 71yo) exhibiting the C9ORF72 (Gijselinck et al., 2012; Renton et al., 2011) gene mutation, but no behavioral or clinical symptoms of FTD at the

time of measure, were also recruited.

All patients but one were followed-up by the same neurologists that made the initial, and reexamined to validate the diagnosis. Morphological and functional imaging deficits of all participants were evaluated by the same neurologist without information on the oculomotor performances of specific patients.

Two control groups of young or elderly healthy adults were also recruited, and their eye movements recorded. The first group, hereafter denoted as the young adults (YA) group, was composed of 25 participants (8 female) and ranged in age between 22yo and 38yo (avg. 27.6yo, sd. 4.19yo). The second group, hereafter denoted as the older adults (OA) group, was composed of 26 participants (16 female), ranging in ages from 53yo to 75yo (avg. 64.1, sd. 13.6yo) - cf Figure 4.1).

The general cognitive performance of older control was evaluated using the MMSE test, and a minimal score of 27 (over 30) was set for inclusion in the study. No one was excluded.

The procedures were approved by the Université catholique de Louvain Ethics Committee and in accordance with the Declaration of Helsinki. After full description of the experiment, participants gave informed consent before taking part in the experiment. For patients who assented to participating but lacked full capacity to consent, we received consent from a family member.

4.3.2 Behavioral testing

Participants were sat in a dark room, 151 cm from a 197x150 cm screen placed in front of them, spanning approximately 65° (horizontal) by 50° (vertical) of their visual field. Chin and forehead

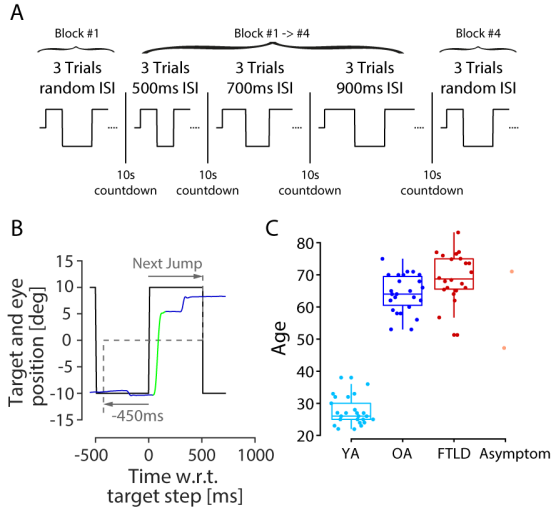

Figure 4.1: Panel A : Overview of the protocol. Panel B : Criteria for valid saccades. The dashed lines indicate thresholds in time (vertical lines) and in space (horizontal lines). Panel C: Age Distribution.

rests restrained their head movements. A cine8 Barco projector (Barco Inc., Kortrijk, Belgium) displayed stimuli at a refresh rate of 100Hz while eye movements were recorded at 1000Hz by an Eyelink 1000 (SR Research, Ottawa, Ontario, Canada). The display was handled by an in-house toolbox, while *Eyelink*® interactions were handled by the Psychtoolbox (Kleiner et al., 2007).

Each trial began with an initial fixation, during which a yellow target dot (0.8°) was displayed in the center of the screen for a random duration between 500 and 1000ms. After this, the target instantly jumped 10° to the left/right (pseudo-randomly distributed across blocks), then made 10 more 20° steps from one side of the screen to the other. The time between two steps (Inter Stimulus Interval - ISI) was either random (among 500, 700, 900, 1200ms) – the random condition – or constant (500,700,900) – the predictable condition – within a trial. Participants were instructed to keep

looking at the displayed target to the best of their abilities.

Trials were always presented in groups of 3 with the same ISI condition (random/500/700/900). There were 4 blocks, which always contained the 3x3 trials of the predictable condition in the same ascending order (cf. Figure 4.1A). In addition, the first block started with an additional 3 random trials, and, for 50 of the participants ($\approx 65\%$), another 3 random trials were included at the end of the last block. Calibration targets were presented at the start of every block. Finally, there were mandatory breaks: after each trial, a countdown was displayed (5s between trials, increased to 10s every 3 trials) and the participants were instructed to stay still while resting their eyes by looking downward or blinking. After each block, participants were free to take a break. The duration of an experiment was around 12 minutes.

4.3.3 Data processing

Data were processed using $Matlab^{®}$ ($MathWorks^{®}$) and R (R Core Team, 2018). Missing values in the eye position data were considered blinks and removed (along with safety margins of up to the first local minimum of vertical eye movement on each side of the blink). Eye position signals were low-pass filtered at 48Hz, and eye velocity and acceleration were obtained using a central difference algorithm on a $\pm$10ms interval. We detected saccade onsets and offsets by using a simple $500°/s^2$ threshold on eye acceleration.

4.3.4 Criteria for saccades selection

To match participant's saccades with the relevant target steps, we used a few criteria (cf. Figure 4.1B): 1) Saccade onset within 450ms before the step, up to the next step (500-1200 ms after); 2) The

saccade must cross the middle of the screen; 3) The amplitude must be at least 25% of the target step size. If several saccades met those criteria, the earliest saccade was chosen.

4.3.5 Saccade features

For each valid saccade, we computed the Latency with respect to the associated target step, as defined by the time (in milliseconds) between the onset of the saccade and the target step. Saccades were categorized as predictive if their latency was lower than 80ms (w.r.t. the target step), and reactive otherwise. In addition, we computed peak velocity as the maximum eye velocity reached between the onset and the offset of the saccades. The gain of saccades was computed as the ratio between the amplitude of the saccade and the distance between the eye and the target towards which the saccade is headed (even if it has not appeared yet).

All further analyses were conducted on saccades from the 4th target step of each trial on, therefore setting aside the first 3, to ensure that participants had time to learn the current ISI.

4.3.6 Statistical analyses

In order to measure the ability of participants to anticipate target steps of different ISIs, we concentrated our analyses on saccades latency. Depending on participants or ISIs, reactive and predictive behaviors were present in different amounts. Therefore, the distribution of latencies was assumed non-normal, and potentially multi-modal. Given this, the typical performance of each participant was characterized by computing median latencies, using the Harrell-Davis method (Harrell & Davis, 1982).

Group comparisons were made on individual medians, on the

interquartile range, and on the differences between medians in the predictable and random trials, using robust trimmed-means ttests and one-way ANOVA (factor group) or two way mixed-design ANOVAs (within factor ISI, between factor group) provided by the R package WRS2 (Mair & Wilcox, 2018), using 20% trimmed means and 2000 bootstrap samples (Field & Wilcox, 2017).

These tests compare central tendencies on the basis of 20% trimmed means (by removing 20% of data on each side of the median), which makes them more robust to most non-normality problems and outliers (Field & Wilcox, 2017). The trimmed means ttest used was yuenbt, which uses a bootstrap procedure to sample each group with replacement nboot times and apply the t-test on each, then outputs a p-value and a confidence interval based on the results, as well as the difference between the groups M_{diff}. The one-way ANOVA used was t1waybt, which uses a percentile-t bootstrap to perform a heteroscedastic one-way ANOVA to test the hypothesis of equal trimmed means. It outputs a F-value F_t, as well as a bootstrapped p-value. Post-hoc corresponding to this anova are provided by mcppb20, which again performs a bootstrap to evaluate the hypothesis of equal trimmed means between 2 groups, outputting $\hat{\psi}$, the difference between the groups, a 95% confidence interval, and a bootstrapped p-value. Finally, the two-way mixed-design used the function *bwtrimbt* of the packages WRS2 and WRS (Wilcox, 2017), which produce a F-value and bootstrapped p-values for each main and interaction effect.

Significant main effects and interactions were further explored using simple effect analyses based on robust t-tests, correcting p-values with the Holm-Bonferroni method to account for multiple comparisons.

Furthermore, we used linear discriminant analysis to build a

linear classifier of OA and FTD participants, so as to predict the group to which asymptomatic participants belong. For that, we used the function *lda*, from the R package MASS. The training variables were the corrected saccades latencies medians for each predictable ISI, as well as the overall percentage of predictive saccades.

4.4 Results

Participants made saccades to track target steps grouped in trials of 11 steps, with either constant (predictable) or random ISIs. Blocks presented predictable trials in 3 groups of 3 having the same ISIs, in ascending order (500-700-900), while groups of 3 random trials were presented before the first and after the last block. This design encouraged predictive saccades in all predictable trials. Unless otherwise specified, the saccades considered in this section are saccades from the 4th target step onwards, to ensure that participants have had enough time to learn the current ISI.

4.4.1 Oculomotor behavior

Overall saccadic behavior tended to differ between the groups, in ways similar to the representative participants whose position traces are shown in Figure 4.2 (random ISI not shown). As can be seen in panel A, the YA participant's saccades tended to closely match target steps, while the OA participant's saccades (panel B) had more variable and more anticipative saccade onsets. FTD patients (panel C and D) also exhibited more variability than YA in saccade latencies, but did not make as much predictive saccades as either YA or OA, in particular at the 500ms ISI. In addition, FTD patients sometimes failed to initiate saccades altogether. For some

patients (such as the FTD patient 2 of Fig. 4.2C), this variability and reactive behavior were also seen at longer ISIs, with latencies reaching 500 milliseconds.

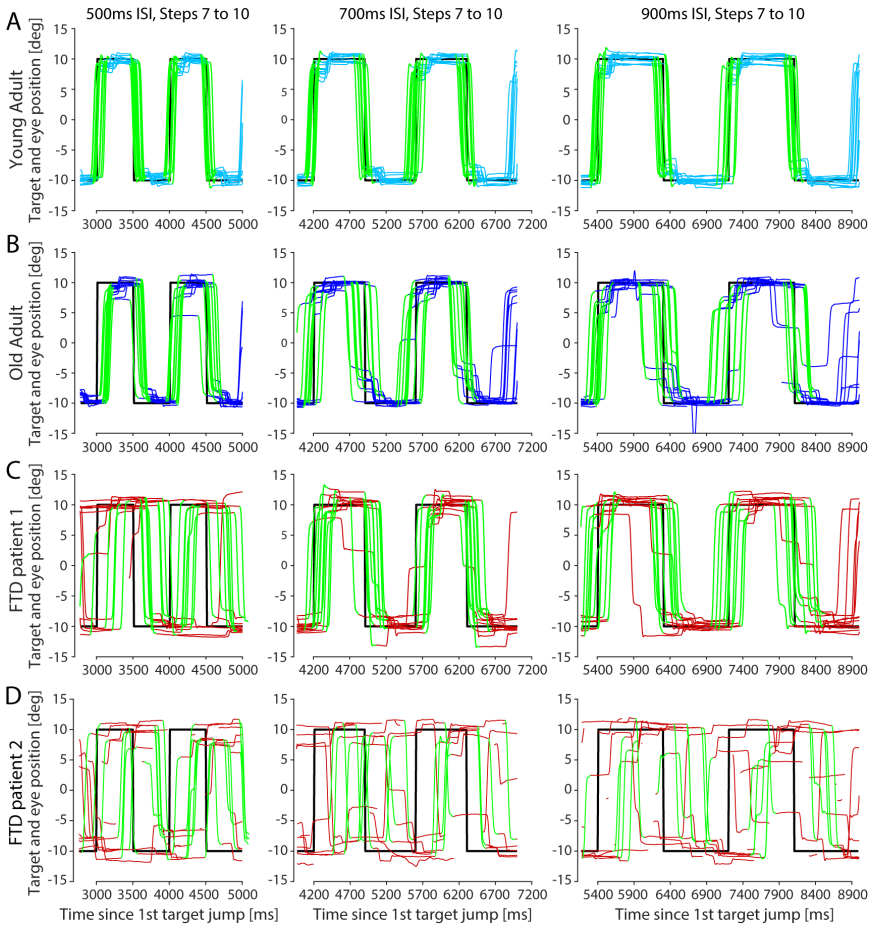

Figure 4.2: Traces corresponding to steps 7 to 10 of predictable trials for typical participants from all groups, with FTD being represented by 2 such participants.

A broader view of the evolution of saccadic latencies within trials, allowing comparisons between groups and ISIs, is shown in Figure 4.3. In trials of predictable ISIs, control participants exhibited a rapid decrease of saccadic latencies across target steps, typically going from reactive to a predictive plateau within 1 to 3 steps (cf. 1st row and first 3 columns of the 2nd row of Figure 6). In contrast, in trials of random ISIs (cf. "ISI random" in Figure 6), this decrease in latency was much smaller and control participants made mainly reactive saccades with latencies over 80ms, as well as a few predictive ones.

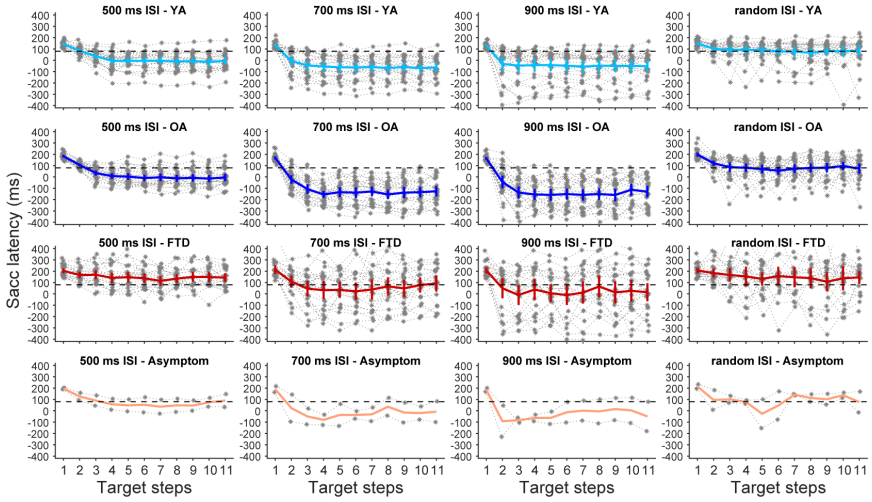

Figure 4.3: Median latencies across target steps. Connected grey dots are individual medians across trials and blocks, and colored error bars show the median of individual medians.

Overall, FTD patients exhibited much more difficulties. Some patients were able to perform the task, exhibiting similar patterns of a rapid decrease of latency across the first 3 steps of predictable ISIs. However, at all ISIs there were some patients unable to generate predictive saccades (grey traces over the dashed line marking 80ms), which was rarely observed in control groups. The most strik-

ing difficulties were seen for the 500ms ISI, for which most of the FTD patients were unable to generate predictive saccades, to the extent that it appears almost undistinguishable from the random ISI. During random ISI trials, patients showed behavior similar to controls, although their group variability appeared higher.

4.4.2 Group differences of saccade latencies during random ISIs trials

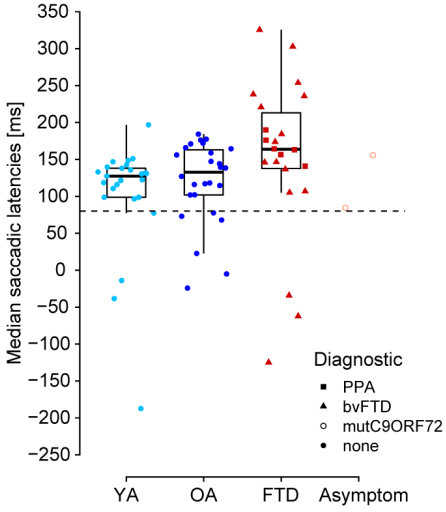

Figure 4.4: Saccade latencies in the random ISI condition. Dots represent individuals, boxplot the 25th, 50th and 75th percentiles, along with whiskers up to the last non-outlier data point. PPA: Progressive Primary Aphasia, bvFTD: behavioral variant of FTD. mutC9ORF72: mutation carrier.

In random ISIs trials, since target steps were unpredictable, valid saccades tended to be reactive – although inter-individual variability was high (cf. Figure 4.4). The 20% trimmed means of saccadic latencies were lowest for the YA group, followed by the OA and the FTD groups (cf. Table 4.1). Group-level comparisons of individual median latencies showed a significant difference between groups (Ft(2,23.49)=3.149, p_{boot} =.047). However, simple effect tests could not highlight significant differences between pairs of groups: not between YA and OA ($\hat{\psi}$ =-7ms, CI=[-39.36,25.11],

p=.586), or YA and FTD ($\hat{\psi}$ =-43.68ms, CI=[-86.59,15.73], p=.061), nor OA and FTD ($\hat{\psi}$ =-36.68ms, CI=[-82.73,30.34], p=.115).

4.4.3 FTD patients have higher latencies in shorter predictable ISIs

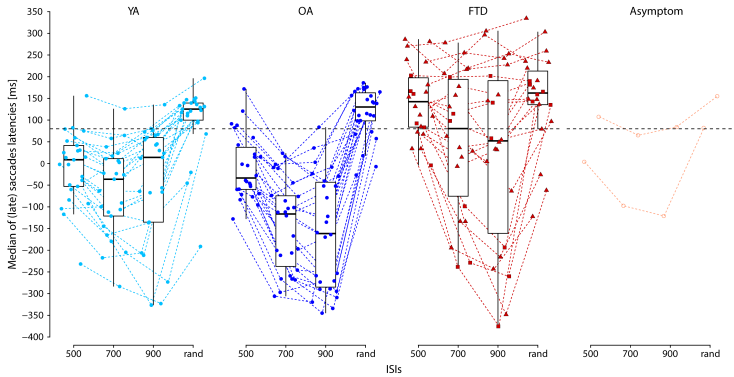

Figure 4.5: Median latencies in predictable ISI conditions. Connected dots, square and triangles are individuals.

As shown in Figure 4.5, median latencies in both control groups were well below 80ms in all predictable trials. However, the FTD group had comparatively higher latencies, notably in the 500ms ISI, in which 75% of patients had medians latencies over 80ms. Comparing the median latencies across groups and (predictable) ISIs showed significant main effects of group (F(2,26.64)=8.81, p=0.0045), ISI (F(2,28.7)=24.64, p<0.0001), and interaction group x ISI (F(4,26.61) = 6.03, p = 0.012). Simple effect tests showed significant differences at the 500ms ISI, between YA and FTD (Mdiff=-141.32, CI=[−195.17, −87.48], Y_t = −5.26, p_{corr} <0.0001), and between OA and FTD (M_{diff} =-158.62, CI=[−213.76, −103.45], Y_t =-5.69, p_{corr} <0.0001); at the 700ms ISI between the OA and FTD groups (M_{diff} = −216.43, CI

=[-334.36, -98.49], Y_t =-3.91, p_{corr} =0.007); and at the 900ms ISI between YA and OA (M_{diff} = −154.93, CI=[59.76, 250.10], Y_t =3.35, p_{corr} =0.021).

4.4.4 FTD patients make less predictive saccades

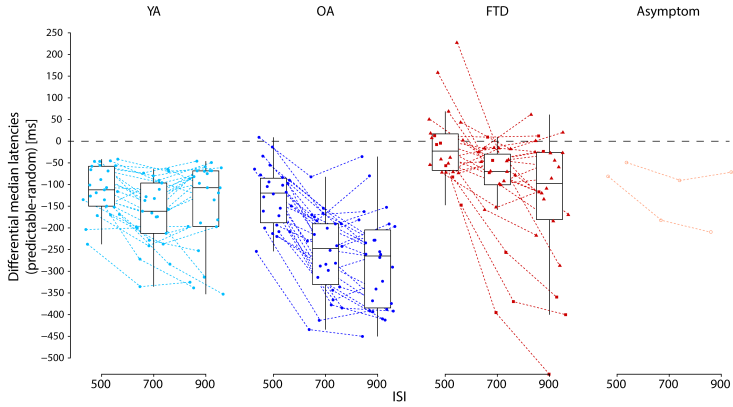

Figure 4.6: Differences between median latencies in predictable and random ISI conditions. Connected dots, square and triangles are individuals.

Because of large differences in latencies between participants, as well as prior research suggesting overall higher latencies in FTD patients, we compared the ability to generate predictive saccades using the difference between the predictable and random ISI conditions. As can be seen in Figure 4.6, the FTD group had lower levels of differences compared to the control groups, meaning that, even accounting for higher latencies, patients made less predictive saccades. Comparing these differential latencies confirmed significant main effects of group (F(2,27.73)=21.41, p<0.0001) and ISI (F(2,33.85)=33.78, p<0.0001), as well as a significant interaction group x ISI (F(4,27.32)=7.83, p=0.0002). Post-hocs with robust t-tests showed significant differences between the OA and FTD

groups at all ISIs (p<.005), while the differences between YA and FTD or OA were significant (p<.005) for all ISIs except for the non-significant difference YA vs OA at the 500ms ISI (M_{diff} =21.89, CI=[-21.46, 65.23], Y_t =1.05, p_{corr} =0.583), and the non-significant difference YA vs FTD at the 900ms ISI (M_{diff} =-22.54, CI=[-87.3588, 42.2734], Y_t =-0.664, p_{corr} =0.583).

4.4.5 The variability of saccade latencies did not significantly differ between OA and FTD

We evaluated individual variability using interquartile ranges, for each predictable ISI, and compared groups using robust two way mixed-design ANOVA with group and ISI factors. This revealed main effects of group (F(2,26.18)=10.89, p=0.0004) and ISI (F(2,23.55) = 57.66, p<0.0001), as well as an interaction group x ISI (F(2,25.74) = 3.94, p=0.0126). The main effect of the group appeared to be mainly driven by the YA group, as post-hocs with robust t-tests only showed significant differences at the 900ms ISI between YA and OA (M_{diff} = −75.84, CI=[-113.97, -37.7], Y_t = −2.49, p_{corr} =0.0045), as well as between YA and FTD (M_{diff} = −107, CI=[-161.06, -52.94], Y_t = −4.3, p_{corr} =0.012). The same two-way mixed-design ANOVA, when limited to the OA and FTD groups, similarly found no group effect (p>0.1) or interaction group x ISI (p>0.1), although the main effect of ISI remained (p<0.0001).

4.4.6 Rate of valid and predictive saccades was lower in FTD patients

In addition to their difficulties to produce predictive saccades, patients also made less valid saccades overall. In Figure 4.7, we show the overall percentages of valid saccades (x-axis) and compare it to the percentages of valid saccades that were predictive (Y-axis), for three different contexts. As can be seen at a glance, the rate of valid saccades was very high (>94%) in control groups for all contexts, while it was systematically lower in FTD patients. Figure 4.1 gives a group overview of the data in Figure 4.7.

This lack of valid saccades stemmed mainly from two of the selection criteria (cf. Methods): no saccade within latency thresholds, and no crossing of the center (which tended to overlap with the criterion on amplitude), in similar proportions. As such, the higher rate of valid saccades of FTD patients in the first steps (Fig. 4.7A) is consistent with its lower amplitude (10°).

In the random ISI condition (Fig. 4.7B), both control groups had high levels of valid saccades, while FTD patients had significantly lower levels, with an average of 74.4% of valid saccades ($\chi^2(2)=261.47$, $p<.0001$), with high inter-individual variability.

In the predictable ISI conditions (Fig. 4.7C), control participants had no trouble doing the task, with over 94% of valid saccades in both groups, and a strong tendency to make predictive saccades (>78%). Although individual variation was high, this was more difficult for FTD patients, with a group average of 70% of valid saccades ($\chi^2(2)=2822$, $p<.0001$), and less predictive saccades (cf. Table 4.1 and Figure 4.7).

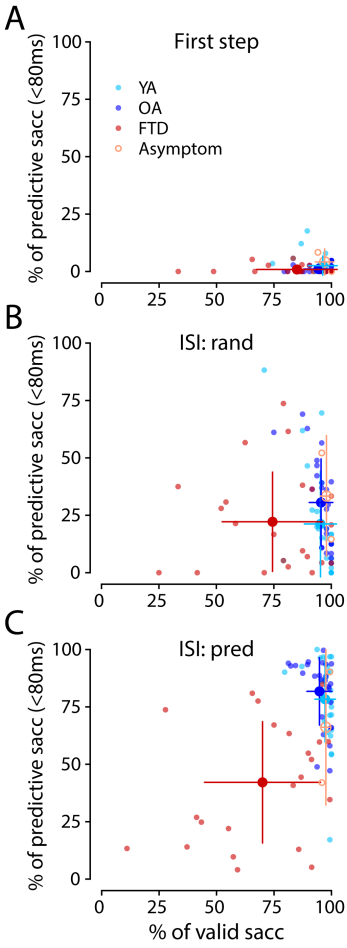

Figure 4.7: Percentages of valid saccades (X-axis), and percentage of valid saccades that are predictive (Y-axis), for the first target steps (panel A), the random ISI steps (panel B), and the predictable ISI steps (panel C). Small dots are individuals, large dots averages across groups, and error bars indicate standard deviations

4.4.7 Differences in saccadic amplitude and velocity

Finally, we investigated the peak velocity and gain of the saccades. The 20% trimmed means of individual peak velocities were highest in YA ($mean_{20\%tr}$ = 375.6, $CI_{95\%}$ = [358.47, 392.74]), followed by OA ($mean_{20\%tr}$ = 350.57, [331.06, 370.07]) and FTD patients ($mean_{20\%tr}$ = 340.53, [303.47, 377.59]). These differences between

Group	Overall % valid mean, [sd]	% predictive mean, [sd]	Latency 20% trimmed mean, [95% CI]
First step			
YA	96.2% [6.4]	2.5% [4.4]	136.05ms, [128.22, 143.89]
OA	94.4% [6.6]	1.1% [1.7]	169.85ms, [161.15, 178.55]
FTD	84.9% [17.7]	0.9% [1.8]	190.64ms, [165.03, 216.25]
Random ISI			
YA	95.3% [7.2]	21.2% [23.2]	123.58ms, [111.64, 135.51]
OA	95.5% [5.3]	30.6% [19.2]	130.58ms, [106.59, 154.56]
FTD	74.4% [22.1]	22.2% [21.8]	167.26ms, [130.51, 204]
Predictable ISI			
YA	97.3%, [4.6]	78.3%, [18.9]	-20.8ms, [-47.6, 6]
OA	94.8%, [5.6]	81.8%, [14.9]	-94.9ms, [-132.4, -57.6]
FTD	70%, [25.3]	41.7%, [26.9]	104.7ms, [68.9, 140.37]

Table 4.1: Saccadic performance in different contexts. Percentages of valid saccades are relative to the total number of steps, while the percentage of predictive saccades is relative to the number of valid saccades.

groups weren't significant (Ft(2,25.89)=2.987, $p_{boot} = 0.0735$). However, there were significant differences of gain between the groups ($Ft(2, 25.66) = 10.64$, $p_{boot} < 0.0001$), with YA having the highest ($mean_{20\%tr} = 0.95$, [0.94, 0.96]), followed by OA ($mean_{20\%tr} = 0.92$, [0.89, 0.94]) and FTD ($mean_{20\%tr} = 0.88$, [0.85, 0.91]). Subsequent simple effect analyses showed significant differences of gain between all groups: YA and OA ($\hat{\psi}$ =0.032, CI=[0.005, 0.059], p=.005), YA and FTD ($\hat{\psi}$ =0.067, CI=[0.027, 0.102], p<0.0001), or OA and FTD ($\hat{\psi}$ =0.035, CI=[-0.006, 0.071], p=.037).

4.4.8 Classification of 2 asymptomatic C9ORF72 mutation carriers

To compare the 2 asymptomatic participants to OA and FTD participants, we used a linear classifier trained on the OA and FTD groups (see Methods). The resulting classifier had an accuracy of 0.917 (95% CI=[0.800, 0.977]), a sensitivity of 0.864 and a specificity of 0.962 (with FTD being the positive class). The resulting posterior probabilities for the OA, FTD and asymptomatic partic-

ipants are shown in figure 4.8. As can be seen, 1 OA and 3 FTD participants were misclassified, while one of the two asymptomatic participants was classified as FTD, with a posterior probability of 0.747.

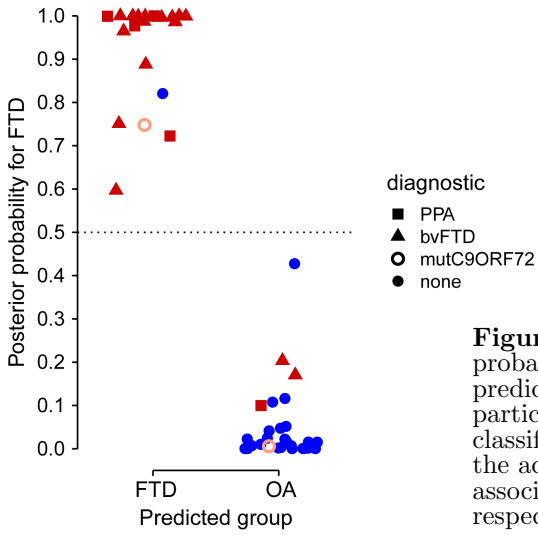

Figure 4.8: Posterior probability of being FTD, and predicted group of the participants, based on a linear classifier. Color and shape give the actual group and the associated diagnostic, respectively.

4.5 Discussion

In this study, we show evidence that, as a group, FTD patients made significantly less predictive saccades than OA controls during a predictive saccade task. In a more reactive task, however, they exhibited moderately higher latencies ($\approx$ 40ms) without the difference reaching significance.

4.5.1 Low numbers of valid saccades were predominantly associated to FTD patients

The lower rate of valid saccades observed in FTD patients stemmed both from failures to initiate a saccade in time and hypometric sac-

cades. The first of these causes could be explained by a lack of engagement (apathy being a common symptom of FTD), attention deficits leading to increases in blink rate and duration (McIntire, McKinley, Goodyear, & McIntire, 2014) but also lesions in the basal ganglia (Leigh & Kennard, 2004; Stuphorn, 2015), which can be present in FTD (Landin-Romero et al., 2017). Hypometrical horizontal saccades have been previously documented in bvFTD and are related to contralateral lesions in the FEFs (Boxer et al., 2012; Douglass et al., 2018).

4.5.2 Saccades to random ISIs targets: small non-significant differences between groups

The latency of saccades made during random trials, a reactive condition, did not significantly differ between any two groups, although, given the presence of an overall group effect, a few facts must be kept in mind. First, the FTD group had a high variability, and approximately 40ms higher saccade latencies compared to the other 2 groups. Second, participants had no uncertainty regarding the position of the future target, which has been shown to increase the probability of predictive saccades (Lukasova et al., 2018). Indeed, a handful of participants across all groups favored such behavior. Finally, our individual summary measure was the median of latencies, as it is a more robust measure of the central tendency of non-normal distributions, and because we wanted to characterize the typical performance of patients for predictive saccades. Therefore, mean latencies could lead to different conclusions.

Nevertheless, finding similar latencies of patients and controls in reactive, horizontal saccades would be in agreement with prior

studies on clinically-diagnosed FTD patients (Boxer et al., 2006; Garbutt et al., 2008), and on autopsy-confirmed FTLD patients (Boxer et al., 2012), but in disagreement with a couple of studies on bvFTD patients (Douglass et al., 2018; Meyniel et al., 2005). However, this might be due to differences in populations, such as age, severity of dementias and underlying neuropathologies, known to be heterogeneous in FTD patients. Despite the lack of specific group differences, one could note that the six patients with the highest saccadic latencies did belong to the bvFTD subgroup, which might warrant more investigation with bigger samples of bvFTD patients.

4.5.3 Predictive saccades: different behaviors across groups

In the predictive condition, overall behaviors differed across control groups: while the YA group tended to maintain constant predictive latencies across ISIs, the OA group predominantly anticipated more with increasing ISIs, in a way consistent with a transfer of the first ISI to the next ones (Shelhamer & Joiner, 2003). The last type of behavior, reactive latencies, was predominantly found in patients.

Indeed, as a group, FTD patients had significantly higher latencies than the OA group in the predictive task for the shorter ISIs, therefore making less predictive saccades. Even after accounting for individual differences in latencies, patients still differed from older controls by having significantly smaller differences between latencies in the predictive and reactive conditions. While the only study of predictive saccades in FTD, more specifically bvFTD, did not highlight such differences (Douglass et al., 2018), it tested an ISI of 1000ms while we tested several sub-second ISIs, and involved

younger participants. Although the effect we observed does appear to decrease with increasing ISI, this needs to be confirmed in further studies.

The lesional patterns of the brain structures involved in eye movement control might explain the predictive saccades differences we highlighted. Cortical lesions in the FEF could explain both reactive latencies and saccade hypometry (Leigh & Kennard, 2004), while lesions to the SEF or DLPFC would explain the reactive latencies without affecting saccade amplitude (Gaymard et al., 1998; Nyffeler et al., 2008; Pierrot-Deseilligny et al., 2003). In addition, impairments to subcortical timing-related areas, including the putamen and cerebellum (Hove, Fairhurst, Kotz, & Keller, 2013; Lee et al., 2016), have also been documented in FTD (Henley et al., 2014; Landin-Romero et al., 2017).

Still, while both subtypes (bvFTD and PPA) exhibited deficits, inter-individual variability was high, with some patients exhibiting normal behavior and others being unable to make predictive saccades. This might be due to the inherent variability of the localization of neurodegenerative lesions in FTD, the degree of brain damage in specific eye-movements related areas, or the presence of unknown subcategories within our population (such as their underlying neuropathology).

4.5.4 Performance of participants carrying the C9ORF72 mutation

The two asymptomatic participants carrying the C9ORF72 mutation exhibited qualitatively different behaviors in predictable trials. The younger of the two made predominantly predictive saccades at all predictable ISIs, while the older one made mostly reactive sac-

cades at ISIs 500ms and 900ms. Furthermore, even when correcting for latency in the random condition, the latter's behavior appeared more similar to FTD patients that to the older controls, while the former was undistinguishable from the controls.

A more objective comparison with the FTD and OA groups, using a linear classifier, reached similar conclusions by classifying the older asymptomatic participant as FTD and the younger as OA. Incidentally, of those two participants, only the older one began exhibiting symptoms 3 years after his participation.

4.5.5 Is this a deficit in timing?

Our initial hypothesis stated that we expected an impairment in the timing of FTD patients, particularly for the longest ISIs.

Our results do not support this hypothesis, as, while some FTD patients exhibited timing impairment, it either did not increase with ISI or was worse at the shortest ISI. Furthermore, the variability of individuals latencies did not significantly differ between OA and FTD groups.

A first alternative hypothesis is that 500ms is too short an interval for most FTD patients to elicit predictive saccades. While predictive saccades in the sub-second range are typically regarded as simple tasks, because they could be encoded as a rhythmic movement in the basal ganglia or the cerebellum (Lee et al., 2016), such a behavior might first require processing in cortical areas. As such, FTD patients might come short because of an accumulation of small delays due to degeneration in prefrontal areas implicated in temporal processing and predictive saccades (Lewis & Miall, 2003; Lukasova et al., 2018). Seen within the context of decision-making paradigms and urgency signals (Cisek, Puskas, & El-Murr, 2009;

Thura & Cisek, 2016), FTD patients might be unable to increase the rate of their 'rise to threshold' past a certain limit, therefore exhibiting a lower bound on their decision time.

Our second hypothesis is directly related to the processing of time by the brain, which is a complex mechanism that is still not well understood (Merchant, Harrington, & Meck, 2013). Still, the existence of a centralized clock mechanism is now regarded as less probable than an intrinsic timing ability of cortical networks, at least for short intervals (Burr & Morrone, 2006; Merchant et al., 2013). The sub-seconds predictable ISIs that were used in this study certainly fall under that category. As such, instead of an accumulation of delays suggested in the previous hypothesis, patients might exhibit damage to the cortical network responsible for the processing of timing, such that they are limited in their ability to measure small intervals of time, or that they consistently over-estimate it, causing them to initiate the saccade too late.

4.5.6 Effect of age on this task

There were significant differences in the saccadic behaviors of YA and OA. While their saccadic latencies did not differ in the random condition and in the 500ms and 700ms predictable ISIs, they significantly differed in their differential latencies (the difference between their latencies in the predictable and random condition) in the 700ms and 900ms ISIs. Looking at the differences between the predictable ISIs, it is apparent that OA exhibited more anticipative latencies with increasing ISIs.

Our interpretation is that OA relied more on their memory of the previous ISI timing, which mean that they tended to make predictive saccades much earlier than necessary. This might be a

strategy deployed by the participants in order to compensate limitations in their processing of time (Turgeon, Lustig, & Meck, 2016) or their greater variability, or the symptoms of a greater weight given to memory rather than sensory inputs. In contrast, most of YA had latencies that were almost constant across predictable ISIs. As a consequence of these differences between OA and YA, FTD patients are more similar to YA at the 900ms ISI, because at this ISI OA anticipate the step by around 150ms, while YA are at 0ms, approximately matching the FTD group latency.

4.5.7 Limitations of the study

In this study, we did not have perfectly matched FTD and OA groups, with an average age difference of 4.6 years, which could affect the latency of the saccades (Irving et al., 2006). Furthermore, our sample of FTD patients was not sufficiently large for comparisons across subtypes. Finally, we did not know the underlying neuropathies of our FTD group, some of which might be predisposed to some types of eye movement deficits than others (Boxer et al., 2012).

4.6 Conclusion

In conclusion, we show that FTD patients of both subtypes bvFTD and PPA exhibited difficulties to make predictive saccades. In addition, they made less valid saccades, mostly because they failed to initiate any or because they made very hypometric saccades. Furthermore, one asymptomatic C9ORF72 mutation bearer who had similar patterns exhibited FTD symptoms within 3 years post-measure. We believe that predictive saccades with sub-seconds ISIs can be a promising tool to evaluate the integrity of reactive and

predictive pathways in FTD and possibly provide diagnostic aid. Future studies could investigate larger populations of patients, and complement predictive saccades with real-time functional imagery to identify the brain structures involved in the deficits.

Chapter 5

Main contributions and Perspectives

Over the course of this work, we set out to better understand the core features of oculomotor memory and its integration. First, we investigated the process by which oculomotor memory is acquired and updated, and concluded that this process was fast and based on reliability. Then, we further investigated the process that estimates this reliability by considering a population of amblyopic patients whose visual system developed in the presence of visual noise. Finally, we investigated deficits of time processing, an important component of oculomotor memory processing, in a population of frontotemporal dementia patients.

In this section, the main contributions of this work are discussed, then used as a basis to discuss future work to be done on oculomotor memory integration and potential improvements to our reference smooth pursuit model.

5.1 Main contributions

Oculomotor memory is acquired fast and integrated based on reliability

The second chapter of this work shows that smooth pursuit is driven by a dynamic reliability-based integration of visual and memory inputs, by showing that the memory of prior target motion has more influence on the movement when the visual input is noisy. By doing so, we validate one of the predictions made by Orban de Xivry et al. (2013) on the basis of their model.

We also demonstrated that this memory of target motion influenced pursuit eye movements well after the end of the open-loop phase of pursuit, because our measures were made on the gains during the steady state of the pursuit. It is possible that, at that time, the difference between predicted and measured retinal slip was not sufficient to drive a correction. However, before drawing this conclusion, we would first recommend to test longer ramp durations or bigger velocity differences, as it is possible that subjects anticipated the end of the pursuit and did not correct for the error.

Furthermore, the design of the protocol, having no step-ramp (Rashbass, 1961), did not inhibit catch-up saccades, which allowed us to observe them and prove the existence of an effect of the short term memory on their amplitude, mirroring the effect found in smooth pursuit. Thanks to that, we were able to provide further evidence of a shared representation of the target between the saccadic and pursuit system.

Another contribution provided by this work is that we clearly demonstrated that humans can acquire a short-term memory of target motion over very few trials, and that this memory can inte-

grated with visual inputs in much the same way as a prior. In contrast, previous studies investigating priors in humans approached them as statistical distributions, obtained through the repetitions of hundreds of trials of a task within a specific context, before testing their integration with new evidence from a different context (Kording & Wolpert, 2004). Furthermore, we reproduce in humans results from a recent and similar study made on monkeys (Darlington et al., 2017).

Amblyopia and reliability estimation

Through our work in chapter 3, we first provide more insight into the smooth pursuit behavior of amblyopic patients, which has not received much attention (Ciuffreda et al., 1979a; Raashid et al., 2016; Schor, 1975; Von Noorden & Mackensen, 1962b).

Overall, amblyopic patients had more difficulties pursuing the target, exhibiting higher rate of trial rejection and lower pursuit gains than controls. To some extent, this was expected due to the presence of strabismus in most patients, since it tends to induce asymmetrical and more saccadic pursuit (Mustari & Ono, 2011). However, this wasn't the only reason, since some anisometropic patients without strabismus also had lower gain than controls. Furthermore, our attempts to only take into account the preferred direction of the patients produced similar results. Therefore, there was another cause for a deficit in pursuit gain in amblyopic patients, which we identified as the lower reliability of their visual information.

A surprising observation, regardless of the overall difficulties of amblyopic patients, was the presence of a couple of patients who, despite low acuity (1/10 to 2/10 Snellen), were able to elicit pursuit

gains of around .9, comparable to most controls. Although anecdotal, this illustrates the extent to which acuity measures and eye movements can provide different outlooks on such disorders.

As described in chapter 3, the results of our experiments, contrarily to our hypothesis, did not show significant differences of the prior weight across groups. This was relatively surprising based on the results of chapter 2, and we suggested that, while we cannot rule out the existence of a difference, this could mean that amblyopic patients weight prior similarly to controls. If that is the case, it could in turn suggest that prior information is processed binocularly, and that the fellow eye compensates for the noisier input of the amblyopic eye during the development of the areas involved. What remains at the core of the problem, however, is whether subjects managed to create a memory of the target motion that was reliable enough to influence pursuit. To mitigate this problem in a future work, it would be simplest to use bigger velocity changes and more repetitions, as well as a symmetrical design to improve statistical power and be able to compare potential differences between increase and decrease of target velocity.

Still, the weight of visual information in smooth pursuit movements did differ across groups, supporting our hypothesis of noisy visual inputs. Nevertheless, catch-up saccades did not exhibit this difference of visual information weight. Such a pattern points towards a deficit within the processing of motion in areas MT and MST. Postulating that the MT/MST are within the visual processing pathway of the model described in 1.3, we would indeed expect noisy inputs (due to the disruption of V1 documented in Amblyopia) to produce lower estimations of velocity due to the Kalman filter. Furthermore, there were indications of a ceiling effect on the eye velocities of amblyopic patients, with the pursuit of a 20°/s

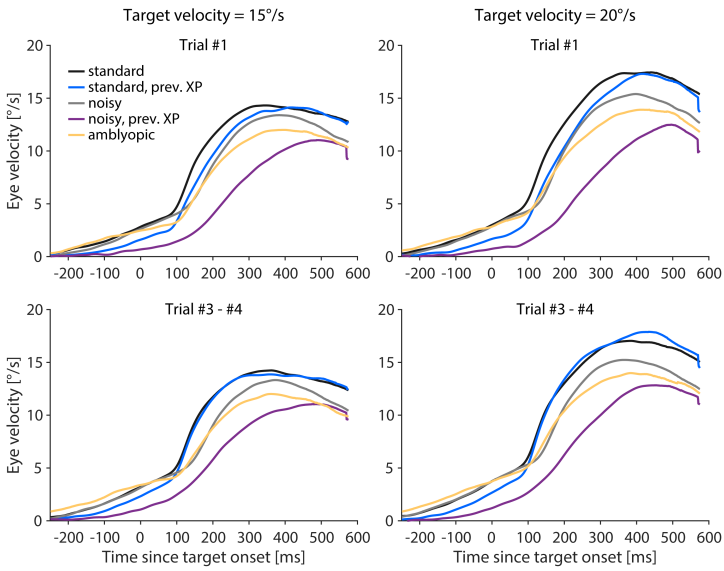

Figure 5.1: Comparison of pursuit traces of the group participating in the experiments of the 1st and 2nd chapters. Columns indicate the target velocity (15 or 20°/s, the first row corresponds to the 2nd trial, and the second row to the last 3 trials.

target being undistinguishable from a 25°/s target, which could again be explained by motion processing in MT/MST exhibiting a signal-dependent-noise.

Another insight was brought out of the comparison of the results of chapters 2 and 3, and showed how small differences of protocols can affect performance. As seen in Fig. 5.1, the standard and noisy groups both had slower steady-state pursuit in the first experiment compared to the second. Furthermore, while the difference between the two standard groups was reduced in later trials, this was not the case for the two noisy groups.

We ended up converging to two explanations. The first was that, due to the passive trial at the start of the 1st experiment, the pursuit response in the next trials had lower initial velocity and

slightly longer latencies. Indeed, the lower initial velocity is quite apparent in the traces of the standard group from the previous experiment. However, this does not explain why the 2 noisy groups still differ after several active trials (2nd row of Fig. 5.1). Our second hypothesis pinpointed the cause on the fixation target and a form of reliability-based integration: because this target was always an uniform, reliable disk in the Chapt. 2 experiment, participants in the noisy group, tracking a noisy target, had more difficulty to disengage from fixation than the standard groups. In Chapt. 3, the fixation target was the same as the pursuit target, which prevented this conflict, and the noisy group had an easier time initiating pursuit. Interestingly, this mechanism is reminiscent of the way the superior colliculus handles fixation and other potential targets (Goffart et al., 2012; Krauzlis et al., 2017). If this reasoning is true, replacing the gap of a gap-paradigm by a blurred target should elicit behavior intermediate to the ones of gap and no-gap conditions.

FTD and predictive saccades

Predictive saccades have rarely been studied in FTD patients, but given the overlap of the brain pathways involved in their control with pathways affected by FTD, they might become a useful tool to better understand the underlying neurodegeneration. Through our work with FTD patients, we were able to highlight a sizable impairment in their ability to generate predictive saccades. As such, we identified a very simple protocol for which the performance of patients was significantly below controls. In addition, we showed that, of two asymptomatic C9ORF72 carriers, the one whose performance was most similar to FTD patients was also the one who exhibited FTD symptoms within 3 years.

Furthermore, we obtained anecdotal evidence of the existence of a subset of FTD patients that is unable to generate predictive saccades at all, which might merit further investigations.

Another interesting outcome of this work was the highlight of different behaviors in Young and Old adults, with Old adults anticipating target steps excessively, and Young adults maintaining almost constant latencies around the time of the target step. Such behavior suggest that Old adults relied more on the memory of previous timings than on the current timing, or compensated for worse timing capabilities, or increased variability.

5.2 Work in progress

In the study presented in Chapter 3, we focused on the adult subset of a wider sample of amblyopic patients, notably because of predictive eye movement differences between children and adults (Ego et al., 2016). We are currently in the process of recruiting and acquiring data from more age-matched healthy children, which will allow us compare the performances in this age group.

Furthermore, in the context of the study of FTD patients, we also acquired smooth pursuit data with a task designed to reproduce the results of (Coppe et al., 2012), which we did not have time to include in this thesis. Compared to the previous study, we will have access to a Young Adults group as reference, which will also allow us to draw comparisons based on the age of subjects.

5.3 Future work

Oculomotor memory and reliability-based integration

As many oculomotor studies before it, our study of reliability-based integration relied on extremely simple target motion in head-restrained conditions. As such, it is unlikely to push the limits of our oculomotor memory, which would have the potential to reveal more about its inner workings and priorities. Therefore, future work might use a similar protocol featuring more complex target motion, such as circular or accelerating motion, from which oculomotor memory would have to be built.

In addition, new protocols could be designed to better disentangle the visual and memory reliabilities, as a memory built from a noisy visual input is expected to have lower reliability than one built from standard inputs. One way to do so would be to use the same target for training trials, then switch to the other for the test trial. In this case, further investigation should first assess the intrinsic effect of switching targets.

Furthermore, the influence of the fixation target on pursuit that we highlighted might warrant further investigation. As such, a variant of the gap paradigm in which the gap is replaced by a noisy target should induce motor performance in-between those induced after normal fixation and after a gap.

Finally, a few more parameters of the protocol might be changed to better highlight the effects: longer ramps would give the occasion to estimate real-time learning of target velocity within test trials; the velocity changes could be made bigger, and either be proportional to the training velocity or absolute; the two training

velocities should be comparable to both increasing and decreasing test velocities by adding one more training velocity.

Amblyopia and reliability estimation

While it produced valuable results, our study of amblyopic patients had some limits that can inspire future work. Here, three further opportunities for research that appear valuable to pursue are presented.

First, increasing the sample size of amblyopic patients, especially in the anisometropic subgroup, would allow to draw comparisons between them. Due to the differences in oculomotor control between those groups, these comparisons might highlight other differences in their weighting of visual and memory information.

Second, our study was limited by the fact that we only had time to measure the amblyopic eye. However, not only does the fellow eye also exhibit deficits, it also contributes to oculomotor control in the everyday life of the patients. Therefore, it would be valuable to be able to compare the performance of patients in 3 conditions: monocular vision with the amblyopic eye, monocular vision with the fellow eye, and binocular vision.

Third, we could compare amblyopic patients to control participants of matching acuity, for example by incrementally blurring a psychophysical test using software (Dehnert et al., 2011), or through optical degradation (Niechwiej-Szwedo et al., 2012).

FTD and predictive saccades

Because the results of this experiment surprised us, a few additional experiments designed to better understand them appear worthy of

interest.

First, it would be interesting to assess whether FTD patients are able to generate a serie of saccades separated by a 500ms duration, even reactively. Indeed, the deficit we observed might be associated to saccade initiation more than to timing. In a further experiment, timing could be tested with single predictive saccades following a cue.

Second, a more expensive study could investigate more patients with different types of FTD, so that comparisons between them could be drawn. Even more than that, longitudinal studies, both with healthy age-matched control and FTD patients could assess the value of predictive saccades as a diagnostic aid.

Third, having access to brain imagery of both cortical and subcortical areas would allow looking for correlations between the oculomotor deficits and damaged brain areas.

Finally, the differences between controls at the longer ISIs of 700 and 900ms warrant further investigation to explain their origin. For example, presenting the ISIs in the reverse order would be an easy way to discriminate between lower timing capabilities or higher reliance on prior ISIs.

Potential for future model development

One path to the improvement of the model would be to add a position pathway to it, as well as the ability to generate saccades. An important result from chapter 2 was that catch-up saccades also took into account the oculomotor memory of target velocity. As such, this would need to be reflected into the improved model, along with the position input to smooth pursuit. Currently, we

know of one such attempt by Coutinho et al. (under revision), which was applied to better understand the trigger of catch-up saccades.

Furthermore, if the improved model is to become a full gaze model, simulating fixation would also be necessary. In this context, the gap effect and the results we describe in the Amblyopia subsection of the main contributions would provide valuable insight into the articulation of fixation and other eye movements.

Finally, as our last experiment with FTD patients outlined, the processing of time is an important component of oculomotor control that can be affected by specific deficits. Therefore, a full gaze model would need to simulate time processing over different timescales, such that some of them could be affected by specific deficits while others would be preserved.

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