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Eye-Hand Coordination in Goal-Directed Action: Normal and Pathological Functioning

Introduction

Moving an arm to contact a target is a skill employed daily in tasks as seemingly simple as turning on the light, opening a door, or picking up a glass of wine. In addition, we often have to make series of movements that vary in spatial-temporal difficulty, such as dialling a telephone, using a calculator or entering a security code in a bank terminal. The apparent simplicity of these types of movements belies the underlying complexity involved in the temporal organization and spatial control of the eye-head-hand system.

A great deal of research has already examined the visual control of upper limb movements (Proteau & Elliott, 1992). However, because of technological limitations, former studies on the visual control of upper limb movements were essentially based on performance measures (e.g., initiation time, movement time) and kinematic variables reflecting changes in the limb movement (e.g., primary velocity and acceleration profile, discontinuities in acceleration), *without* examining eye movements. In 1996, the Motor Behaviour Lab of McMaster University and the Perception and Performance Lab of K.U.Leuven were one of the first few labs that used synchronous measurements and high-speed sampling of temporal and spatial features of *both* the eye and limb movements to examine speeded multiple-degree-of-freedom aiming (e.g. Helsen, Starkes, & Buekers, 1997; Helsen, Starkes, Elliott, & Ricker, 1998c). These experiments offered a unique opportunity to study the natural coupling between eye and limb movements and to challenge recent models of speed-accuracy relations in limb control (see Elliott, Helsen, & Chua, 2001). The goal of the present chapter is to highlight the role of visual afference in manual goal-directed movements in normal and pathological functioning.

Retinal versus extra-retinal information

When visually inspecting the outside world, our eyes rapidly travel from one location to the other to gather relevant information to interact with the world in an efficient way. The main intention of these rapid eye movements or saccades is to bring point of gaze (i.e., the spot where the eyes focus) to relevant environmental features. During these fixations, in normal adults the point of gaze is stably focused on a specific point of the outside world. The eyes are oriented in such a way that the object of interest

is projected onto the most sensitive part of the retina. This important spot is called the fovea and it is a very limited area of only 1° that guarantees the highest possible visual acuity. Around the fovea, peripheral vision provides less detailed information of the surroundings. *Retinal* visual information is the primary source of information guiding goal-directed movements. Secondly, there are a variety of *extra-retinal* visual signals that can be processed and used in the planning and updating of goal-directed movements. These signals arise from the saccades made from one point to the other. They include afferent information from the muscles orienting the eyes as well as from the oculomotor efferent commands.

Both before and during limb movements, visual afference is processed and used in the planning, updating and correction of the ongoing movement. In this chapter, we review different methodological strategies that have been employed to study the role of vision in the planning and control of goal-directed movements. First, we discuss various outcome parameters, such as reaction or initiation time (i.e., the time between stimulus presentation and movement onset), movement time (i.e., the time to travel from the initial home position to the target position) and total response time (i.e., the sum of initiation and movement times). The relative time associated with each of these movement components gives an indication of the time spent on movement planning versus on-line control. Second, kinematic variables, such as peak acceleration, peak velocity, and time to peak velocity provide insight into the typical characteristics of the on-line movement regulation and are examined in single and repetitive aiming movements. Specifically, in the absence of visual feedback, the limb movements typically have a bell-shaped velocity profile suggesting that no adaptations are made on-line. Alternatively, more time is spent during the movement for updates and corrections when there is opportunity for visual feedback processing (Elliott, Binsted, & Heath, 1999). This results in a skewed velocity profile that is characterized by a relatively greater amount of time spent after peak velocity. Third, eye movement parameters are examined to provide additional insight into the processes underlying the interactions between eye and hand movements (see Starkes, Helsen & Elliott, 2002 for a review). Fourth, we present the results of functional imaging of brain regions involved in eye-hand coordination. Finally, the potential use of eye movements as mirror of our thoughts is discussed in the context of motor imagery. Part I of this chapter focuses on normal functioning while Part II is dedicated to the study of eye-hand coordination in pathological functioning.

Visual-Motor Control in Normal Functioning: Part 1

Temporal Relationship Between Eye and Hand Movements in Single Aiming

In a first experiment, Helsen et al. (1997) addressed the coordination between point of gaze (PG) and hand movements in a speeded aiming task to predictable targets of three different eccentricities (35, 40, and 45 cm). In each condition subjects moved the eyes, head, trunk and hand freely (see Figure 1).

Insert Figure 1 about here

Analyses were conducted for: (1) the frequencies for initiation order of PG and the hand, (2) the correlation between initiation latencies of PG and the hand, and (3) initiation, movement and response times of PG and the hand. Regardless of the distance to be covered, there was a remarkable temporal relationship between the arrival of the eye and the limb on the target. Specifically, point of gaze always arrived on the target area first and at roughly 50% of the hand response time. Varying eccentricity increased initiation time of PG but not of the hand. Despite differences in hand response time by as much as 100 ms, an invariant feature was found for the proportional arrival time across conditions. As such, both PG and hand movements were fixed with regard to movement endpoint, and optimization of proportional time across conditions resulted from independent alteration of the individual component effectors.

Regarding the possible functional importance of proportional time in the visual control of voluntary movements, Helsen et al. (1997) speculated that, by PG arriving on the target area first and at roughly 50% of the hand response time, there would be ample opportunity for the eye to provide extra-retinal information on the position of the target either through oculomotor efference or proprioceptive feedback resulting from the large primary saccade. In the remaining time before the arrival of the hand this could readily be combined with ongoing visual and proprioceptive information about the limb position. Given the preponderance of aiming models that propose a dual submovement structure (for a review see Elliott, 1992), proportional time may be a very good way of making the best use of information provided by PG as a result of the first primarily ballistic

submovement. In a somewhat similar way, invariant termination of PG and limb movements has also been reported by Carnahan and Marteniuk (1991).

Spatial-Temporal Characteristics of Eye Movements and Limb Kinematics during Single Aiming Movements

To further examine the meaning of the invariant relationship between the arrival of the eyes and the limb on the target position, Helsen, Elliott, Starkes, and Ricker (1998a) investigated the temporal and spatial coordination of both point of gaze and hand kinematics in a speeded aiming task to an eccentrically positioned visual target. On the majority of trials, PG showed a pattern of a large initial saccade that undershot the target slightly, then one or more smaller corrective saccades to reach the target. The hand exhibited a similar pattern of first undershooting the target and then making small corrective movements. In line with Helsen et al. (1997), again an invariant feature was found for the ratio of PG and hand response time (50%). In line with these results, a striking temporal coupling was found between completion of the primary eye saccade and time to peak acceleration for the limb. Spatially, peak hand velocity coincided with completion of 50% of total movement distance. Thus, during the latter portion of the hand movement, the eye is already over the target area and well-placed to provide visual information regarding the relative positions of both the hand and the target for closed-loop limb control (see Figure 2).

Insert Figure 2 about here

In a follow-up study, Helsen, Elliott, Starkes, and Ricker (2000) examined the temporal and spatial coupling of point of gaze and movements of the finger, elbow and shoulder during a similar speeded aiming task. On the majority of trials, a large initial saccade undershot the target slightly, and one or more smaller corrective saccades brought the eyes to the target position. The finger, elbow and shoulder exhibited a similar pattern of undershooting their final position followed by small corrective movements. Eye movements usually preceded limb movements, and the eyes always arrived at the target well in advance of the finger. There was, again, a clear temporal coupling between

primary saccade completion and peak acceleration of the finger, elbow and shoulder. The initiation of limb segment movement usually occurred in a proximal to distal pattern. Increased variability in elbow and shoulder position as the movement progressed clearly served to reduce variability in finger position.

Spatial-Temporal Characteristics of Eye Movements and Limb Kinematics during Repetitive Aiming Movements

In addition to the execution of single aiming movements, in daily life we often have to make series of movements that vary in spatial-temporal difficulty, such as using a calculator or entering a security code in a bank terminal. To examine to what extent eye-hand coordination in three-dimensional single movement trials is different from repetitive one-dimensional aiming movements, we used a paradigm in which participants wore an orthosis on the preferred limb that was aligned to the anatomical axis of the wrist joint (Lavrysen, Elliott, Buekers, Feys, & Helsen, 2007). The orthosis was built in such a way that it restricted wrist movements to flexion and extension. Wrist angular position was registered by means of non-ferromagnetic high-precision shaft encoders fixed on the movement axis of the orthosis. It was also designed for future use in an fMRI environment.

Insert Figure 3 about here

Participants performed a unimanual wrist flexion-extension aiming task. They were seated in a comfortable armchair with the forearms resting in supports, so that the hand movements were made in the horizontal plane only. A cardboard panel prevented direct vision of the forearm. Wrist angular position was presented as a cursor of 10 mm diameter on a 17-inch monitor that was located 50 cm in front of the participants. Flexion of the right hand resulted in a displacement of the cursor to the left. Consequently, extension of the right hand resulted in movements of the cursor to the right. The required wrist angle of 40° corresponded with 200 mm cursor displacement on the screen. Thus, the visual angle to cover the distance was approximately 20°. To facilitate the comparison of wrist and eye positions, the angle corresponding to this distance was normalized to 40°

for both effectors. The participants were asked to align the cursor to the left and right end of the line at the rhythm of a metronome.

In this repetitive or cyclical aiming task, saccades were only initiated after the hand had already left the target. This reversed initiation pattern as compared to discrete aiming is probably related to the specific task demands. The subsequent saccade was postponed to provide stable visual target information to the ongoing hand movement ('gaze anchoring', Neggers & Bekkering, 2000). As such, of greater interest was the termination of point of gaze which was always concluded before the hand reached peak velocity (similar to Helsen et al., 1998a, 2000 where a discrete aiming paradigm was used). This temporal aspect of eye-hand coordination in a cyclical aiming task has been shown to be quite consistent and independent of afferent perturbations as induced by visual illusions (Lavrysen et al., 2006).

Insert Figure 4 about here

The only factor influencing the timing pattern was the functional disparity between hand/hemisphere systems (see Chapter 12 and Buekers & Helsen, 2000; Helsen, Starkes, Elliott, & Buekers, 1998b; Lavrysen et al., 2007; Mieschke, Elliott, Helsen, Carson, & Coull, 2001). Specifically, in a group of strongly lateralized right-handers, the execution of fast continuous wrist flexion-extension movements has been shown to differ according to the hand used to perform the task (Lavrysen et al., 2007). Not surprisingly, the preferred hand enjoyed advantages in some aspects of movement execution such as more consistency in movement time. More interestingly, the timing of hand peak velocity and eye fixation onset both occurred earlier when using the left than the right hand. Surprisingly, strong left-handers exhibited the same pattern of performance (Lavrysen et al., 2007). Thus, the mode of control was different when using the left or the right hand, independent of hand preference. Perhaps, the need for more on-line guidance when using the left hand creates a need for earlier saccade completion. In this way, visual afference is available earlier in the movement, so that enough time is available for visual information to be processed and used to guide the movement.

Neural Architecture

In addition to the examination of behavioral and kinematic eye and limb parameters, in more recent years we have attempted to bridge the gap between the behavioral and the neurosciences. In this context, fMRI is a technique that allows us to visualize underlying neural substrates of movement based on magnetic resonance imaging (MRI). During scanning, participants are subjected to a strong and homogeneous magnetic field (MR magnet, conventionally 1.5 or 3 Tesla) that induces an alignment of various atomic nuclei parallel to this field, in particular the proton nucleus of the hydrogen atoms. Application of a radiofrequency pulse (RF pulse) changes the alignment of the proton magnetic moments from being parallel to the static magnetic field. The ‘excited’ protons recover their original alignment within a time called ‘relaxation time’ and the created magnetization effect induces an exponentially decaying radio signal that can be detected and reconstructed in an image (see Huettel, Song & McCarthy, 2004).

Functional MRI makes use of the transverse relaxation time (T2), which is especially associated with local field inhomogeneities, due to susceptibility differences of tissues or specific particles (e.g., oxy- and deoxyhaemoglobin). A sensory, motor or cognitive task produces a localized increase in neural activity. This results in a local vasodilatation followed by a temporary increase of blood flow to compensate for the increased local metabolic demands due to oxygen and glucose consumption. The relative amount of oxygenated and de-oxygenated haemoglobin produces relative differences in magnetic properties that can be detected during scanning. This signal is called the blood oxygen level dependent (BOLD) contrast. In the present research, the 3.0 T Intera Philips scanner at the University hospital of Gasthuisberg (Leuven) was used to visualize the brain areas involved in eye-hand coordination. Given the asymmetric visuomotor control strategy that participants adopted in previous work (e.g., Lavrysen et al., 2007), it was hypothesized that the brain processes underlying the movements with the left and right hand might be different. In this context, Lavrysen et al. (2008) conducted a functional magnetic imaging (fMRI) experiment in which right-handed participants performed movements with their right or left hand in isolation, or coordinated with saccades.

Insert Figure 5 about here

The results showed that there were similarities but also differences between brain areas involved in the specific eye-hand coordination conditions with the right and the left hands. The cyclical aiming task was used in fMRI environment enabling integrated data recording of eye and hand movements with cerebral activation patterns. The areas involved in eye-hand coordination, inferred by contrasting the coordinated with the isolated eye and hand movement conditions, revealed a network involving the cerebellum as well as cortical and subcortical structures. Interestingly, for eye-hand coordination using the left hand, there were significantly higher activated areas in the ipsilateral cerebellar lobule, the thalamus and the parietal cortex than when performing eye-hand coordination with the right hand. As these areas are all involved with on-line guidance and feedback processing of the movement, the functional activation differences might be related to the differences in specializations of the hands. The left hand might elicit the engagement of more regions in order to compensate for its greater variability in force production or for the increased demands for coordinated versus independent eye and limb movement control. Alternatively, the results could simply reflect a difference between the dominant right and non-dominant left hands of right-handers.

A next step, to substantiate that the observed differences were due to functional specialization difference between both hand/hemisphere systems and not to hand preference effects *per se*, was to evaluate the same patterns in left-handers. Therefore, another study was conducted under identical conditions with eleven extremely left-handed participants (Lavrysen, 2005). Firstly, the behavioral data revealed that the time to peak velocity was earlier when aiming with the left (48.9%) than with the right hand (60.3%). Because this was also the case with right-handers (Lavrysen et al., 2008), it appears that the mode of control is different when using the left and the right hand. This difference is independent of hand preference. However, the eye-hand coordination did not change with the hand used.

When evaluating the functional imaging data (Lavrysen, 2005), again, similar asymmetries were observed that are consistent with what has been described in the right-handed group in Lavrysen et al. (2008). The results of the contrast between coordinated versus isolated movement conditions are presented in Figure 6 for both left- and right-handers. A remarkable parallel can be drawn between the activated loci for eye-hand coordination using the right (two upper panels) and the left hands (two lower panels). When using the left hand, activation is more pronounced in ipsilateral cerebellar and

contralateral sensorimotor areas, while using the right hand produces more bilateral occipital activation.

Insert Figure 6 about here

Visual inspection of these data indicates that the activated network for eye-hand coordination is different according to the hand used. However, a statistical comparison revealed no significant differences between both coordination modes for the left-handers. This suggests that in this group, similar regions are being allocated for the coordination of the left and the right hand with the accompanying eye movements. In comparison with right-handers, this suggests that left-handers do not benefit from the right hand/left hemisphere advantages to the same degree because of lack of practice with this hand. Alternatively, it could be that left-handers already engage more areas with their preferred hand so that it reaches the same level of activation of the less-practiced non-preferred hand. A third possibility is that left-handers are not a homogeneous group and that between-person variability makes it difficult for any consistent pattern of activation to emerge.

Eye Movements as a Mirror of Our Thoughts: Motor Imagery

In this final section of part I, the potential use of eye movements as a mirror of our thoughts is examined in the context of motor imagery. Motor imagery can be defined as the mental rehearsal of a motor act in the absence of an overt motor output (Crammond, 1997). It can be performed in different modalities such as visual, auditory, tactile, kinesthetic, olfactory, gustatory, or any combination of these senses. The visual modality, which is the most well known, can be described as imagining seeing yourself performing the task. This technique, also known as ‘visualisation’, has already been used for many years by athletes to improve their performance (Murphy, 1994). Recent studies suggest that mental training based on motor imagery can also be of value in the training of musicians (Meister, Krings, Foltys, Boroojerdi, Muller, Topper, & Thron, 2004), highly skilled manual technicians such as surgeons (Rogers, 2006) and even in the rehabilitation of patients with neurological disorders (Jackson, Lafleur, Malouin,

Richards, & Doyon, 2001). As such, motor imagery represents an intriguing additional practice method which can be used in different domains to increase the amount of training without adding to the physical demands. Besides, it can serve as an alternative practice strategy for people who are (temporally) unable to execute the movements physically due to, for example, injury, illness, immobilisation or paralysis (see Part 2 of this chapter).

When studying such new applications, there is a need to monitor whether the participants are performing the imagery tasks correctly. Possible confounds can be that persons are simply unable to accurately imagine the required movement in the temporal and spatial domain and therefore they use alternative strategies or even fail to suppress muscular activity during imagery (Sharma, Pomeroy, & Baron, 2006). Methods that are traditionally used to assess motor imagery performance are questionnaires, interviews and mental chronometry. Unfortunately, these methods have the disadvantage of being rather subjective. In addition they mainly focus on the global movement instead of offering a detailed monitoring of the ongoing mental process. Therefore, in a recent study (Heremans, Helsen, & Feys, 2008), we aimed to develop an alternative approach to objectively measure and monitor the motor imagery processes, based on the technique of eye-movement registration. This approach was based on two lines of evidence. First, a very tight temporal and spatial coupling has been shown between eye and hand movements during goal-directed single aiming (Helsen et al., 1998a, 2000) and repetitive aiming (Lavrysen et al., 2006). Secondly, recent studies within the field of imagery research have found that eye movements reflect the content of the imagined stimulus during the imagery of auditory scenes, recently viewed pictures and moving stimuli (De'Sperati, 2003). Heremans et al. (2008) aimed to investigate whether the latter findings can be generalized to the imagery of movements of our own body, and more specifically, to goal-directed movements of the arm and hand. Eye movements of right-handed subjects were recorded using EOG during both physical execution and visual motor imagery of a cyclical aiming task (identical to the one described earlier), performed at three different inter-target distances. We found that 89 percent of the subjects made task-related eye movements during imagery with the eyes open and 84 percent of participants also did so during imagery with the eyes closed. Both the number and amplitude of the eye movements during imagery closely resembled those of the eye movements made during physical execution of the task (see Figure 7).

Insert Figure 7 about here

Based on these findings, we suggested that both the motor and visual components of the movement are re-enacted during motor imagery of the task, implying that the coupling between eye and hand movements remains intact even when hand movements are merely imagined as opposed to being physically executed. We hypothesize that the observed eye movements during imagery are not merely epiphenomenal, but instead help us to correctly position the imagined hand movements within the mental space. This would imply that an internal visual representation exists, which is treated in a similar way to the external world. This interpretation, however, remains speculative and is now being investigated in more detail.

In summary, the observations of Heremans et al. (2008) showed that eye movements provide a unique window into the mind during motor imagery of goal-directed wrist movements. As such, eye movement recordings can be considered as an objective complementary technique to evaluate subjects' compliance and motor imagery ability for the majority of normal subjects.

Summary: Part 1

Using an integrative methodology linking behavioral, kinematic and brain imaging techniques, a unique opportunity is provided to study the natural coupling between eye and limb movements. This approach also allows us to update the current models of speed-accuracy relations in limb control. As such, our findings are consistent with a two-component model of rapid, goal-directed limb movements (see Chapter 1). This model of manual aiming holds that the first portion of an aiming movement is controlled by a centrally-prepared set of motor commands that provide the initial accelerative, and perhaps decelerative, impulse which moves the limb into the vicinity of the target. This ballistic portion of the movement typically undershoots the target position and a second visually-directed phase of the movement brings the limb onto the target. Presumably this second portion of the movement is designed to correct any error associated with the initial movement impulse.

Our accomplishments in this regard over the past decade can be summarized as follows:

1. Regardless of the distance to be covered, there is a remarkable temporal relationship between the arrival of the eye and the limb on the target position. Because point of gaze (PG) always arrives on the target area first and at roughly 50% of the hand response time, there is ample opportunity for the eye to provide (extra)retinal information on target position either through oculomotor efference or visual and proprioceptive feedback resulting from the large primary saccade.
2. There seems to be an invariant relationship between the spatial-temporal characteristics of eye movements and limb kinematics in goal-directed movement that is optimal for the pickup of visual feedback. Specifically, the end of a saccade toward a target corresponds temporally to the peak acceleration of the hand. Spatially, peak velocity of the hand coincides with 50% of the total movement distance. Thus, during the latter portion of the hand movement, the eye is already over the target area and well-placed to provide visual information regarding the relative positions of both the hand and the target for closed-loop limb control.
3. A significant relationship has been found between the number of secondary corrective eye movements and finger movements, both temporally and spatially.
4. In terms of manual asymmetries, a right hand advantage was found for movement execution, and a left hand advantage for movement initiation. Evidence has been found that right hand advantages for movement execution can be attributed to a left hemisphere propensity for utilizing response produced feedback during the homing-in phase.
5. With practice, an initial temporal improvement and decreased variability of response has been found within the first 10 trials. In addition, the arrival of PG on target is optimized towards 50% of hand response time. This temporal invariant related to end position can also be demonstrated through secondary analyses of earlier data from, for example, Vercher, Magenes, Prablanc, and Gautier (1994).
6. Cerebral activation patterns underlying eye-hand coordination might reflect the asymmetries in information processing capacities of the left and the right hand independent of hand preference.
7. The natural coupling between eye and hand movements remains intact even when hand movements are merely imagined as opposed to being physically executed.

Visual-Motor Control in Cerebellar Pathology: Part 2

Eye-hand coordination in healthy subjects is, as described in the previous section, characterised by a precise temporal and spatial coupling that enables the accurate execution of goal-directed movements. It was demonstrated that the temporal and spatial coupling is adapted according to the environmental conditions as well as the limb characteristics (Helsen et al., 2000). The temporal coupling between saccadic and ballistic hand movements is adapted to the type and amount of visual information that is available during movement execution (Lavrysen et al., 2006), regardless of whether the right or left hand is being used (Lavrysen et al., 2008). This underlines the extent to which the neural networks are involved in programming coordinated movements of the eye and hand.

This section focuses on visuomotor control in patients with neurological deficits. In this regard, the cerebellar system is a particular region of interest, because it is involved in the control of both the eye and the hand movements separately as well as in the coordination of these two effectors. This was clearly shown by the results of an fMRI study as there was a greater activation during co-ordinated eye-hand tracking compared to independent motor activity of both systems (Feys et al., 2005; Mial, Reckess, & Imamizu, 2001). Furthermore, the cerebellum is highly involved in the acquisition of novel coordinated eye-hand movement tasks (Miall & Jenkinson, 2005). We first address eye and hand movement deficits in patients with cerebellar dysfunction. Then pathological eye-hand interactions during visually guided arm movements are discussed. Next, a potential mechanism is presented that may explain the increased reliance on visual feedback for accurate motor performance. In this respect, the particular interplay between proprioceptive and visual motor control is of major importance. Finally, the potential use of eye movements in the study of motor imagery in pathological functioning is discussed.

Eye and Hand Movement Deficits in Cerebellar Pathology

Movements of patients with cerebellar pathology are typically characterised by ataxia. Ataxia or atypical chaos in the movement has multiple characteristics such as increased reaction time, delayed antagonist function, prolonged movement duration, abnormally curved paths, over- and undershooting (dysmetria) and tremor (Diener &

Dichgans, 1992; Sailer, Eggert, & Straube, 2005). The timing of the activation of different muscles involved in movement, is considered to be a crucial parameter regulated by the cerebellum. The delayed onset of antagonist activity leads to insufficient breaking of the ballistic movement and movement overshoots (Bastian & Thach, 1995; Hore, Wild, & Diener, 1991). Hypermetria resulting in target overshooting is also a common finding in patients with cerebellar deficits and in Multiple Sclerosis (MS) with tremor (Deuschl, Wenzelburger, Loffler, Raethjen, & Stolze, 2000; Quintern et al., 1999; Topka, Konczak, & Dichgans, 1998). Above-described ataxic features are found in patients with miscellaneous cerebellar deficits with and without the additional presence of tremor (Bonnetoi-Kyriacou, Legallet, Lee, & Trouche, 1998; Day, Thompson, Harding, & Marsden, 1998; Rand, Shimansky, Stelmach, Bracha, & Bloedel, 2000; Topka et al., 1998).

Cerebellar ataxia in general, and tremor in particular, are also observed in persons with MS as it is a chronic progressive disease of the central nervous system, characterized by heterogeneous patterns of inflammation, demyelination and axonal loss. Depending on the location of lesions and atrophy within the brain, MS may clinically occur with a variation of motor symptoms such as muscle weakness, spasticity and incoordination, leading to severe limitations of daily life activities (ADL). Limb tremor is estimated to be clinically present in 25-50% of the MS population and is strongly related to impairment, disability and handicap (Alusi, Worthington, Glickman, & Bain, 2001; Pittock, McClelland, Mayr, Rodriguez, & Matsumoto, 2004). Tremor in MS is not seen during rest, but typically emerges during the maintenance of a limb posture towards gravity (postural tremor). In particular, patients suffering from intentional tremor due to MS may also show an increased amplitude towards the termination of visually-guided goal-directed movements (intention tremor, also known as cerebellar tremor) (Deuschl, Raethjen, Lindemann, & Krack, 2001). MS tremor has been associated with disruptions of the cerebellar afferent and efferent pathways such as the cerebello-rubro-thalamocortical tract (Deuschl, Bain, & Brin, 1998). In support of this view, Liu, Ingram, Palace, and Miall (1999) linked the action tremor in an MS patient with multiple focal lesions in the ipsilateral cerebellar hemisphere, the cerebellar peduncles, the reticular formation and the inferior olive. An MRI study by Feys et al. (2006) also demonstrated that the amplitude of intention tremor, measured during the performance of a visually-guided goal-directed task, was significantly related to the infra-tentorial lesion load (i.e.,

volume of lesions in the brainstem and cerebellum). More specifically, the results of this study demonstrated that MS tremor amplitude correlated with the lesion load in the contralateral pons, and patients with more severe tremor in both arms had a greater lesion load bilaterally in the pons.

In about one third of MS patients, one can also clinically observe abnormal eye movements such as gaze-evoked nystagmus, saccadic overshooting (hypermetria), fixation instability and impaired smooth pursuit movements (Armstrong, 1999; Averbuch-Heller, 2001; Clanet & Brassat, 2000; Eggenberger, 1996). Abnormal eye movements are also related to damage of the brain stem and/or cerebellum (Bogouslavsky, Fox, Carey, Vinitzki, Bass, & Noseworthy, 1986; Downey, Stahl, Bhidayasiri, Derwenskus, Adams, & Ruff, 2002; Eggenberger, 1996; Serra, Derwenskus, Downey, & Leigh, 2003). The cerebellum plays an important role in fine tuning of eye movements and eye fixations by means of projections to the brain stem nuclei formation (Averbuch-Heller, 2001; Versino, Hurko, & Zee, 1996). Many eye-movement abnormalities appear immediately after a cerebellar insult and after experimentally induced blocks (Versino et al., 1996). Ocular motor abnormalities such as acquired pendular nystagmus and saccadic intrusions, which occur frequently in MS, interfere with steady fixations on a target. Pendular nystagmus, related to multiple lesions disrupting connections between dentate, inferior olive and red nucleus (Armstrong, 1999; Lopez, Bronstein, Gresty, Du Boulay, & Rudge, 1996) reflects abnormalities of internal feedback circuits such as the reciprocal connections between brainstem nuclei and the cerebellum (Averbuch-Heller & Leigh, 1996). Saccadic intrusions are involuntary, abnormal quick eye movements with or without intervals. Macrosaccadic oscillations in cerebellar patients may reflect saccadic dysmetria with continuous overshooting of targets (Averbuch-Heller, 2001). Patients with Friedreich's ataxia show various combinations of cerebellar, vestibular and brain stem ocular signs, including fixation instability. It appears that both intention tremor and oculomotor incoordination are commonly associated with dysfunction of the cerebellum or its afferent and efferent connected structures (Alusi, Glickman, Aziz, & Bain, 1999; Averbuch-Heller, 2001; Eggenberger, 1996; Versino et al., 1996).

From a clinical point of view, abnormal eye movements such as multiple saccades and saccadic dysmetria are commonly observed in patients with limb ataxia (Eggenberger, 1996; Sailer, Eggert, & Straube, 2005; Serra et al., 2003). Through

synchronous measurements of both eye and limb movements, researchers have systematically investigated the occurrence of eye-movement deficits during the execution of hand movements. In this regard, the first studies in patients with cerebellar deficits were conducted by Brown, Kessler, Hefter, Cooke, and Freund (1993) and van Donkelaar and Lee (1994). During tracking tasks, it was shown that both the eye and the hand movements were characterised by a delayed movement onset as well as significant inaccuracies that resulted in a series of corrective saccades or submovements before achieving the appropriate position. Based on these studies, the authors suggested a reciprocal exchange of information between eye and hand movements. A candidate for this integration process was the cerebellum and its connected structures since these receive input from both the eye and the hand motor commands and, as such, either directly or indirectly impact on the efferent commands of both systems (van Donkelaar & Lee, 1994). In support of this, eye-movement deficits such as saccadic dysmetria were observed in more than 75% of MS patients selected based on the presence of cerebellar tremor (Feys, Helsen, Lavrysen, Nuttin, & Ketelaer, 2003a). In addition to the study of eye-hand coordination in normal subjects, extensive research on eye-hand coordination in MS patients with cerebellar eye and hand deficits is challenging to disentangle the interactions between eye and hand movements.

Eye-Hand Coordination and Interactions in Cerebellar Pathology

Patients with cerebellar dysfunction have often served as a pathological model for studying visuomotor control in eye-hand coordination (Day et al., 1998; Sailer et al., 2005; van Donkelaar & Lee, 1994). MS patients with intention tremor can also serve as a pathological model for investigating eye-hand coordination during visuomotor control. This approach was supported by the following observations.

1. Intention tremor severity in the arm correlates with the lesion load in the infratentorial brain (Feys et al., 2005; Liu et al., 1999; Nakashima, Fujihara, Okita, Takase, & Itoyama, 1999).
2. The infratentorial brain also controls oculomotor function. Therefore, it is not surprising that oculomotor deficits such as saccadic dysmetria and unsteady gaze fixation are present in MS patients with tremor (Feys et al., 2003a; Feys et al., 2005; Nakashima et al., 1999).

3. MS patients with tremor are more dependent on the visual feedback of their performance for the on-line control of hand movements (see below) (Feys, Helsen, Liu, Lavrysen, Loontjes, & Nuttin, 2003b; Liu, Miall, Aziz, Palace, Haggard, & Stein, 1997). This is probably a result of their reduced capacity for predictive control which is suggested to be associated with the cerebellar system (Miall, Weir, Wolpert, & Stein, 1993).

Studies in MS patients with arm intention tremor demonstrated abnormal eye movements during discrete goal-directed hand movements (Feys et al., 2003a; 2005). The amplitude and speed of the primary saccades were enlarged (saccadic dysmetria) and prolonged, while the ballistic hand movement was also characterised by target overshoot and slower execution. However, the temporal coupling between the primary saccadic and hand movements was largely preserved during the performance of a wrist step-tracking task. As in healthy subjects, eye and hand initiation times were highly related and the saccadic completion time corresponded with hand peak velocity. The latter relationship indicated that patients' hand initiation and antagonist muscle activity were also delayed during the discrete goal-directed tasks since saccades were prolonged (Feys et al., 2005). In other words, the unfolding of the ballistic hand movement was adapted to the characteristics of the saccade. In the spatial display, both the saccadic and ballistic hand movements of cerebellar patients were larger than those of healthy controls. Therefore, although eye and hand movement deficits were observed, the coordination between goal-directed eye and hand movements is well preserved in MS patients with cerebellar deficits. A similar conclusion was made for planned movements in patients with other cerebellar lesions (Sailer et al., 2005).

During the homing-in or target phase of aiming movements, patients also showed deficits in gaze fixation on the target (Feys et al., 2003a; 2005). It must be noted that both MS patients and healthy controls made fixational eye movements, indicating that these are a normal behavior to refresh the image with visual information on the retina (Hotson, 1982). However, the amplitude of the fixational eye movements is obviously greater in the MS patient group, indicating an unsteady target fixation. In fact, an association was found between the number of fixational eye movements and the number of hand oscillations (Feys et al., 2005). Therefore, further studies were performed to differentiate

between these relations on programming level versus interactions on perception-action level.

Insert Figure 8 about here

It was found that the eye movements in MS patients with tremor had a substantial impact on the hand movements. The comparison between coordinated eye-hand and isolated eye or hand tracking revealed that the target overshoot of the hand was reduced or was even similar to normal target undershoot when patients fixated the target continuously (i.e., when they did not make an enlarged saccade towards the target; see Figure 8). This clearly suggested that the saccadic dysmetria (overshoot) contributed to target overshoot of the primary hand movement.

In the target phase, the overall amplitude of both fixational eye movements and arm intention tremor was greater during a coordinated eye-hand tracking condition than during an isolated hand tracking condition with continuous target fixation (Feys et al., 2005). On the one hand, this may suggest that the amplitude of fixational eye movements was enlarged during coordinated tracking because of the impact of the preceding (deficient) saccades. An unsteady gaze fixation is likely to compromise the accuracy of the visual afferents about the precise hand position relative to the stationary target position. The subsequent corrective hand movements may then be less accurate and require additional voluntary hand error-correction movements, thereby enhancing the overall amplitude of intention tremor. On the other hand, the amplitude of hand tremor in the target phase may be modulated by the size and the speed of the preceding ballistic hand movements in the transport phase and be independent of the enlarged fixational eye movements. Therefore, in a follow-up study, factors contributing to eye and hand movement deficits were disentangled (Feys, Helsen, Nuttin, Lavrysen, Ketelaer, & Swinnen, 2008). Specifically, magnitudes of the primary saccadic and hand movements were modified to differentiate between the effects of the primary saccadic and hand movements in the transport phase on fixational eye movements on the one hand and hand tremor amplitude in the target phase on the other. An important finding in MS patients, but not in healthy controls, was that the amplitude of fixational eye movements at the target was dependent on the amplitude of the preceding saccade, while the overall tremor

amplitude increased when the amplitude of fixational eye movements was greater. In this way, it was demonstrated that the size of the fixational eye movements influenced MS intention tremor. It is hypothesised that the unstable target fixation in MS patients with tremor compromised the accuracy of the visual information about the precise location of the target relative to the hand. As a consequence, this impeded accurate motor performance thereby elicits more voluntary correction movements and involuntary tremor by means of a perception-action cycle.

In contrast to the profound impact of eye movements on hand tremor, hand tremor severity did not significantly influence the fixational eye movements as revealed by comparing coordinated eye-hand with isolated eye movements and eye movements accompanying the left and right hand in patients with asymmetric tremor severity. The post-saccadic eye-fixation deficits were observed regardless of whether intention tremor was present or not, and independent of the tremor severity. However, it is important to note that there was no relationship between the eye and hand movement deficits during coordinated action. MS patients with mild oculomotor deficits may have marked hand tremor and vice versa. However, irrespective of whether MS patients exhibited mild or severe oculomotor deficits, experimental manipulations induced similar changes in both the size of fixational eye movements and hand tremor severity (Feys et al., 2003, 2005, 2008).

A similar one-way influence of eye movements on motor behavior has been reported in patients with various cerebellar dysfunction. Crowdy, Hollands, Ferguson, and Marple-Horvat (2000) demonstrated that oculomotor deficits negatively influenced visually guided stepping. These patients were able to improve their locomotor stepping performance after rehearsal of accurate eye movements (Crowdy, Kaur-Mann, Cooper, Mansfield, Offord, & Marple-Horvat, 2002). As such, MS patients with tremor may also show a reduced hand tremor amplitude if the saccadic amplitude is reduced by sequentially executing eye and hand movements to reach an object.

Visual Movement Control in Cerebellar Pathology

It is well known that patients with cerebellar deficits show a specific difficulty in using visual information to control arm and hand movements, independently of unsteady gaze fixation (Cody Lovgreen, & Schady, 1993; Day et al., 1998; Liu et al., 1997; Stein & Glickstein, 1992). In addition, growing evidence suggests that this patient group has difficulties in the on-line processing of kinesthetic information even though no manifest

sensory deficits are present (Grill, Hallett, & McShane, 1997; Shimansky, Saling, Wunderlich, Bracha, Stelmach, & Bloedel, 1997). An abnormality associated with on-line processing of proprioceptive information regarding the hand position during aiming or reaching tasks may explain the enhanced reliance on visual feedback (Cody et al., 1993; Liu et al., 1997; Rand et al., 2000). The cerebellar system may be heavily involved in the on-line control of visually guided goal-directed movements, as the cerebellum is regarded as the neural locus of internal models that mutually connect sensory information and motor actions (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003; Glickstein, 2000; Liu, Robertson, & Miall, 2003; Wolpert, Miall, & Kawato, 1998). To provide further support for the above-mentioned hypothesis, we investigated the tracking behavior of MS patients with tremor during both visual and proprioceptive movement control (without vision). We discuss the effects of visual information on both movement accuracy as well as involuntary cerebellar tremor severity.

In healthy subjects as well as in MS patients with tremor, a decrease in performance accuracy is typically observed in the absence of visual information of the hand position. However, the decrease in accuracy was greater in the MS patients with tremor than in the healthy controls (Feys et al., 2003b). The increased movement error in the absence of visual feedback is not regarded as an artefact of tremor, as tremor amplitude is significantly smaller during memory compared to visually guided tracking (Feys et al., 2003b; Liu et al., 1997). In other words, MS patients are more reliant on visual feedback of the hand position for accurate motor performance than healthy controls.

To better understand the mechanism of increased reliance on visual feedback, the processing of proprioceptive information was studied through artificial stimulation of the muscle spindles by means of tendon vibration (Feys, Helsen, Buekers, Ceux, Heremans, & Nuttin, 2006). Tendon vibration is a strong stimulator of muscle spindle afferents, thereby biasing the information about muscle length resulting in predictable movement illusions. During memory guided movements, tendon vibration typically leads to a reduction of movement amplitude and/or target undershoot (Verschueren, Cordo, & Swinnen, 1998). To differentiate between possible additional effects caused by tremor and the disease of MS, MS patients with tremor were compared with MS patients without tremor and healthy controls. As expected, the application of tendon vibration during memory guided movements induced a reduction of movement amplitude. However, the

vibration-induced decrease of movement amplitude was significantly smaller in the MS-tremor group than in the control groups without tremor. The results indicated that proprioceptive information was used for the on-line control of movements, but to a lesser extent in MS patients with tremor compared to MS patients without tremor or healthy controls. The different behavior of MS patients with and without intention tremor suggested that MS patients with tremor have specific deficits in using proprioceptive information. One could also argue that the decreased use of the muscle spindle afferent information is directly related to the MS lesions causing intention tremor considering the role of the cerebellum in sensorimotor integration (Desmurget, Grea, Grethe, Prablanc, Alexander, & Grafton, 2001; Jueptner Ottinger, Fellows, Adamschewski, Flerich, Müller, 1997; Wolpert et al., 1998;). The patient's brain lesions in the cerebellar system may have caused proprioceptive deficits as the cerebellum has been attributed a role in sensory discrimination itself (Feys et al., 2005; Gao, Parsons, Bower, Xiong, Li, & Fox, 1996; Jueptner et al., 1997). However, although patients with cerebellar degeneration exhibit a dysfunction in perception of movement velocity and duration, no difficulties in perceiving the limb position or movement amplitude have been reported (Grill, Hallett, Marcus, & McShane, 1994; Maschke, Gomez, Tuite, & Konczak, 2003). Therefore, it is hypothesized that patients with cerebellar deficits may have adopted strategies over time to cope with noise in the proprioceptive input signals which compromises the accuracy of the perceived hand position. The compensatory strategy may be to reduce the weight of noisy proprioceptive input during on-line movement control to avoid excessive movement errors (Liu et al., 1999). As such, patients with cerebellar deficits are more reliant on visual feedback for accurate motor performance than persons who can fully benefit from using their proprioceptive information.

The Use of Eye Movements to Study Motor Imagery in Pathological Functioning

In healthy subjects, partially overlapping neural networks, including bilateral premotor and parietal areas, basal ganglia and cerebellum were shown to be activated during both real and imagined hand movements (Gerardin, Sirigu, Lehericy, Poline, Gaymard, & Marsault, 2000). During real movements, the consequences of a dysfunction of one of these areas are clearly expressed in motor behavior. Due to the concealed nature of imagery, it is far less clear to which extent imagery of a movement is also affected if the function of one (or several) of these areas is impaired, as is the case in patients with

neurological disorders. For example, in patients with a hemiplegic upper limb after stroke, it was shown that their ability to imagine movements of the paralysed arm was still intact, even after years of limb disuse (Johnson, Sprehn, & Saykin, 2002). However, this ability has been shown to be compromised in patients with lesions in the parietal cortex or putamen (Danckert, Ferber, Doherty, Steinmetz, Nicolle, & Goodale, 2002; Li, 2000). In patients with Parkinson's disease, a disease caused by deficits in the basal ganglia, the motor imagery ability showed contrary results, dependent on the design which was used (Frak, Cohen, & Pourcher, 2004; Tamir, Dickstein, & Huberman, 2007).

Although promising results are reported considering the use of mental practice based on motor imagery as an additional therapy within the field of neurological rehabilitation, we should be aware that the success of this therapy depends on the preservation of the imagery ability of the individual patient. Therefore, for neurological patients, it is absolutely necessary to test their imagery ability before implementing imagery techniques in their rehabilitation. As mentioned previously, we recently developed a method to monitor motor imagery in our lab (Heremans et al., 2008). This method is based on the similarities in eye movements made during physical execution and imagery of goal-directed movements. Up to now, this monitoring method was only validated in young healthy persons. Follow-up studies are now being conducted to examine whether it can also be used successfully to evaluate the imagery ability of neurological patients.

In a related study of Heremans, Helsen, De Poel, Alaerts, and Feys (under review), we investigated whether the use of external cues might facilitate subjects' motor imagery performance. In healthy persons, it was found that visual and auditory cues during imagery result in an increase in imagery vividness and an enhancement of eye-movement accuracy during visual motor imagery. In a study of Helsen, Tremblay, Van den Berg, and Elliott (2004), the importance of making accurate eye movements while practicing a motor skill was shown during physical practice. As such, we may expect that accurate eye movements may have a similar facilitating effect during imagery. As such, we speculate that imagery practice may benefit from the use of external cues eliciting accurate eye movements. The use of cues might be even more important when imagery is used in the rehabilitation of certain groups of neurological patients. In patients with Parkinson's disease, for example, it was shown that external cues enhance motor performance during physical execution of a task (Brown & Marsden, 1988; Siegert et al.,

2002). Also in MS patients with tremor, the use of additional (visual) cues during imagery might be useful, since, as mentioned earlier in this chapter, these patients are shown to be more reliant on visual feedback for accurate motor performance than healthy persons. In future studies, it remains to be seen whether the positive effect of cueing found during physical practice in these groups also generalizes to mental practice in pathological functioning.

Summary: Part 2

Patients with cerebellar dysfunction not only show deficits in limb motor function but also manifest abnormal eye movements. MS patients with tremor were selected as a pathological model to study eye-hand coordination and interactions. Interestingly, an invariant coupling between the saccadic completion time and hand peak velocity was found suggesting that the temporal coupling was very much preserved in these patients (Feys et al., 2005) during predictable goal-directed movements.

Interactions between eye and hand movements, however, occur during visually guided movements with eye movement deficits having a one-way negative impact on hand motor performance. This is observed during the ballistic as well as the homing-in phase of the hand on the target. Near to the target, enlarged fixational eye movements induce an unsteady gaze fixation leading to inappropriate movement corrections.

Despite eye movement abnormalities disturbing the accurate perception of the target and hand position, patients with cerebellar dysfunction show an increased reliance on visual feedback for accurate motor performance. This paradoxal finding may be explained by studies demonstrating a decreased capacity in the on-line processing of proprioceptive feedback.

Overall Summary and Future Directions

Over the last decades, in daily life (e.g., reading and typing of text messages), as well as in many professional settings (e.g., mouse-PC interaction), an increased reliance on the visual control of voluntary movement has emerged. The apparent simplicity of these types of movements in healthy adults belies the underlying complexity involved in the temporal organization and spatial control of the eye and hand movements. From the

study of pathological functioning, however, it becomes clear that even mild brain damage may have a detrimental impact on the smooth execution of goal-directed aiming movements. The goal of the present chapter was to examine the role of visual afference in normal and pathological functioning to get a better understanding of the acquisition and performance of goal-directed aiming movements.

Surprisingly, the behavioral, kinematic, brain imaging, and motor imagery data presented in this chapter are still consistent with a two-component explanation of the control of rapid, goal-directed limb movements. This model of manual aiming (for a review see Elliott et al., 2001) holds that the first portion of an aiming movement is controlled by a centrally-prepared set of motor commands that provide the initial accelerative (and subsequent decelerative) impulse which moves the limb into the vicinity of the target. The ballistic portion of the movement typically undershoots the target position and a second visually-directed phase of the movement brings the limb onto the target. In this respect, visuomotor control has been shown to consist of a versatile process that is flexible enough to adopt a strategy that will make the most use of the information available, consistent with the specific demands of the task and the cues at hand. While some readers may think that all of these observations mean that we should think about the hand system being slave to the ocular system, perhaps it is good to mention that it may probably be more appropriate to consider the eyes as the best possible servants of the hand.

In the present chapter, we attempted to provide the reader with a starting point for future research in the area of eye-hand coordination, bridging the gap between the behavioral and the neurosciences. From a research point of view, we may look ahead and expect the outcomes of the following future directions in the near future:

1. The theoretical and empirical emphasis on the acquisition and performance of rapid visual control, combining measurements of eye *and* limb movements, may further moderate the field's current infatuation with open-loop processes.
2. The study of both normal and pathological functioning may result in new insights into the neural plasticity associated with the *learning* of motor skills.
3. The *integration* of neural-imaging descriptors of performance with the behavioural and kinematic parameters has the potential to provide new insights into the cooperative interaction of the two cerebral hemispheres, as well as into the sensory (parietal) and

motor (pre-frontal) brain areas in the acquisition and performance of goal-directed movement.

Although our research interests were primarily theoretical, we may also anticipate practical and clinical implications:

4. For optimizing man-machine interactions (e.g., bank terminals), in particular in special circumstances (e.g., eye-hand coordination under magnification in surgeons), and for improving robots (e.g., grasping tasks).
5. For a better understanding of pathologic functioning, especially with respect to those movement disorders in which closed-loop control takes precedence over open-loop control (e.g., Parkinsonism, cerebro-vascular accidents), with the potential to reveal new rehabilitation treatments that may improve daily life functioning.

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Figure captions

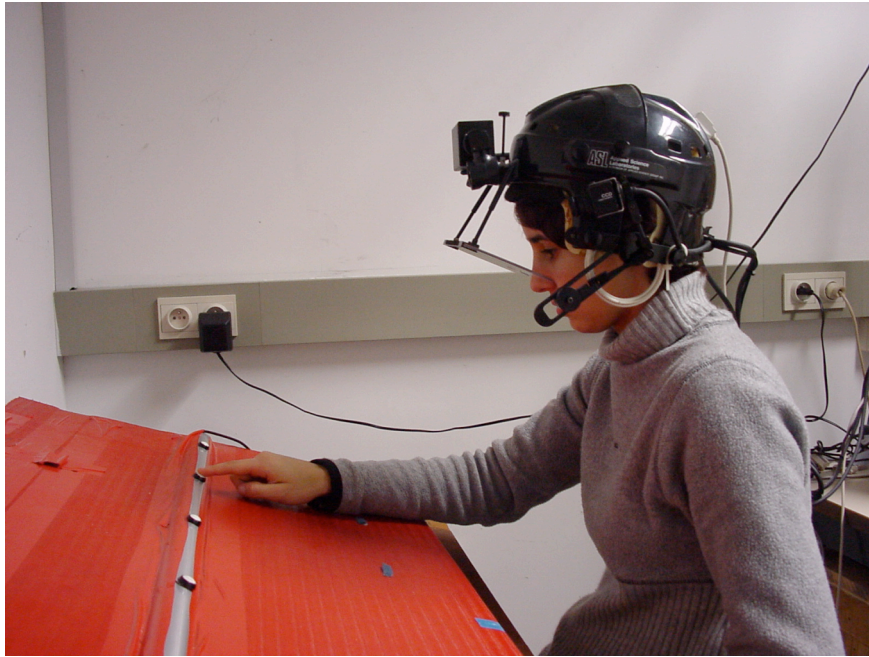


Figure 1: Experimental setup of a discrete aiming task that consisted of moving as quickly as possible from the home button in front of the participant to one or two target buttons in response to a visual stimulus. The participant is wearing a head-mounted gaze tracker ASL-4100®.

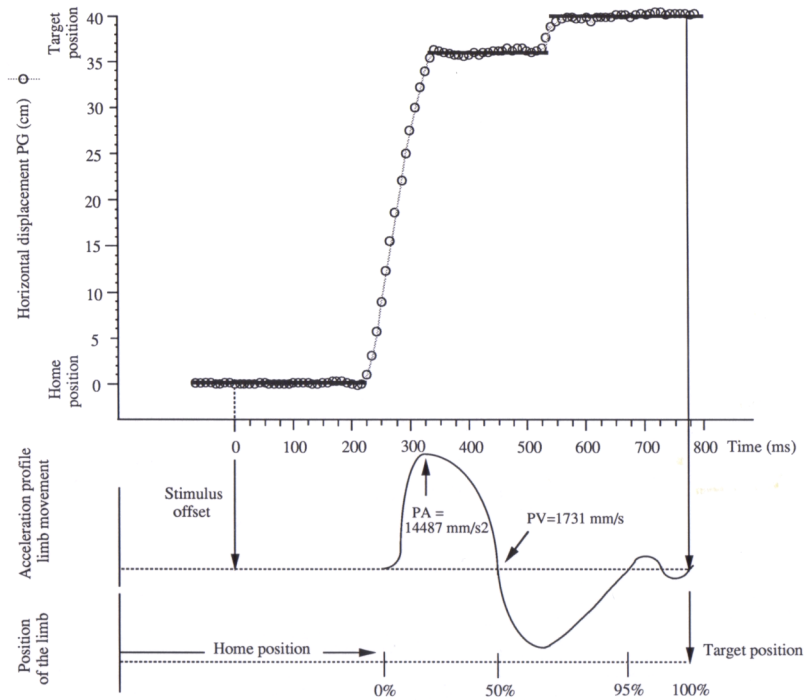


Figure 2: Spatial-temporal coordination between point of gaze and hand movements. The arrival of the saccade (upper part) is closely linked to the hand movement kinematics (lower part). (Figure from Helsen et al., 1998a)

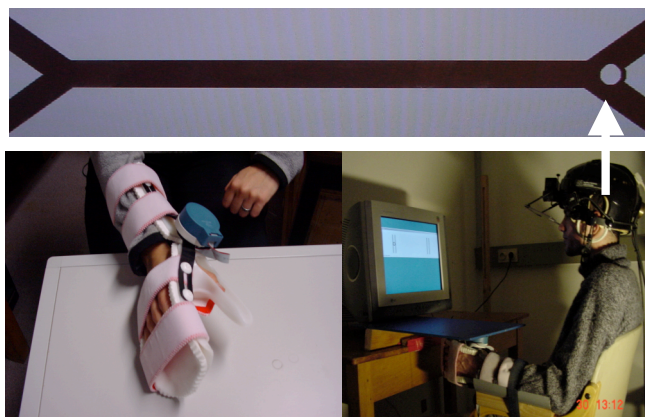


Figure 3: Right-hand orthosis with shaft encoder, allowing only flexion/extension movements at the wrist and presentation of both visual stimuli and hand representation (movement feedback) on a monitor.

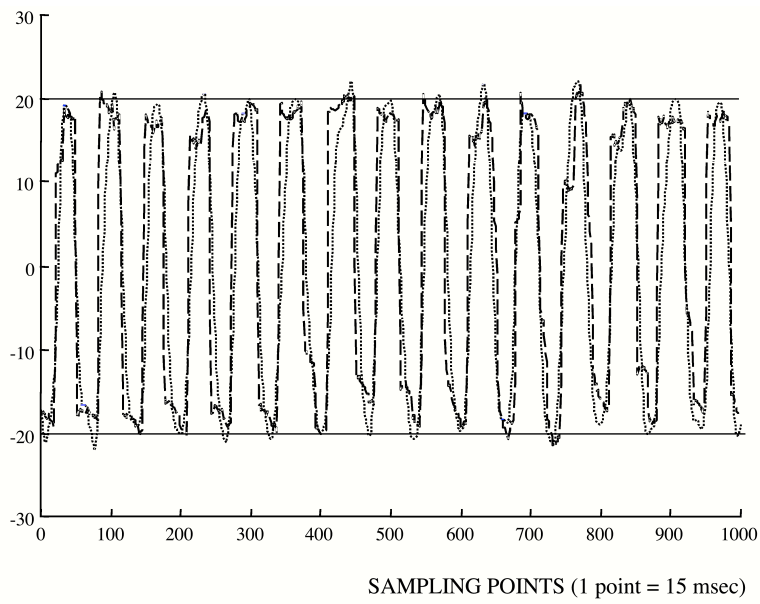


Figure 4: Example trial for one subject when aiming to a pointing-in figure in a SAC-cursor condition (angular position --- and point of gaze --).

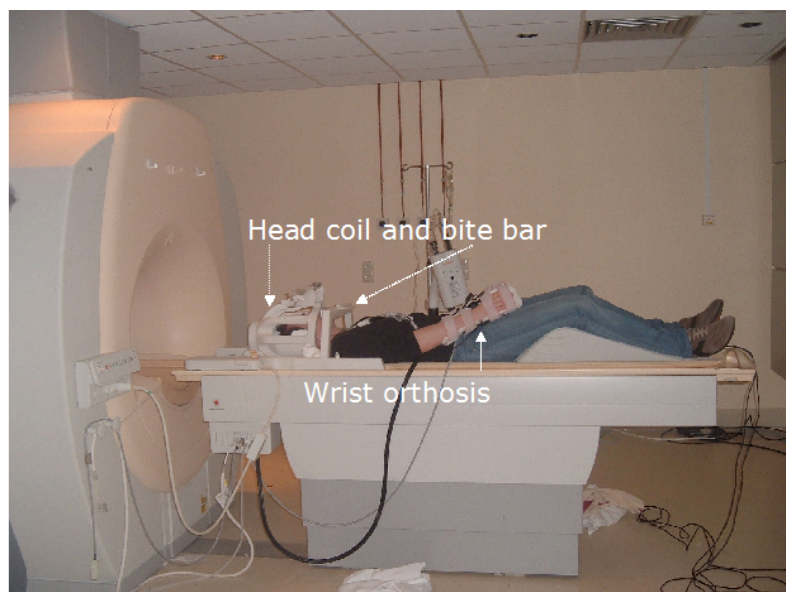


Figure 5: Experimental setup of the cyclical aiming task in the MR scanner of the University Hospital.

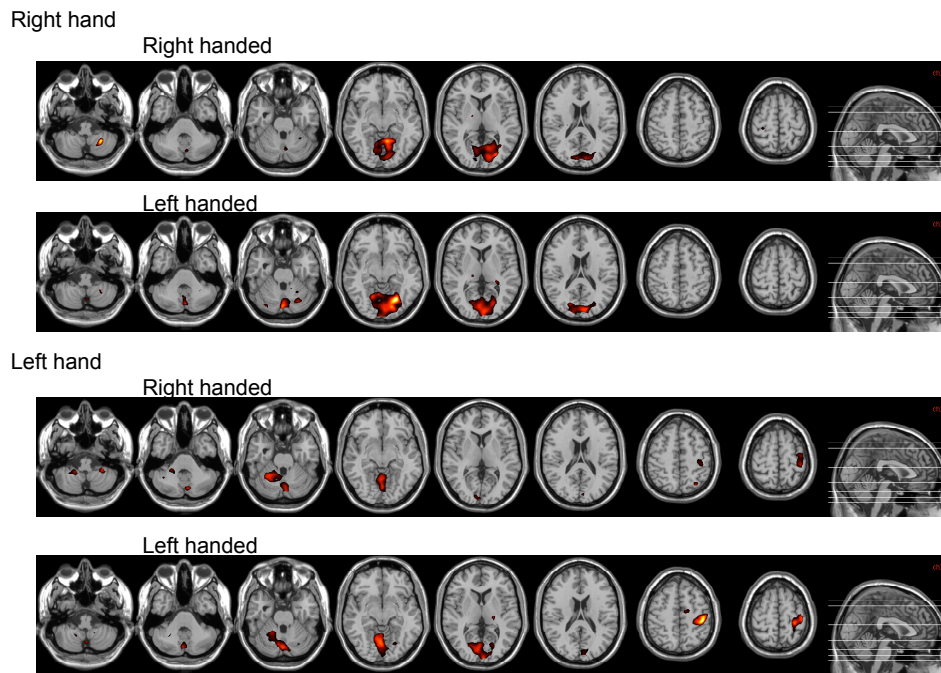


Figure 6: Group statistical parametric maps (SPMs) for coordinated versus isolated eye and hand movements for the right and left hands of right- and left-handers. The SPMs (thresholded at $z = 4.15$) are displayed on horizontal slices (z -value from left to right: -46, -36, -27; -9, 0, 19, 53 and 63). The right side of the scans corresponds to the right side of the brain.

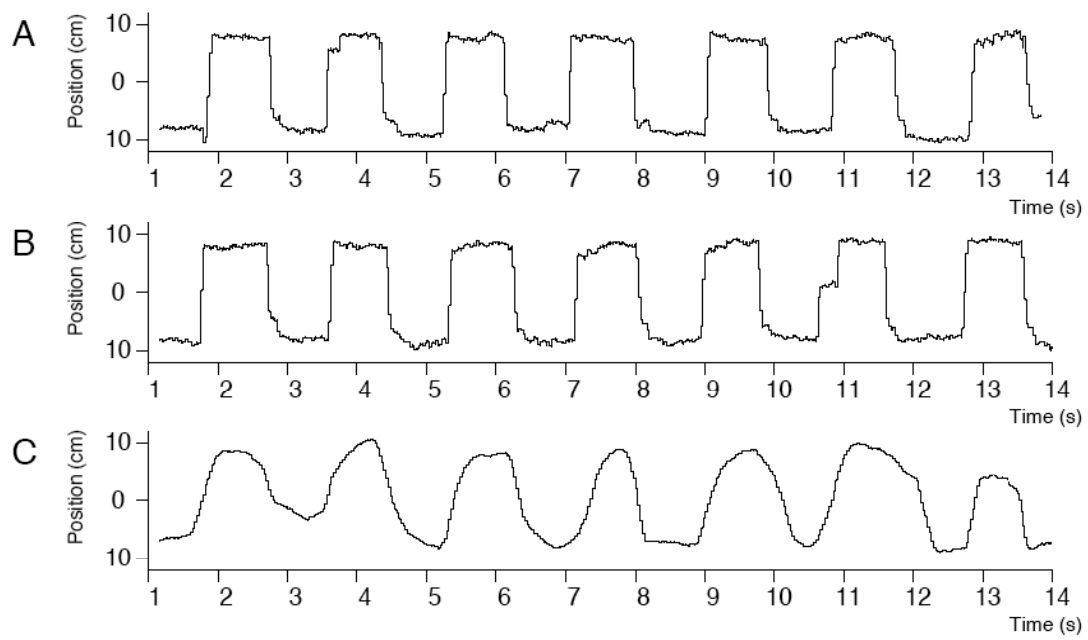


Figure 7: Typical examples of eye movement patterns during (A) physical execution, (B) motor imagery with the eyes open and (C) motor imagery with the eyes closed.

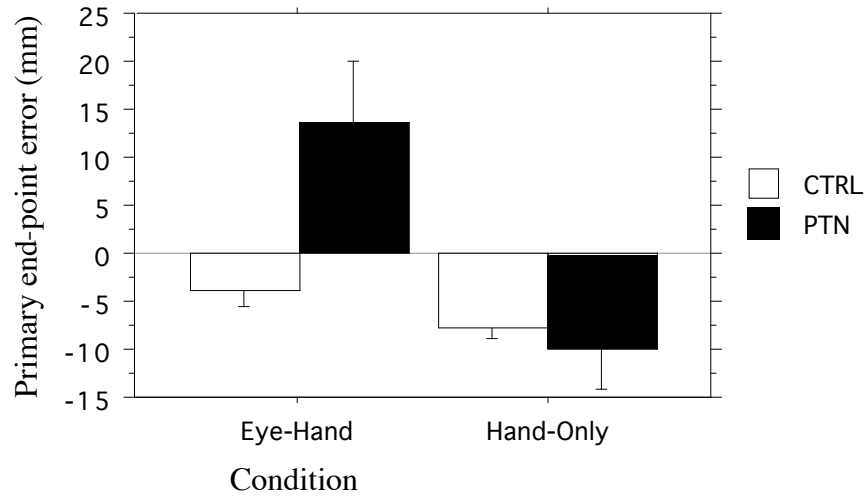


Figure 8: Time to mean end-point error (and standard error) of the hand after the ballistic hand movement in conditions with simultaneous eye and hand movement execution (eye-hand condition) and isolated hand movement execution with continuous target fixation (hand-only condition) for both healthy controls and MS patients with tremor.