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Vorstand: Prof. Dr. med. Dr. h. c. Thomas Brandt, FRCP

CONTROL OF ATTENTION BEFORE REFLEXIVE AND INTENTIONAL SACCADES

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Susana Maria Casaña Pérez

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(Spanien)

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Berichterstatter: Prof. Dr. A. Straube

Mitberichterstatter: Prof. Dr. I. Rentschler
Prof. Dr. R. Haberl

Mitbetreuung durch den
promovierten Mitarbeiter: Dr.-Ing. T. Eggert
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Para mi familia, os quiero!

Munich, 18th May 2004

Preface

Spatial attention plays an important role in many aspects of perception. Moreover, spatial attention plays a crucial role in the generation of goal-directed movements. Such goal-directed movements have been well researched in saccadic eye movements. Saccades are fast, ballistic eye movements, which can be classified in many different ways, for example, depending on the location or the nature of the target that triggers the saccades. In humans and primates, it is possible to differentiate two types of saccades: reflexive saccades and intentional saccades. These two types differ from each other in their dynamics and metrical properties. There is a close relation between the programming of saccades and attentional control that has been recently broadly discussed. Before a saccade is made, a saccadic goal or target is selected. During the preparation phase of the saccade to a target location, the attention shifts to that location. Whether, or to what extent, the differences between intentional and reflexive saccades reflect differences in the underlying attentional control is not known in detail. Previous research suggests that there is a difference between reflexive and voluntary control of attention. This study investigates the effect of spatial attention on a visual discrimination task.

The first part of the study examines in a healthy control group how the discrimination performance is affected, when attention is guided by reflexive and intentional cues, and how the effect of attention on the discrimination performance depends on whether an eye movement to the cued location is under preparation or not. The results may provide further information about the coupling between saccade programming and control of attention used for perception. They could also lead to further insight into the generally accepted dissociation between reflexive and intentional saccades as a consequence of differences between the underlying attentional mechanisms.

The second part of this research analyses the physiological and anatomical correlation between the control of saccades and attention. Among other functions, the cerebellum and the basal ganglia control body movements. Diseases affecting the cerebellum as well as diseases of basal ganglia are known to affect saccades. We will investigate whether there is a difference between cerebellar and basal ganglia lesions on the control of attention.

1 Eye Movements

The maximal visual acuity in our eyes relies on a small depression in our retina called the fovea, which consists of a single layer of cones (important for detailed vision) and has no capillaries. To clearly see an object its image must be held in this area, otherwise our visual acuity declines when moving to the periphery. For this reason we have to direct our eyes towards an object when we want to see it in detail.

There are many classifications of eye movements depending on their different properties (for example, physiological properties, functional properties or anatomical substrates). Regarding the functional properties, eye movements can be classified into seven types (Leigh RJ, Zee DS, 1999):

a) Vestibulo-ocular reflex (VOR) - During low frequency and short head movements, the VOR hold the image stable in the fovea producing a compensatory eye movement in the opposite direction. One can test the VOR by doing a very simple experiment, fixating the gaze on a word in this text and shaking the head from side to side (“no” gesture). It is possible to observe that despite head movements one can still read.

b) Optokinetic reflex (OKR) – Like the VOR, the OKR also compensates head movements but in this case the head movements are sustained. To produce this compensatory eye movement the eyes use the information about the velocity and direction at which the image is moving across the retina from the photoreceptors.

c) Saccadic eye movements - The saccades are fast eye movements that shift the gaze from one place to another in order to foveate objects of interest (cf. chapter 2).

d) Smooth Pursuit – If a car drives past a certain person and this individual follows the car movement with his/her gaze. The smooth pursuit system is activated matching the car velocity to the eye movement velocity in order to maintain the car image in the fovea. The principal stimulus of these eye movements is the object velocity information. These eye movements have a strong relationship with the OKR.

e) Vergence eye movements - Move both eyes in the same direction in order to hold the image stable in both foveae at the same time, enabling binocular vision.

f) Nystagmus quick phases - During self-rotations direct the fovea towards an oncoming visual scene and reset the eyes during prolonged rotations.

g) Visual fixation - Small eye movement (max. 1 degree) during fixation, that holds the image of a stationary target stable on the fovea and prevents the bleaching of the rodopsin.

2 Saccadic eye movements

2.1 Introduction

The saccadic eye movements are fast (the fastest of the eye movements), ballistic movements, which are used to bring a new peripheral target into the fovea. A person performs thousands of saccadic eye movements for many different activities every day. For example, while reading the gaze jumps from one word to the next one, each of these eye movements is a saccade.

2.2 Classification

Saccades include both, voluntary and reflexive changes of fixation, the quick phases of vestibular and optokinetic nystagmus and the rapid eye movements produced during the REM sleep phase (Table 2-1).

TABLE 2-1: CLASSIFICATION OF SACCADES

Classification	Definition
• Volitional saccades	Elective saccades made as part of purposeful behaviour.
Predictive, anticipatory	Saccades generated in anticipation of or in search of the appearance of a target at a particular location.
Memory-guided	Saccades generated to a location at which a target has been previously present
Antisaccades	Saccades generated in the opposite direction to the sudden appearance of a target (after being instructed to do so).
To command	Saccades generated on cue.
• Reflexive Saccades	Saccades generated to novel stimuli (visual, auditory or tactile) that unexpectedly occur within the environment
• Express Saccades	Very short latency saccades that can be elicited when the novel stimulus is presented after the fixation stimulus has disappeared (gap stimulus).
• Spontaneous Saccades	Seemingly random saccades that occur when the subject is not required to perform any particular behavioural task.
• Quick Phases	Quick phases of nystagmus generated during vestibular or optokinetic stimulation or as automatic resetting movements in the presence of spontaneous drift of the eyes.

From Leigh RJ, Zee DS: The neurology of eye movements, 3rd Ed. New York, Oxford University Press, 1999.

The two types of saccades that will be investigated in this study are intentional and reflexive saccades. Intentional saccades are directed to a particular location after a symbolic cue, reflexive saccades are triggered by an unexpected peripheral stimulus in the environment. In controlled experimental conditions it is possible to generate both of them, using either a central cue or a peripheral cue. The former is used to instruct the subjects to make an intentional saccade to the exact position where the cue (usually an arrow or a triangle) is pointing. Reflexive saccades can be generated with a peripheral cue that appears suddenly in the peripheral location to which the saccade must be directed.

The main difference between these two movements is the latency of the saccade (cf. chapter 2.3). Moreover, the programming of both types of saccades is different (Walker et al. 2000). Theeuwes et al. (1999) suggest that reflexive saccades involve a posterior pathway projecting to the superior colliculus and that intentional saccades are programmed in the anterior pathway in the frontal eye fields.

2.3 Saccade latency

The time between the appearance of a visual target and the start of the saccadic eye movement is called saccade latency or the reaction time of the saccadic system. This delay represents the time that the brain needs to accomplish the required action. It is not possible to present a precise delay range for the latency, due to the fact that it varies depending on different environmental conditions and on the type of the saccade. The variability is so high that the same subject has different saccade latencies from trial to trial (Table 2-2).

TABLE 2-2: FACTORS THAT AFFECT SACCADE LATENCY

Increase	Decrease
Very small or large target eccentricities	Target predictability
Increase target uncertainty	Increase target luminance or contrast or both
Increase target complexity	Heightened attention
Increase age in adults	Forewarning period
Inability to disengage attention	
Decrease motivation	

From: Eye movements basics for the clinician. K.J.,Ciuffreda, B., Tannen. Mosby-Year Book, 1995.

For express saccades, which can only be observed under special conditions, the reaction time is short (< 150 ms). Nevertheless the latency for voluntary saccades is higher and can take more than 250 milliseconds (Leigh RJ, Zee DS, 1999).

The environmental conditions that can affect the saccade latency are the eccentricity of the target, the number of possible targets, room and target luminance or the contrast between both, subject motivation, and target complicity among others.

- **Gap and overlap stimuli**

Under experimental conditions the saccade latency can be modified by applying the gap/overlap paradigm. To trigger saccades in the laboratory, subjects are asked to fixate on a specific point before the new peripheral target appears. The time between the fixation point offset and the onset of the peripheral target is very important for the latency of the saccade. In the gap paradigm the light of the fixation stimulus switches off between 100 and 400 milliseconds before the new peripheral target switches on. In this situation the saccade latency is reduced and the subjects do more express saccades than when the fixation light switches off after the target appears (overlap paradigm), where the saccade latencies are greater (Leigh, RJ, Zee, DS, 1999). This facility improves with practice and the luminance properties of the target do not seem to affect it.

2.4 Control of saccadic eye movements

2.4.1 Peripheral oculomotor system

The premotor circuitry that controls saccadic eye movements is very well understood due to many experiments performed in awake animals and clinical evidence from patients with diseases involving any of the areas that make up the saccadic pulse generator. This circuitry is made up of: Motoneurons (MN) that control the movement of the six extraocular eye muscles (cranial nerve nuclei III, IV and VI in the brainstem) and neurons in the brainstem reticular formation. The motor system that controls the movement of the eyeball is relatively simple; only six muscles are responsible for moving the eyes in any direction (Figure 2.3).

The eye ball (bulbus oculi) can rotate in any direction around its centre, but translatory movements are avoided. For the movements in the horizontal plane (from left to right and vice versa), two muscles are responsible, the *medial and lateral rectus muscles*, the movements in the vertical plane are predominantly performed by two muscles *superior rectus* (elevation movements of the eye ball) and *inferior rectus* (depressing movements, downward), movements in the sagittal axis (rotatory eye movements) are mainly due to the contraction of two muscles, the *superior and the inferior oblique muscles* (Findlay JM, Gilchrist ID, 2003).

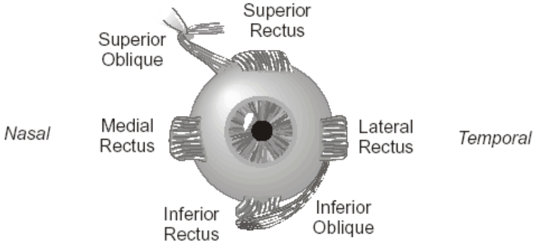

FIGURE 2.3: Eye muscles.

The binocular vision is conjugated, that means that both eyes move together and in the same direction to ensure that the same image falls onto corresponding points on both retinae. For example, when we want to look to the right side, the lateral rectus muscle of the right eye contracts and the medial rectus relaxes, but for the left eye the opposite occurs, the medial rectus contracts and the lateral rectus relaxes (Ciuffreda KJ, Tannen, 1995).

The six extraocular eye muscles are controlled by three bilateral cranial nerves: the third cranial nerve (oculomotor nerve) controls the superior and inferior rectus, the medial rectus and the inferior oblique; The fourth cranial nerve (the trochlear nerve) sends its efferent fibres to the superior oblique muscle; and the sixth cranial nerve or abducent nerve, provides the motor efference for the lateral rectus muscle.

The somata of these three cranial nerves are located in the cranial nerve nuclei in the brainstem. For the accurate control of the eye movements, the three cranial nerve nuclei are interconnected by the medial longitudinal fasciculus pathway.

Located between these three nuclei is the brainstem reticular formation (RF). The RF has three important types of neurons that contribute to the saccadic pulse generation: the burst neurons (BN), the omnipause neurons (ON), and the long lead burst neurons (LLBN).

The BN can be inhibitory (IBN) or excitatory (EBN). Between 8 and 12 milliseconds before all types of saccadic eye movements, the EBN fire at a very high frequency. They discharge preferentially for ipsilateral saccades, excite the ipsilateral MN for the desired eye movement direction and the IBN. Their discharge frequency is correlated to the amplitude of the eye movement. The amplitude, duration and velocity of saccades are coupled to the number of spikes generated, burst duration and peak firing rate of the burst activity, respectively (Findlay JM, Gilchrist ID, 2003; Ciuffreda KJ, Tannen, 1995).

The IBN are excited by the EBN, their function is to inhibit the contralateral MN, avoiding any activation in the antagonist muscle. IBN and EBN have a different location according to the axes in which the saccade is being programmed; they are located in the paramedian pontine reticular formation (PPRF) for horizontal saccades and within the rostral interstitial nucleus of the medial longitudinal fasciculus (MLF) for torsional and vertical saccades.

The second type of neurons in the RF are the omnipause neurons (ON), they are located in the nucleus raphe interpositus and inhibit the EBN and IBN. They fire continuously and at a constant rate during fixation, stop firing a few milliseconds before the saccade starts and continue after the saccade finishs, in other situations, such as blinking, they also stop firing. They are highly related to the rostral pole of the superior colliculus and project to this area with an inhibitory main effect. The stimulation of the ON during a saccade, causes the interruption of the saccade immediately because of the inhibition of the EBN. This evidence shows that the silence of the ON during saccades is critical for their triggering.

The Long-Lead Burst Neurons (LLBN) are another kind of neuron involved in the saccade programming. LLBN have two main locations in the midbrain and in the Nucleus Reticularis Tegmenti Pontis (NRTP). The LLBN in the midbrain lie near the third cranial nerve and project to the superior colliculus, they discharge irregularly and at low frequency rate several milliseconds before a saccade exciting the EBN. Their function is not very clear, it seems that they may serve in a feedback loop turning the retinotopical map (sensory information) of the superior colliculus into a motor command. The LLBN that lie in the NRTP are mostly connected with the cerebellum and seem they have an important role in a spatial-temporal transformation of saccadic commands (Munoz et al. 2000).

2.4.2 Central oculomotor structures for saccades

The higher-level system that controls saccades is less understood. It involves the frontal eye field (FEF), parietal lobe, superior colliculus and cerebellum. Their global function is the localization of the target and the calculation of the final eye position.

2.4.2.1 Superior Colliculus (SC)

The SC, whose structure has been intensively studied (Munoz et al. 2000; Noda H, 1991), provides the main input to the pontine and midbrain saccade pulse-generator system. The SC afferent fibres come from many cortical and subcortical areas and its efferent fibres control, directly or indirectly, all the premotor areas involved in the control of eye and head movements.

The SC is divided into 7 layers: the dorsal layers, also known as superficial or upper layers, have visual properties, receiving direct retinal projections, and the ventral layers, most important for the understanding of the control of saccades, have motor properties. The structure of the ventral layers is known as “motor map”, due to the fact that its stimulation evokes a saccade whose direction and size depends on the location of the stimulation in the SC. The smallest saccades are evoked rostrally and the largest caudally, saccades in the upward direction are produced by stimulating the medial side, and downward saccades are produced by stimulation of the lateral side. Stimulation in the rostral pole of the SC suppresses saccades; this area is called the “fixation zone” and the neurons in this area are called fixation neurons (FN). FN and ON are connected and an activation of the FN is followed by an increase of the ON firing.

Outside the fixation zone in the SC there are 2 types of saccade related neurons (Wurtz RH, 1996):

Collicular-burst neurons - They are located dorsally in the SC and start firing around 20 ms before a saccade occurs. Each neuron fires strongly for some saccades, but weakly or not at all before others. Their function is to encode the desired change in amplitude and direction (error signal) that is used by the pontine oculomotor circuitry to control saccades.

Build-up neurons - Their function is the same as that of collicular-burst neurons, but their activity spreads towards the fixation zone during a saccade, and when the firing reaches this area the saccade ends.

2.4.2.2 Frontal Lobe

Three regions of the frontal lobe are related to the voluntary control of saccades. They are the frontal eye field (FEF), the supplementary eye field (SEF), and the dorso-lateral prefrontal cortex (DLPC).

The neurons of the FEF fire 30-45 ms before a saccade, their structure is very similar to that in the SC but the main difference is that their discharge does not encode any error signals, thus the FEF program saccades using retinotopic coordinates (Pierrot-Deseilligny, 1994). They seem to play an important role in visual and motor aspects of memory-guided visually guided and predictive saccades (Pierrot-Deseilligny et al, 2003). The eye movements elicited by stimulation of the FEF must be also relayed to the oculomotor centres via structures other than superior colliculus, since Schiller (1997) demonstrated that after ablation of the SC, normal saccades can be produced by stimulating the FEF on the side of the brain where the SC was ablated. This finding supports the idea that FEF and SC form two parallel pathways in the generation of visually guided saccades.

The contribution of the SEF discharge in the control of saccades is not known, but its neurons fire prior to a voluntary saccade and saccades with vestibular inputs. The SEF uses spatiotopic or even craniotopic coordinates to program saccades.

The function of the DLPC is to hold in memory the position of the visual target towards which a saccade is going to be made.

2.4.2.3 Parietal Lobe

The posterior parietal cortex is important for shifts of visual attention, while the parietal eye fields (PEF) are implicated in the programming of saccades toward a visual target.

The posterior parietal cortex is involved in the mechanism responsible for disengaging attention from its current location and redirecting it to a stimulus that appears at an unattended location (M.A. Steinetz and C. Constantinidis, 1995)

Electrophysiological recordings from neurons in the inferior parietal lobule from awake animals have shown that neurons in this area respond to contralateral stimuli when the animal have any kind of reaction towards a voluntary relevant object. When the same response is done spontaneously the increase in firing does not occur. Neurons in this area seem to respond to sensory, motor and limbic contingencies (M. -Marsel Mesulam, 1983).

2.4.2.4 Role of other structures in saccade generation

a) Basal ganglia

The basal ganglia are connected to the cerebral cortex and the thalamus (Kennard C, 1994). Their main task is to control body movements and make them more accurate and smooth. There are five functional anatomical components of the basal ganglia: caudate nucleus (CN), putamen (PU), globus pallidus (GP), substantia nigra (SN) and the subthalamic nucleus (STN). The substantia nigra is divided into the pars reticulata (SNr) and pars compacta (SNc). The GP can be divided into parts with different functions; the external part (GPe), which is mainly connected with other basal ganglia nuclei and the internal part (GPi), which is together with the SNr, an important output station of the basal ganglia. CN and PU together form what is called the striatum, the major input station of the basal ganglia (Hikosaka et al. 2000).

The SNr laterodorsal part has visual properties and is one of the major inputs to the intermediate layers of the superior colliculus (SC). The neurons in this area have a very high basal fire rate of 50-100 Hz that decreases somewhat before a voluntary saccade, but no change has been found prior to a reflexive saccade. Wurtz and Hikosaka (1986) demonstrated using antidromic activation the inhibitory nature of the connexions between SC and SNr, when the SNr neurons fire, the SC neurons stop their firing and vice versa.

The SNr receives information from the striatum in two main pathways, the direct pathway and the indirect pathway (Hikosaka, O., Takikawa, Y., Kawagoe, R., 2000).

The direct pathway (also called the caudate-nigro-collicular pathway) is basically made up by the CN and the SNr. The area of the caudate nucleus (CN) with visual properties receives projections either directly from the SC or from FEF, SEF, DLPC, and other structures related mainly to voluntary control of eye movements. Caudate neurons on the longitudinal zone have a low spontaneous discharge that increases prior to voluntary or memory-guided saccades. CN projects directly to the SNr. All the connections in this pathway are GABAergic, therefore the final effect of the CN on SNr is inhibitory (Figure 2.4). The CN neurons discharge only before a saccade, therefore their basal firing rate is very low, thus under normal circumstances the SNr inhibits the SC suppressing saccades. But before a contralateral saccade is to be made the CN basal rate increases stopping the inhibitory effect of the SNr on the SC.

The indirect pathway (Figure 2.4) involves the subthalamic nucleus (STN), GPe and the SNr. The STN receives direct projections from FEF, SEF and also from GPe, which receives

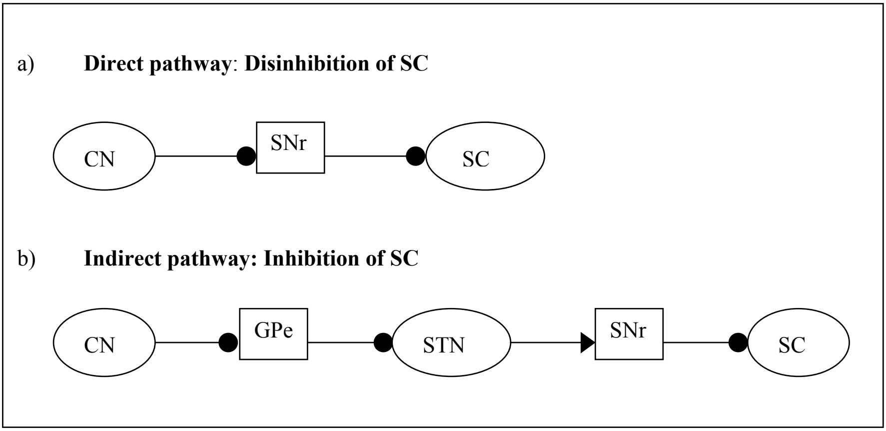

Fig 2.4: Main connections between basal ganglia and superior colliculus before a saccade.

a) Direct pathway mechanism, the final effect is an enhancement of the firing rate in the SC.
b) Indirect pathway mechanism.

Legend: Circle ending for inhibitory synapses, triangle for excitatory.

afferents from CN. The SNT sends efferent fibres to the SNr. As in the direct pathway, all the connexions in the indirect pathway are inhibitory except the one between STN and SNr that is excitatory using glutamate as a neurotransmitter. As the number of inhibitions before the STN is two, the final effect of the indirect pathway is the opposite of the one for the direct pathway. The indirect pathway seems to play an important role in contributing to the maintenance of visual fixation. The STN firing rate is very high during visual fixation suppressing saccades and stops firing before a saccade is made when the direct pathway becomes active.

The SNc modulates the activity in both pathways by means of dopaminergic connections with CN. Without the inhibitory effect of the indirect pathway and the disinhibitory effect of the direct pathway on the SC, the SC will be exposed to an excitatory chaos in which almost every input indicates to make a saccade to a different context. Thus, the BG does not provide a drive for a saccade but helps the SC to select the appropriate one.

b) Cerebellum

Two parts of the cerebellum are known to have a role in the control of saccades: the posterior lobe vermis and, its projection, the caudal fastigial nucleus (CFN) (Robinson FR, Fuchs AF, 2001).

The oculomotor vermis consists of lobules VI and VII and fires about 15 milliseconds before a saccade (Fuchs et al. 1993). Stimulation of the vermis produces ipsilateral saccades. Saccadic direction depends on the location of stimulation in the cerebellum, as it also happens with the SC or FEF. The amplitude and duration of the saccade are functions of the stimulus intensity.

The CFN receives inputs from the dorsal vermis and from pontine nuclei, such as, Nucleus Reticularis Tegmenti Pontis (NRTP), which sends a copy of the saccadic commands from the SC and FEF. The NRTP has neurons, which fire in relation to different eye movements, including saccades. Its main inputs are the supplementary eye fields (SEF) and frontal eye fields (FEF), in the medial portion, and the superior colliculus (SC) sends inputs to the caudal part of the NRTP. The major NRTP outputs are to the dorsal vermis, caudal fastigial nucleus and PPRF (Versino M, 1994).

CFN outputs include omnipause neurons, burst neurons in the medulla, pons and midbrain, the mesencephalic reticular formation and the rostral pole of the SC. Discharge of neurons in CFN occurs about 10 ms prior to a contralateral saccade, lags the start of ipsilateral saccades (Fuchs et al. 1993).

Many lesion, physiological and anatomical studies support the idea that the task of the cerebellar vermis is to modify on-line the program settle for the pulse generator so that the oncoming saccade will drive the eyes to the desired position avoiding dysmetria.

Figure 2.5 presents a schematic circuit of the neuronal structures involved in saccade generation.

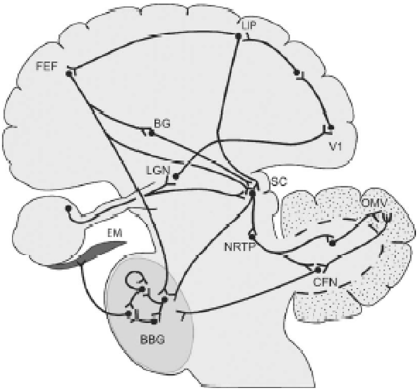

FIGURE 2.5: Highly schematic circuit of the neuronal structures involved in saccade generation. Neuron-like elements are simply meant to indicate the forward flow of information and not actual synaptology; for clarity, reciprocal connections are not included. Visual information regarding target position enters the brain via the optic nerve and is distributed to the lateral geniculate nucleus and superficial layers of the superior colliculus (SC). Visual signals are processed through striate (V1) and extrastriate visual areas to produce descending signals via the frontal eye field (FEF) and lateral intraparietal area (LIP) to the SC. The FEF influences the brainstem burst generator (BBG) directly, indirectly through the SC, and more circuitously through the basal ganglia (BG) and SC. The oculomotor vermis (OMV) of the cerebellum and the caudal fastigial nucleus (CFN) receive strong projections from the nucleus reticulari tegmenti pontis (NRTP) and weaker ones from other pontine and brainstem nuclei (not shown). Both the CFN and intermediate and deep layers of SC provide direct inputs to the BBG, which in turn produces the appropiate contraction of extraocular muscles (EM) to generate a saccade. From Hopp, J.J., Fuchs, A.F.,2004. The characteristics and neuronal substrate of saccadic eye movement plasticity. Progress in Neurology 72, 27-53.

3 Visual attention

3.1 Covert and overt attention

Attention is the process by which a person concentrates on a part of the environment to the detriment of the others. William James wrote at the beginning of the twentieth century the most famous definition of attention, he wrote: “Every one knows what attention is. It is the taking possession by the mind…of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness is of its essence. It implies withdrawal from some things in order to deal effectively with others….”.

In the 19th century, Hermann von Helmholtz preparing a set of experiments realized that his screen was too large to view without moving his eyes, but if he fixated in the centre of the screen he could decide in advance where he would pay attention. This ability to pay attention to one location without moving the eyes is what we know now as covert attention, on the other hand, the ability to move our eyes when we want to attend to some new visual target is called overt visual attention.

As explained above, depending on the eye movements there are two different types of attention, overt and covert attention. However, this is not the only classification of attention. We can also classify attention according to the purpose. Sometimes we direct our attention to a location just because we want to do it and sometimes because some external event in the environment attracts our attention. These two types of attention shifts are called voluntary (or internally guided) and reflexive (or externally guided) shifts of attention, respectively.

3.2 Brain areas involved on selective visual attention

Two main pathways are known to be implicated in visual selective attention and perception (Figure 3.1). Both pathways have a common start point, which is the primary visual cortex (V1) in the occipital lobe. The ventral or “what” pathway runs from V1 to the ventrolateral prefrontal cortex via the inferotemporal cortex. This pathway is involved in object perception and recognition and is mainly used for object discrimination and identification. The dorsal or “where” pathway projects from the V1 to the dorsolateral prefrontal cortex via the posterior parietal cortex. The “where” pathway is specialized in object localization in the visual space and spatial configuration of different objects in a scene. Although descriptions of both systems are always explained separately for practical reasons, Milner and Goodale (1993) concluded: “these two streams cannot function in isolation from each other. In short, there must be some form of integration, which reflects the essential unity and cohesion of most of our perceptual experience and behaviour.”

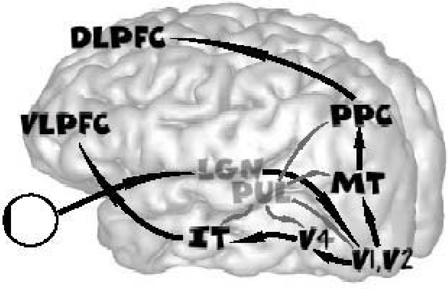

FIGURE.3.1 Major brain areas involved in the deployment of selective visual attention. Although single- ended arrows are shown to suggest global information flow (from the eyes to prefrontal cortex), anatomical studies suggest reciprocal connexions, with the number of feedback fibers often exceeding that of the feedforward fibres. Several subcortical areas including LGN and Pul play important roles in controlling where attention is to be deployed. Key to abbreviations: LGN: Lateral geniculate nucleus; Pul: Pulvinar; V1, V2, V4: early cortical visual areas; MT: Medial temporal area; PPC: Posterior parietal cortex; DLPFC: dorsolateral prefrontal cortex; IT: inferotemporal cortex; VLPFC: ventrolateral prefrontal cortex.

Adapted from: L.Itti, Modelling Primate Visual Attention, In: Computational Neuroscience: A Comprehensive Approach, (J: Feng Ed.) pp 635-655, Boca Raton: CRC Press, 2003

4 Relationship between visual attention and saccades

The relationship between attention and saccades is neither unidirectional nor obligatory since in the 19th century Hermann von Helmholtz demonstrated that is possible to shift the attention without doing any eye movement. In 1976 Wurtz and Mohler studied the organization of the monkey superior colliculus, concluding that there is an enhancement of the cells in the superficial layers of the superior colliculus in response to a spotlight, when this light is used as a target for a saccadic eye movement. Since then, a lot of studies have involved the relationship between the preparation of saccades and attention. In general four main theories have been supported: the first one supports the independence of both systems, the second proposed by Posner (1980) is a functional relation, the third position is the premotor theory of attention developed by Rizzolatti et al., and the last theory (VAM), developed by Schneider, proposes a common attentional mechanism for the selection for a spatial motor action and for spatial perception.

4.1 Independence hypothesis

In 1980 Klein et al designed two experiments to demonstrate and explain what is known as the "Oculomotor Readiness Theory", based on the idea that if there was a close relation between attention and the preparation of saccades when a subject is preparing a saccade to a location, first, the saccade made to the attended location should be facilitated, and second, performance at that location should be better that in any other position. The subjects' task was to make a manual response (pressing a key) when a brightening of a dot located in one of the two targets in the peripheral field was detected, and to make a saccadic eye movement when an asterisk appeared at either of the target locations. The brightening of the dot and the asterisk were so similar that the task was very difficult to perform and Klein found effects for exogenous cues, but not for endogenous, concluding that, although exogenous cues summon both saccade programming and attention, the same does not happen for endogenous cues. As some evidence for this coupling has been found, these results have been widely discussed. Klein accepted that generating a saccade and shifting covert attention, can occur together under normal circumstances. His conclusion is that the same system does not control both processes and that under fixation conditions "readiness to move the eyes to a location plays no role".

Remington (1980) designed four experiments to investigate three issues (time course of attention shifts with saccades, response of both systems to change in stimulus parameters and relationship of attention to saccadic suppression) related to the relationship between saccadic eye movements and movements of spatial attention. His conclusion was close to Klein's, accepting a closer relation between attention and reflexive cues than voluntary cues. When a saccade is triggered by a peripheral event, shifts of attention occur and this does not depend on the subjects' intention to move their attention with their eyes. It is automatic. But when the eye movement is triggered by a central cue, no evidence for attention shifts are found, or at least not before the onset of saccadic suppression.

4.2 Reciprocal Relation

In 1986 Shepherd, Findlay and Hockey designed an experiment to search for the relationship between eye movements and spatial attention. Their objective was to reject one of the three possible hypotheses that could explain this relationship: the identity hypothesis, the independence hypothesis, and the interdependence hypothesis. The first hypothesis or identity hypothesis holds the view that the processes involved in the generation of eye movements might be identical to the processes that enhance stimulus processing from selected parts of the visual field. This hypothesis was rejected automatically since our capability to shift the attention with the eyes fixed (covert attention) has been demonstrated. The problem was to decide which of the other two hypotheses could better explain the link between both. The independence hypothesis supports the independency of the two processes and the interdependence hypothesis is an intermediate view and says that these two sets of processes share, at some stage of their execution, a common resource. In their experiment, spatial attention was manipulated by varying the probability that a central arrow correctly predicted the location of the probe stimulus (50/50,20/80 and 80/20, with the first number being the probability of the probe to appear on the cued side and the second the probability to appear on the non-cued side). The experiment was done under two conditions, saccade condition where the subjects were asked to make a saccade to the same side where the central arrow pointed, and fixation condition where they were asked to fixate at all times of the experiment. The time between cue onset and probe onset (SOA) was also manipulated. The results of this experiment point in favour of a reciprocal or interdependence relationship: the allocation of attention to a peripheral position can be facilitated by preparing to make a saccade to that position, and saccade latencies can be reduced by allocating attention to the target position. They accepted a degree of asymmetry in this relationship, due to the fact that we can move our attention with our eyes fixed, but we cannot move our eyes without moving our attention.

4.3 Functional Relation

Posner (1980) designed three experiments. In the first experiment, three boxes were presented, separated 8° from each other and with the central box as the fixation point. The detection stimulus, a clear dot, occurs with equal probability either in the fixation box or at the target. He measured the reaction times (RT) for detection stimuli at both locations as a function of time following the peripheral eye movements cue. He found a strong tendency for attention to shift to the target position for an eye movement prior to the eye leaving the fixation point, thus rejecting Klein's results, and proposing a firmer link between attention and eye movements. The second experiment was designed to search for the intensity of the link between overt and covert orienting. Posner increased the possibility that the detection stimulus would be presented at fixation rather than at the target position. The subjects were asked in the first condition to remain fixed all the time and in the second to move their eyes as quickly as possible after the target box was presented. The results confirmed the idea that attention moves rapidly prior to eye movement and returns to the original fixation as the fovea settles in at the target. Even with the incentive of a high probability detection stimulus at fixation, subjects do not maintain attention while programming the eye movement. In the third experiment Posner demonstrated that attention could be moved in a direction opposite to the eye movement. These results were fatal for Klein's theory. All in all, Posner demonstrated with these results that the relationship between eye movements and attention can neither be viewed as a complete dependence nor as a efference (Oculomotor readiness theory). He proposed a functional relationship, which often depends more upon the presentation of an important peripheral event that on the eye movement toward that event. If the peripheral event is not important, subjects can avoid moving the attention to it. Posner compares this relationship with that found between eye and hand movements.

4.4 Premotor theory of attention

Rizzolatti and colleagues have proposed the strongest relation between shifts of overt attention and saccades. They reject what they call "The classic theory of attention" and explain the link between the two with the *"Premotor theory of attention"*, formulated on the basis of neuropsychological and psychological findings.

For the premotor theory, selective attention is activated for the same circuits as motor activity. Those maps, or pragmatic maps, that transform spatial information into movements, activate spatial attention. When one of these maps becomes active, it increases the motor readiness to respond to some space areas and processing of stimuli coming from that space sector is facilitated.

Psychological evidence of the premotor theory of attention comes from some experiments performed by Rizzolatti (1987) and Umiltà et al. (1994). In these experiments the subjects were asked to fixate on a central box, surrounded by 12 peripheral boxes forming a square, to direct their attention to the peripheral cued box and to press a key as soon as an imperative stimulus appeared. There were valid trials (imperative stimulus at cued box), invalid trials (imperative stimulus at any other position but not at the cued location) and neutral trials (all the boxes were cued).

The results showed three important effects: first, valid trials were faster than invalid trials; second, invalid trials with the imperative stimulus in the same hemifield as the cued box were faster than when it was in the contralateral hemifield; and, third, invalid trials with the imperative stimulus far from the cued box were slower than those near to it.

These three effects were found with the stimuli arranged horizontally, vertically, above or below, and they are known as the “meridian effect.“

The explanation of the meridian effect with the premotor theory concept was: “As soon as the cue is presented, a motor program is executed to prepare the saccade to the desired location, with the correspondent amplitude and direction. When the two parameters are set, the cued location becomes more salient than the others and the readiness to respond to that location increases. But if one of the two parameters changes, a new motor program must be prepared and a delay in the response will be noticed.”

The evidence of another study supports the premotor theory. In 1994 Sheliga, Riggio and Rizzolatti studied saccade trajectories. The subjects were asked to make a saccade to a box while another box was cued to attract their attention. The hypothesis was that if the two tasks are performed by different circuits, both tasks could be performed without any problems. However, they demonstrated that when a visual stimulus is presented and a saccade is done to another location, the trajectory of the saccade deviates to the contralateral direction to that of the visual stimulus location. This experiment provides experimental support for the idea that both processes share a common neural circuit.

4.5 Visual Attention Model (VAM)

This neuro-cognitive theory explains the relationship between selection-for-visual-perception (discrimination task) and selection-for-spatial-motor-action (saccadic eye movements). Experimental support of the VAM theory comes from studies of Schneider and Deubel

(Deubel and Schneider, 1996 and Schneider and Deubel, 1995). They investigated the relationship between a spatial motor action (saccadic eye movements) and a perceptual discrimination task in a dual task paradigm. In the first experiment, the subjects had to perform a discrimination task while preparing a saccadic eye movement, in the second experiment, the subjects were asked to fixate to the central item and to keep their eyes fixed. For the first and second experiments the possible targets were 3 items located at both sides of a central item. A peripheral cue indicates the saccade target location to the subjects. The perceptual task, which consists of discriminating between an E or a mirror E, could either appear at the saccade location, or ± 1 degree from it. The third experiment kept the discrimination task constant in one location for a number of trials, while the subjects were asked to saccade to another location. The aim of the third experiment is to answer the question whether a saccade target necessarily binds visual attention. The subjects had enough time to prepare the saccade to the cued location, while allocating visual attention to the discrimination object. Nevertheless, discrimination was always better when both locations coincided, demonstrating that it is not possible to direct attention to an object while performing a saccade to another location. The results showed that the performance is always better when both tasks have to be done to the same location, that the saccade target attracts attention, and that this coupling is obligatory, i.e., even pre-knowledge about the location of the discrimination target cannot decouple the attention from the saccade target.

According to this evidence, the VAM theory accepts that a common visual attention mechanism exists for both selection functions and that it takes place in the primary visual area (V1). This selection processing can be done only for a single visual object at a time. After the object selection, the ventral pathway ("what"-pathway) computes visual information for the object identification and the dorsal pathway ("where"-pathway) sets up the motor programs towards the selected object. Thus, the dorsal pathway task is the selection-for-spatial-motor-action and the end of the ventral pathway is the selection-for-visual-perception. VAM and premotor theory of attention postulate an obligatory link between motor programming and attentional control, but while VAM accepts motor programming as a consequence of visual attention processes, the premotor theory supports the opposite. Figure 5.1 represents a basic scheme of the VAM theory. Selection for perception and selection for spatial motor action are controlled by the same attentional mechanism. After the attentional selection process, different visual information is processed in two different streams (Milner, Goodale. 1993). The ventral stream deliver messages concerning object-centered coding, while the dorsal stream may provide entirely viewer-centered information. Both systems are highly interconnected to each other.

In 2002 Godijn and Theeuwes proposed a similar model to the VAM theory. The "Competitive Integration Model" supports the idea that there is a common attentional selection for the saccades and for object recognition. Compared with VAM theory, this model is more concerned with the mechanisms responsible for saccade programming.

5 Questions

In the first part of this study, the relationship between covert, and overt attention and saccadic eye movements will be investigated. The paradigm used for this purpose was a modification of the paradigm used before by Deubel in his studies (Deubel and Schneider, 1996).

The second part of the study tests the hypothesis that the impairment of intentional saccades in PD is a direct consequence of the deficit in control of intentional attention shifts in these patients. The prediction of this hypothesis is that under all stimulus conditions in which PD-patients show impaired saccades, they will also show impaired control of attention. The scheme shown in the figure 5.1 can be used to predict possible consequences of lesions at different locations. The prediction of this hypothesis is that the lesion in PD patients is somewhere between locations 1 and 2 in the figure. If it is before the object selection process (number 1), then the attention mechanism is completely affected, but if the lesion is after this point (number 2), a selection process can occur but the patient would not be able to react to it. In contrast, dissociation between the impairments of saccades and the spatial attention used for perception would indicate that the lesion that affects the PD patient is located after the common pathway for object selection for both tasks (numbers 3 or 4 in figure).

The third part of the study, the hypothesis that cerebellar patients have a specific impairment of reflexive saccades and that this is caused by a specific deficit in reflexive attention shifts, will be tested and compared with the data from experiments 1 and 2.

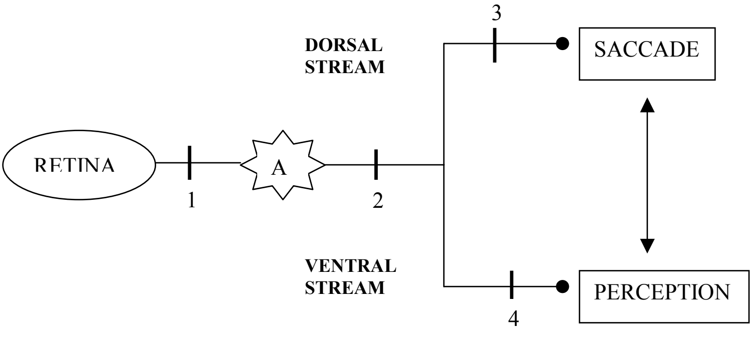

FIGURE 5.1: Scheme showing the common object selection attentional mechanism (A) for both perception (selection for perception) and saccade (selection for motor action). The fat vertical lines with their respective numbers represent the possible locations for a lesion. In the text, the consequences of these lesions in the selection process are explained. The arrow between the boxes „SACCADE“ and „PERCEPTION“ indicates interactions between dorsal and ventral streams (Milner & Goodale; 1993).

6 Experiment 1: Control Subjects

6.1 Methods

The subjects were ten volunteers, 5 males, and 5 females, between 25-45 years. Some of them had previous experience with oculomotor experiments, although 7 were completely naïve as to the purpose of the experiment. Four of our subjects normally wear glasses; their vision was corrected during the experiments. The others had full visual acuity. Each subject performed one session for each experiment, each session was paid with 10 €.

6.2 Apparatus

The subjects were seated in a dark room with their head on a chin rest. They were instructed not to move their head and to look at a computer screen (40x30 cm) located 60 cm in front of them. The video signal had a resolution of 1280 x 1024 pixels at a frame rate of 72 Hz.

The horizontal eye movements of both eyes were measured with a head-mounted infrared reflection device (IRIS, Scalar) with a precision of roughly 0.5 deg. The position signal was digitised with a sampling rate of 1 kHz. The device was mounted before the subjects sat in front of the screen. Since the system is very sensitive to movement relative to the eye, fine adjustment was done after the subjects were in the experiment chair. Subjects were instructed not to move either their head or the infrared device at any time during the experiment. For fine adjustment of the IRIS a pattern consisting of 7 red crosses was present on the screen. The subjects were instructed to look at the cross in the centre and then consecutively to look at the crosses located on the right and the left side. The adjustment was done by the person conducing the experiment on the basis of the inspection of the IRIS signal on the oscilloscope. After checking that the device was firmly attached or, if necessary, after adjusting it again, the experiments began.

A non-linear polynomial calibration (third order) based on fixation data was applied off-line. The targets were presented after the training trials, in the middle of the experiment and, again, at the end of the experiment. The calibration target was a yellow point which jumped with a predictable amplitude and time between the positions ±0°, ±2,5°, ±5°, ±7,5°, ±10°. During the experiment this sequence, consisting of 36 fixations, was repeated 3 times at equidistant time intervals.

A joystick located on the table in front of the subjects was used for signalling the discrimination response at the end of each trial.

The eye movement signal recorded on-line could be used to generate an acoustical feedback to signal improperly executed saccades. In such a case, joystick responses were ignored and the next trial was started immediately.

6.3 Experimental Procedures

With different combinations of two cue types (intentional and reflexive) and two eye movement conditions (saccade and fixation condition), a series of four experiments was done. The order of the experiments was counterbalanced across and within subjects. To investigate the relationship between saccades and visual attention a dual-task paradigm was used. The primary task to be carried out was the eye movement task and the secondary task was a discrimination task. The initial display was common for all the experiments (Figure 6.1), the subjects were asked to fixate to a central triangle (△), also called the fixation point. On both sides of it, located at ± 4 deg, was a pre-mask, consisting of an 8 (⊟) on each side. Letters and characters were displayed by means of a 7-line mask with a width of 0.5 deg and a height of 1.0 deg as shown in Figure 6.1. The intentional cue used was the central triangle which pointed either to the right or to the left pre-mask, the reflexive cue was a couple of lines which appeared above and below of one of the two pre-mask. Both cues could point to the left or to the right randomly, with equal probability. In the saccade condition the subjects were asked to look at the pre-mask indicated by the cue and in the fixation condition they were asked to fixate the central triangle and to shift their attention to the cue location.

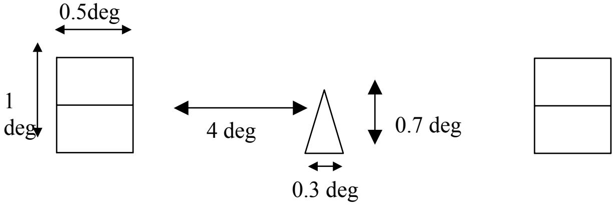

FIGURE 6.1: Initial display used for the experiments.

Before the start of the eye movement, a discrimination character (DC) that could be either a Ǝ or an E was presented at one of the two pre-mask positions. The appearance of one or the other was chosen randomly and with equal probability. The DC presentation time was 100 milliseconds, after this time the pre-mask replaced the DC. The discrimination task was to distinguish between the two of them and to indicated the response by pressing the joystick either to the right side if they thought that the DC was an E or to the left if they recognised it as being a Ǝ. On the opposite side, and at the same time and with the same duration as the DC, a distractor character was presented at the pre-mask position, which could be a 2 or a 5 and the appearance of one or the other was again random.

Depending on the position of the DC related to the cued location, two different types of trials can be differentiated. If the DC appeared at the cued location, the trial is called *valid trial*, and if it was in the other side, it is called *invalid trial*. Valid and invalid trials were presented in random order but with different probabilities.

All experiments were done with two set of probabilities for valid and invalid trials, in the first set the probability was 75% for valid trials and 25% for invalid, in the second the probability was 50% for both valid and invalid trials, being the cue without any information about the DC location.

The experiments were split into three blocks. The first block performed consisted of 15 training trials. Their purpose was to familiarize the subjects with the eye movement task for the corresponding experiments. The pattern used for this purpose was the same as for the subsequent experiment but only with the eye movement task and without the presentation of the DC. If it was considered that the subject did not understand the eye movement task, a new training block was performed and so on, until the subject understood the aim of the experiment properly.

After the training trials, two blocks of 32 trials each were performed, separated from each other by a calibration sequence (see Apparatus section for more information).

6.3.1 Experiment 1.A: Intentional saccade task

The subjects were asked to fixate the central upright triangle. After 3 sec the triangle pointed to the pre-mask located either on its right or left side with equal probability. The subjects were asked to saccade the target on that side, but not before the off-set of the central cue ("go"-signal), which occurred after a random time of 759 ± 26 ms (Figure 6.2). The individual mean saccade latency was detected on-line and the time of the DC on-set was adapted in such a way that the average time between DC-offset and saccade on set was the same for each subject (103 ± 20 ms). When the subject made a saccade before the "go"-signal an acoustic signal could be heard, warning the subject to wait longer for the saccade. The joystick response for these trials were ignored and not included in the data analysis. This was also the case for the trials in which no saccade was detected 2 sec after the “go”-signal.

The discrimination character (DC) was presented at the pre-mask position lasting 100 milliseconds. After this time the pre-mask appeared again ensuring that when the subject gaze was at the pre-mask position the DC was already gone. After the eye movement was correctly performed, the subjects had to press the joystick. They were asked to press the joystick irrespective of whether the trial was valid or invalid. After the joystick response, the central cue appeared again and the next trial started.

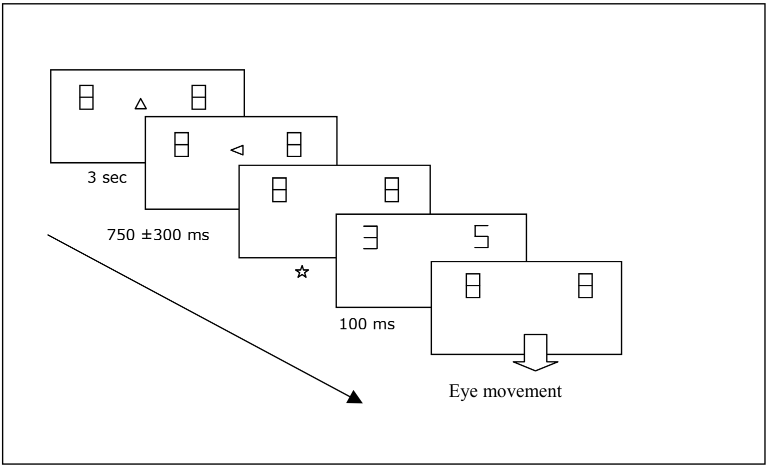

FIGURE 6.2. Sketch of the sequence for the intentional experiments. After the sequence is finished the subjects are asked first to fulfil the eye movement condition and then to press the joystick. The star represents the time that was adapted for subjects in order to get the same saccade latency average for all of them.

6.3.2 Experiment 1.B: Intentional fixation task

The purpose of this experiment is to evaluate the covert intentional attention shifts. The experiment had the same characteristics as the previous experiment (experiment 1.A), but the subjects were ask to fixate all the time on the central cue and not to move their eyes at any time during the experiment. The task in this experiment was only to attend the side where the central cue pointed and to indicate with the joystick which DC they thought was presented on the screen. All the trials in which the subjects did a saccade at any time before the DC presentation time or 400 ms after it were eliminated off-line and were not used for the results.

6.3.3 Experiment 1.C: Reflexive saccadic task

The subjects were asked to fixate the central triangle. After 3 sec the central triangle disappeared and, at the same time, the reflexive cue indicated the future saccade target. The cue was two small vertical lines that appeared above and below one of the two pre-masks (Figure 6.3). The go-signal for this experiment was the onset of the cue. The subjects were asked to saccade to the cued location as soon as possible after the go-signal. The duration of the DC in this experiment was again 100 ms. As in the other experiments the pre-mask replaced the DC immediately after its presentation time. As soon as the peripheral cue was presented, the subjects were allowed to saccade to the target and to give the corresponding joystick response. In the online analyses the trials in which no saccade was detected 2 sec maximum after the go-signal were excluded.

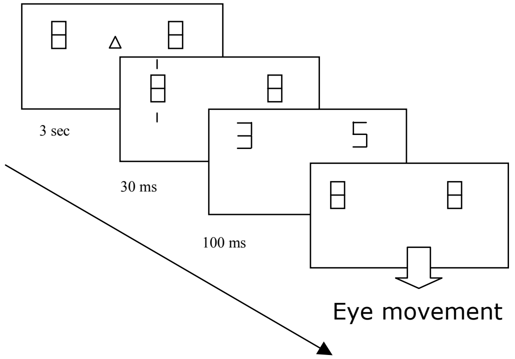

FIGURE 6.3: Sequence for the reflexive experiments.

6.3.4 Experiment 1.D: Reflexive fixation task

This experiment is designed to evaluate the covert shifts of attention for the reflexive cue type. The display used for this purpose was the same as for experiment 1.C (Reflexive Saccadic task), but the subjects were asked as in experiment 1.B (Intentional Fixation task), to hold their gaze stable on the central fixation point and not to move their eyes at any time during the experiment. All the trials in which the subjects did a saccade to anywhere in the screen during the experiment were eliminated off-line and not used for the subsequent data analyses.

6.4 Data analysis

In the off-line analysis, saccades were detected automatically (Figure 6.4) by means of a velocity criterion (v>100 deg/sec). An algorithm was used which searched forward and backward in time, starting from the peak velocity, for the first drop of the velocity below 10% of the peak velocity. In this way the beginning and the end of the saccade were defined.

The saccade amplitude was computed as the difference in eye position between the end and the start of the saccade. The following criteria were used to avoid marking of artefacts as a saccade: the movement duration had to be shorter than 200 ms, the peak velocity had to be within a range of ±300 deg/s around an expected peak velocity, which was calculated by the following formula:

$$PV = \frac{PV_{\max} \cdot A}{A + A_{1/2}}$$

This formula describes the normal relation between peak velocity *(PV)*, and the amplitude A of a saccade. The two parameters of this relation were set as follows. PV_{max}, the maximum peak velocity was set to 700 deg/s and $A_{1/2}$, the amplitude of a saccade, which is executed with the half of the maximum peak velocity, was set to 8 deg.

The timing, position, and the velocity were obtained for all the marks represented in figure 6.4 and exported to a file for subsequent statistical analyses. On the basis of these exported data other important parameters were computed.

The proportion of correct responses for both valid and invalid trials and the proportion of responded valid and invalid trials were used as an attention measures. The effects of valid and invalid trials on saccade latency and joystick latency were also evaluated. The saccade latency was computed as the time differences between the beginning of the saccade and the “go”-signal and the joystick latency was defined as the time difference between the joystick response and DC onset.

To evaluate the attentional effect that the cue has on the discrimination performance the variable *proportion of correct responses* was defined separately for valid and invalid trials. The variable was computed as the number of correct responses divided by the total number of joystick responses separately for each cue type. The total number of joystick responses excluded those trials in which the eye movement task was not properly performed (for the saccade experiment those trials with saccades too early or too late were excluded, as were those trials in which the fixation condition where a saccade was detected).

To evaluate under which conditions the subjects were more confident solving the discrimination task, another variable called *proportion of joystick responses* was defined. This variable was calculated separately for valid and invalid trials by the number of responses divided by the total number of joystick responses. Joystick responses with too long latencies (latencies >2000 ms) were not included in this proportion. If the subjects were very confident about which DC appeared then they would press the joystick more often during the experiment than if they were not so confident.

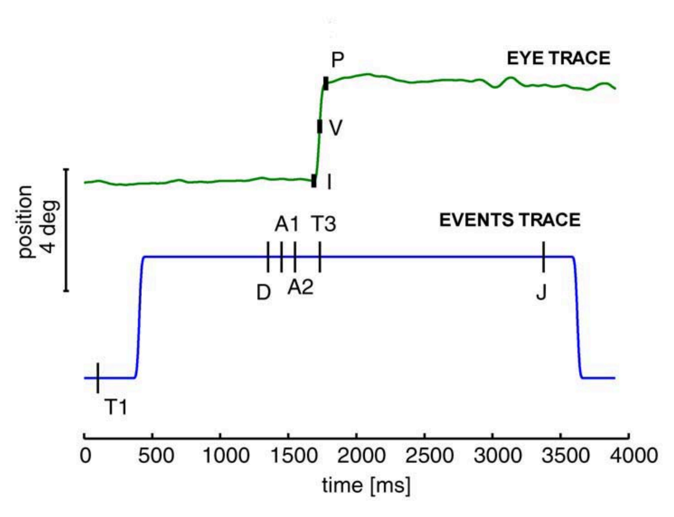

FIGURE 6.4: Example of an analysis window, where the saccades and events are marked. The eye trace (line above) has three marks: I begin of the saccade, V peak velocity and P end of the saccade. The line below is the events trace, with the following marks: T1 target appearance, D cue offset, A1 presenting the character, A2 writing the mask, T3 saccade and J joystick response. The timing, position and movement amplitude of all the marks were exported to a file for statistical work with them.

To evaluate whether the eye movement condition was correctly performed, the variable *proportion of correct saccades* with respect to the total number of trials was computed for all saccade experiments. This variable was calculated as the number of saccades done during the first second after the “go”-signal for each experiment, and separately for valid and invalid trials. This number was divided by the corresponding total number of trials. This proportion gives additional information about the saccadic performance, which is not covered by the variable *saccade latency*. This becomes evident from Figure 6.5 showing a histogram for the saccade latencies. The upper tail of the latency distribution ends below one second. Saccades, which are not included in the proportion of correct saccades, are saccades that do not belong to the population of saccades generated as response in the motor task.

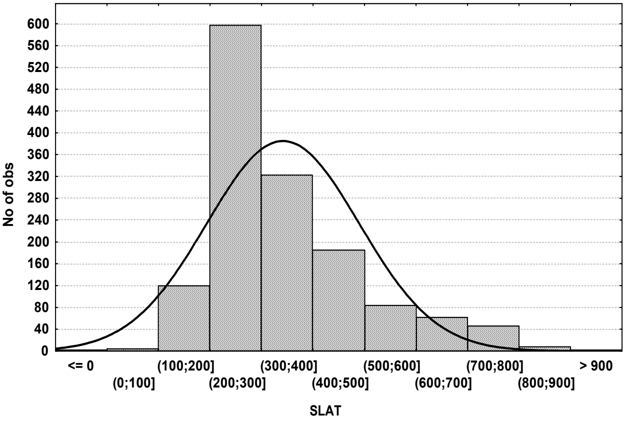

FIGURE 6.5:Histogram showing saccade latencies for the control subjects.

6.5 Results

6.5.1 Discrimination Performance

To examine the attentional effect on the discrimination performance a t-test between the proportion of correct responses for valid and invalid trials for each experiment was carried out (Appendix A). The results are shown in table 6.6. As the variable was not normally distributed a rank transformation was applied to the values before any other operation was carried out. Replacing the data by their ranks has two main advantages: the results are invariable under any monotonic transformation and the moderation of the influence of outliers. It is important to remember that the entire following statistical test has been done with the rank transformation of the original raw data (see Appendix A).

Significant cue effects were observed in all conditions except the fixation condition with the irrelevant cue.

	Cue relevance			
	50_50		75_25	
	Intentional	Reflexive	Intentional	Reflexive
Saccade	**0.006**	**0.01**	**0.0001**	**0.04**
Fixation	0.09	0.1	**0.01**	**0.01**

TABLE 6.6: Results of the t-test calculated for the proportion of correct responses between valid and invalid trials. Each cell contains the significance level (p) of this difference for a particular experiment. Levels below 0.05 (printed in bold) indicate a significant effect of the cue on the performance.

A three factorial repeated measures ANOVA (RM-ANOVA) with the dependent variable *proportion of correct responses* was used to evaluate if the difference between fixation and saccade task in the 50/50 condition became significant. The three factors used for this purpose were: cue type (intentional vs. reflexive), eye movement condition (fixation vs. saccade), and trial type (valid vs. invalid).

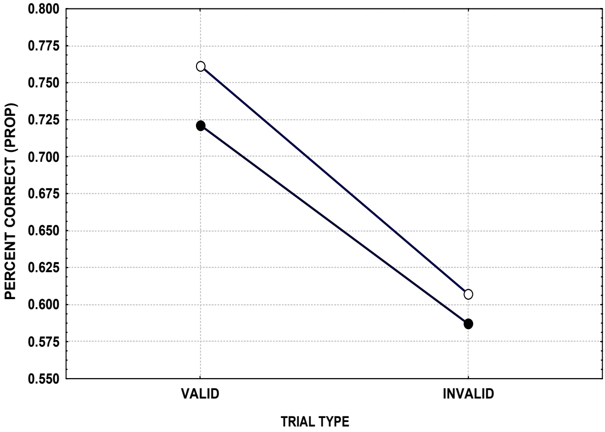

FIGURE 6.7: Proportion of correct responses as a function of the trial type for experiments with cue relevance 50/50. Open circles are used for saccade and filled circles for fixation.

The results of the ANOVA (Figure 6.7) showed no significant effect for the main factor eye movement condition [F (1,9)=1.60; p<.2374], the factor trial type was significant showing that discrimination performance for valid trials is better than for invalid trials. Nevertheless, the interaction between these two factors did not show a significance [F (1,9)=.27; p<.6154] indicating that the cue effect on the discrimination performance was equal for both eye movement conditions.

6.5.2 Confidence

To evaluate the confidence of the subjects to respond, a four factorial repeated measures ANOVA (RM-ANOVA) on the dependent variable “number of joystick responses” was used. The four factors with two levels each were: *cue relevance* (75/25-50/50), *cue type* (intentional/reflexive), *eye movement condition* (saccade/fixation), and *trial type* (valid/invalid). As the proportion was not normally distributed, the same procedure as with the proportion of correct responses was carried out and a rank transformation was applied to the raw data before statistical analysis of the data (see Appendix B). The RM-ANOVA showed a high significance level [F (1,9)=22.33; p<.0011] for the factor cue type, indicating that there were more responses in the reflexive cue experiment compared to the intentional cue. Figure 6.8 presents the mean proportion of joystick responses obtained for intentional and reflexive cue.

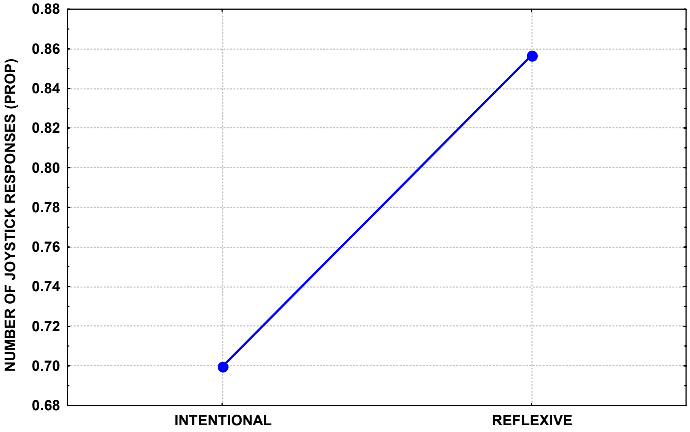

FIGURE 6.8: Confidence as a function of the cue type.

6.5.3 Manual reaction times

To evaluate the influence of the different conditions on the joystick latency (Appendix C), a four-way RM-ANOVA with the factors cue relevance (50-50/75-25), cue type (intentional/reflexive), eye movement condition (fixation/saccade) and trial type (valid/invalid) was carried out. The results showed a significant main effect for the factor cue type [F (1,9)=8.91; p<.015]. Reaction times for the intentional cue were slower than for the reflexive. The reaction times for valid trials were faster than for invalid trials [F (1,9)=17.26; p<.0025], this effect was bigger for the intentional cue than for the reflexive cue, confirmed by the significant interaction between the factors cue type and trail type [F(1,9)=10.39; p<.0104]. Figure 6.9 presents the manual reaction times as a function of the cue type.

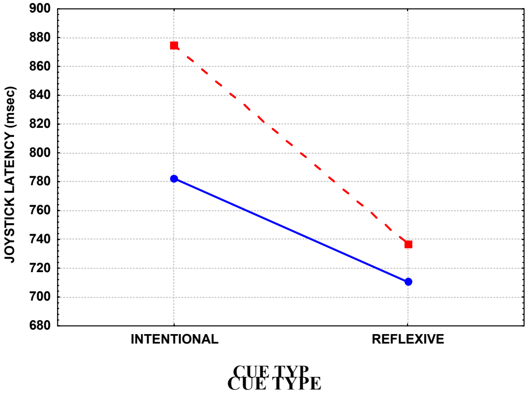

FIGURE 6.9: Manual reaction times as a function of the cue type. The solid line indicates the mean manual reaction times for valid trials and dash line for invalid trials.

The significant interaction [F (1,9)=5.56; p<.0428] between cue type (intentional/reflexive) and eye movement task (saccade/fixation), indicates that the manual reaction time as longer when a intentional saccade was performed, whereas for the reflexive cue type the manual reaction time did show this dependence on the saccade execution (Figure 6.10).

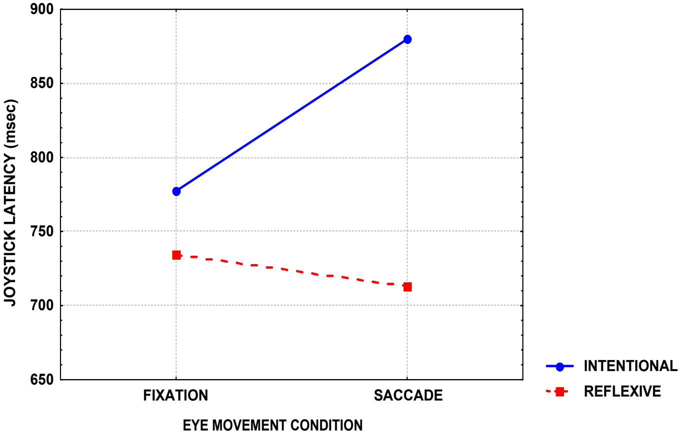

FIGURE 6.10: Manual reaction time as a function of the eye movement condition. The dashed line indicates manual reaction time for reflexive cue experiments and the solid line for intentional cue experiments.

6.5.4 Saccade latency

To check the effect of the different conditions on the saccade latency (Appendix D), a three way ANOVA was used with the following factors: cue relevance (75/25 vs. 50/50), cue type (intentional vs. reflexive) and trial type (valid vs. invalid). Of course, the factor eye movement condition plays no role in these calculations because only the experiments with saccades were evaluated. As expected, the factor cue type showed a significant difference [F (1,9)=26.11; p<.0006], with the saccade latency for the intentional experiment (mean =444.961 ms) being bigger than that for the reflexive experiment (mean=283.893 ms). The main effect of the factor cue relevance [F (1,9)=8.38; p<.0178] showed that the saccade is faster for the 75/25 cue relevance (mean=358.5 milliseconds) than for the 50/50 condition where the cue does not provide any spatial information about the future target location (mean=381 milliseconds). Figure 6.11 presents mean saccade latencies as a function of the cue relevance.

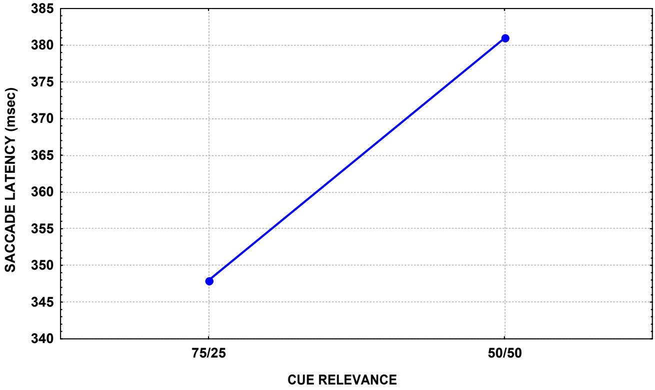

FIGURE 6.11: Mean saccade latencies as a function of the different cue relevances.

6.5.5 Saccade Performance

The proportions of correct saccades (Appendix E) had a mean of (0.79) for intentional experiments and (0.90) for reflexive. After applying the rank transformation to the proportion of correct saccades, the t-test for dependent samples did not show any significant differences between intentional and reflexive experiments.

6.6 Discussion

6.6.1 Discrimination Performance

Discrimination performance is better for valid trials than for invalid trials for all the saccade experiments irrespective of the cue type. These results indicate that attention is engaged to the future saccade target location while the saccade is being programmed. In the fixation experiments attention was shifted to the cued location even without executing a saccade.

For the fixation experiments, discrimination performance is better for valid than for invalid trials under the 75/25 condition, indicating that when the cue has spatial information the subjects shift their attention to the side where the cue is pointing. For the cue relevance 50/50 no differences between valid and invalid cues were found either for the intentional or for the reflexive condition. Nevertheless, the different results between the fixation and the saccade condition in the three-way ANOVA did not become significant.

An additional four-way RM-ANOVA with the factors: cue relevance (50/50 vs.75/25), cue type (intentional/reflexive), eye movement condition (fixation/saccade) and trial type (valid/invalid) showed a significant effect for the main factor trial type [F (1,9)=51.03; p<.0001]. The interaction between the factors cue type and eye movement condition [F (1,9)=6.41; p<.0322] showed that the performance is better for reflexive than for intentional cues and the interaction between the factors cue type and trial type [F (1,9)=5.94; p<.0376] showed a bigger attentional effect for the intentional cue.

The finding that there was no interaction between the factors eye movement condition and trial type shows that spatial selection (indicated by the difference between valid and invalid trials) was very similar for saccade and fixation conditions. This suggests that the selection mechanism does not rely on the execution of eye movements.

The finding that performance was better for the reflexive than for the intentional cue type (for both valid and invalid trials) indicates that the object recognition worked better for the reflexive cue type. Thus, this finding does not reflect an effect on the (common) selection mechanism, but on the perception process in the ventral stream. This could be explained by the hypothesis that reflexive cue types activate the dorsal stream more efficiently than intentional cues, and that activation of the dorsal stream facilitates the object recognition processes in the ventral stream. Such facilitation could be due to an interaction between the dorsal and the ventral stream as indicated in Figure 5.1 (for a review see Milner & Goodale; 1993).

In contrast to this improvement of the discrimination performance in the entire visual field, the interaction between the factors cue type and trial type reveals a difference in the selection process between intentional and reflexive cues. Two non-exclusive interpretations of these differences have to be discussed. First, in the reflexive experiment the time between the appearance of the cue and the offset of the discrimination target (130 ms) may not be long enough for building up the selection process. In the intentional experiment this time was much longer (963.366 ms). The second possible interpretation is that the selection process is more efficient for intentional cues because it may require input from frontal lobes. That frontal input can indeed drive the selection process alone is also supported by another observation: The intentional cue affects the discrimination performance (difference valid/invalid) even in the fixation condition (see cue relevance 75/25). With the intentional cue, there is no automatic activation of the dorsal stream. However, spatial selection is possible on the basis of the high level instruction alone (FEF).

The finding that in the saccade condition, performance was better for valid than for invalid trials even when the subjects knew that the cue did not have any relevance (50/50 condition) supports the idea that the attention is obligatorily engaged at the target location. The attention is shifted to the future target location during the preparation of the saccade no matter whether the cue provides information about the location of the discrimination target or not. Even when the subjects knew that the cue did not have any relevance, they were not able to prevent the shift of the attention toward the saccade goal. This demonstrates that the coupling between the selection process and motor action is obligatory and that the decoupling of both tasks is impossible. This result is in agreement with the results of Deubel and Schneider (1996). In one of their experiments the DC always appeared at the same position and the central cue indicated the saccade target. But, as in the present study, the discrimination performance of their subjects was always better at the saccade target position.

6.6.2 Confidence

The subjects are more confident with the reflexive cue than with the intentional cue (Figure 6.8). The confidence of the subjects is a measure of how difficult is for them to make a decision and press the joystick. As the task is more difficult, fewer joystick responses are expected. It is important to note, that the confidence of the subjects revealed the capability of the visual perception under the different conditions. Thus, the finding that their confidence is greater for reflexive than for intentional cue types supports the hypothesis, explained in the discussion of the discrimination performance, that a reflexive activation of the dorsal stream facilitates perceptual processing. However, there is an obvious dissociation between the subjective confidence to give a joystick response and the probability that this response is correct: There was no difference between the proportion of joystick responses for valid and invalid trials, even though there was a difference for the perceptual performance (see 6.6.1).

6.6.3 Manual reaction time

The manual reaction time consists of different parts: the sensory processing time, the time needed for the discrimination, and the time required for generating the hand movement command. Thus, the changes in the manual reaction times have to be discussed mainly in the context of these three different sub-processes.

The longer manual reaction time in the intentional than in the reflexive experiment parallels the known differences in saccade latencies. Intentional saccades also show longer latencies than reflexive saccades. This effect can be understand as a result of the more complex processing in the intentional task. Reflexive movements occur in a more automatic manner on the basis of the stimulus, while intentional movements need additional activity of the spatial working memory.

The latencies for invalid trials are bigger than those for valid trials. This result indicates an advantage of the cued location for the perception process compared to the non-cued location. In detection experiments other authors have found a similar benefit in the manual reaction times for valid trials (Shepherd, M. et al R.J., 1986; Shelliga et al., 1994; Klein, RM, 1980; Posner, M.I., 1980). Posner found the benefits for fixation as well as for saccade experiments. Shepherd found the benefits for all saccade and fixation conditions under different SOAs. When looking at the results in the discrimination performance, it can be seen that discrimination performance for invalid trials is significantly smaller than that for valid trials. Thus, the cueing effect has benefits for valid trials and costs for invalid trials with regard to the discrimination performance and manual reaction time. Thus, a better discrimination performance corresponds with a shorter manual reaction time and vice-versa.

The interaction between cue type (intentional/reflexive) and eye movement condition (fixation/saccade) showed that in the fixation condition manual reaction times are nearly the same for both cue types, whereas for the saccade condition manual reaction times for the intentional cue are significantly slower than those for the reflexive cue (Figure 6.10). That the manual reaction times were longer for the intentional saccade task compared to the reflexive fixation task suggests that the different intentional actions (saccade + discrimination + hand movement) cannot be processed in parallel, but need sequential processing, which leads to the additional delay in the hand movement. For the reflexive task the execution of the saccade did not cause such a delay of the hand movement. This may indicate that the reflexive saccade can be processed in parallel with the discrimination task and the hand movement. Similar results were observed by Shepherd (Shepherd, M., et al. 1986) in object detection task. They found the longest manual reaction times for saccade conditions. For fixation conditions the latency was shorter. They also found shorter reaction times for valid compared to invalid cues. Our findings differ slightly from the findings on reaction times in object detection tasks. Shepherd et al. (1986) observed different cue effects with different cue relevancies. Effects were smaller with irrelevant cues. It must be noted that the saccades elicited by these experiments were reflexive and no comparison with intentional saccades was done.

6.6.4 Saccade latency

Saccade latencies for the intentional cue (mean= 440 ms) are slower than for the reflexive cue (mean= 280 ms) indicating that the saccades are done under the timing conditions of the experiments. One might think that saccade latencies are very high, but as Hoffman and Subramaniam demonstrated (Hoffman, J.E., Subramaniam, B., 1995), manual responses and saccadic tasks interact, with saccade latencies for experiments with manual responses being bigger than those for experiments without them. Moreover, intentional saccades are programmed at a higher level. Saccade latencies for cue relevance 50/50 were about 30 ms bigger than for the 75/25 condition (Figure 6.11). The VAM theory predicts that saccade latencies increase when the target location of the saccade differs from that of the attention shift. Such dissociation between the saccade target and the spatial goal of attention also occur with the cue relevance 50/50, when the subject does not know in advance if the oncoming trial is valid or invalid. Therefore, it might be a useful strategy to suppress the saccade by trying to split both tasks (saccade task and discrimination). Such an attempt could explain the longer saccade latencies with irrelevant cues. If this strategy would be successful, it would allow the attention to shift to the DC and to saccade to the cued target. But the results shows that, although the latencies were increased, the discrimination performance was still better on the cued side indicating that the attention was still engaged to the direction of the saccade target.

No differences in the saccade latency were found between valid and invalid trials. Thus, saccade latencies for valid and invalid trials increase in the same fashion. This result indicates that large parts of the saccade preparation process were executed before the appearance of the DC. During this time there is no difference between valid and invalid trials. This is an important difference between the reaction times of saccades and the reaction times of the joystick responses. The manual response is programmed after the dissociation between valid and invalid trials, whereas the saccade is programmed before this dissociation.

Previous results regarding the saccade latencies are very disparate. Shepherd et al found facilitatory effects on the saccade latencies for valid trials and inhibitory effects for invalid trials. But, they did not find any significant differences for different cue relevancies. Godijn and Theeuwes also found longer saccade latencies when an onset distractor was present than when it was absent. On the other hand, Deubel and Schneider found neither facilitatory effects for valid trials nor inhibitory effects for invalid trials. The VAM theory accepts saccade programming as a consequence of attentional allocation. The results presented here are consistent with the VAM theory, but not with the others.

6.6.5 Saccade Performance

The results showed that there were no differences in the proportion of correct saccades for the intentional and reflexive cues. This variable has special importance when comparing the saccade performance between control subjects and patients. Therefore, the results concerning this variable will be discussed in comparison with the results in patients (see chapters 7.7.1 and 8.7.1).

7 Experiment 2: Parkinson Disease (PD)

7.1 Introduction

Parkinson’s disease is a basal ganglia disorder, caused by the lost of dopaminergic neurons in the substantia nigra, pars compacta (see: Role of other structures in saccade generation: Basal Ganglia, for more information about basal ganglia anatomy and its function related to eye movements) and in consequence a depletion of dopamine in the striatum (caudate nucleus and putamen). This loss of dopaminergic neurons in the substantia nigra can be seen macroscopically and microscopically. Under microscopy, a progressive loss of cells in the SNc is notorious with depigmentation and subsequent gliosis. In the surviving cells the typical Lewy Body can be often seen. The main consequence of the eye movement impairment in PD is the loss of the modulation that the SNc exerts on the direct and indirect pathways between the striatum and the SC.

Saccadic abnormalities in PD include increased saccade latency and duration and hypometric saccades (saccades which are too short). These parameters are more affected in voluntary or intentional saccades than in reflexive saccades, which are typically preserved (Briand et al., 1999).

Blekher et al. (2000) investigated reflexive and intentional saccades in severe and moderate PD patients before and after pallidotomy. The results confirmed that severe and moderate PD either does not affect reflexive saccades or only very slightly and that severe PD affects voluntary saccades more than moderate PD. After pallidotomy, reflexive saccades are not affected but voluntary saccades are slower and less accurate, in contrast to the improvement in other motor functions (T. Blekher et al. 2000). This points towards anatomically distinct pathways for the skeletal motor system and the oculomotor system.

Ravizza and Ivry (2001) demonstrated that the basal ganglia have an important role in the shifts of attention, that PD patients have a greater deficit in shifting the attention in an intentional manner than in a reflexive manner, and that this attentional deficit cannot be explained by recourse to the motor demands of the task.

The next experiment will test the hypothesis that the impairment of intentional saccades in PD is a direct consequence of the deficit in control of intentional attention shifts in these patients. The prediction of this hypothesis is that under all stimulus conditions in which PD-patients show impaired saccades, they will also show impaired control of attention.

7.2 Methods

The subjects were nine volunteers between 40-82 years old; none of them had previous experience with oculomotor experiments. All of them had Parkinson's Disease, which had been diagnosed at least one year before they took part in the study. All patients were assessed using the Mini Mental State Examination (MMSE) and were also given the motor section of the Unified Rating Scale for Parkinsonism (UPDRS). None of them showed any signs of dementia or abnormal cognitive functioning on the MMSE. The disabilities that they suffered in their day-to-day life ranged from mild to moderate according the classification of Hoehn and Yahr (stages of the patients between 1,5-3). After the UPDRS motor examination, the patients had values between 14 and 31 on a scale from 0 (no impairment) to 108 (complete impairment). The clinical ratings of the PD patients are shown in table 7.1. All the patients were receiving their normal medication at the time of the testing. The vision of those patients, who normally wear glasses, was corrected during the experiments. Each subject performed one session for each experiment, each session was paid with 10 E.

PD patient	Age/Sex	Hoehn-Yahr	Medication
1	82/M	1,5	LD, A
2	40/M	1,5	P
3	61/M	2,5-3	P, LD, S, COMT
4	66/M	2,5	LD; B,
5	48/M	2	CB, LD, A
6	48/M	2	S, PA
7	60/F	2	CB
8	54/F	1	S
9	60/M	3	LD, S

TABLE 7.1. Patient details and parkinsonian motor assessment. Legend: LD: Levodopa; A: Amantadine; P: Pergolide; S: Selegiline; COMT: Entacapone; B: Bromocriptine; CB: Cabergoline; PA: Budipine.

7.3 Apparatus

The same procedure as with the control subjects was used with the PD patients. The eye movements were assessed before the experiments in all patients. If no calibration was possible, the patient was not accepted to take part in the experiments. If it was considered that the patient did not understand the task properly, a complete experiment was run before beginning the real experiments to familiarize the subjects with the experimental procedure. If after this training experiment, they still could not perform the task, the patient was not recorded. The results of the training experiments were not used for the final results. Control subjects were those who participated in experiment 1.

7.4 Experimental Procedures

The PD patients performed the same experiments with the same characteristics for the factors cue type (intentional/reflexive), eye movement condition, (saccade/fixation) and trial type (valid/invalid trials) as with the control subjects. Only the experiments with the cue relevance 75/25 were done with the patients because the experiment requires a lot of concentration and the patients get tired more easily than the control subjects. For one patient (patient 9) only both reflexive experiments were done because of the inability for him to perform the intentional experiment tasks properly.

7.5 Data analysis

The difference in the data analysis between the control subjects and the PD patients relies on the factor eye movement condition. As mentioned above, PD affects the ability of the patients to make voluntary or intentional saccades. Some patients could perform the saccade condition, but not all of them. To evaluate the oculomotor performance in the saccade condition, the variable *proportion of correct saccades* was defined as in the control subjects. All saccades with latencies below one second were counted separately for reflexive and intentional cue types. This number was divided by the total number of trials in the corresponding experiment. As only the saccade performance is important for this variable, all trials including those without joystick response were used for the calculation. This criterion for considering a saccade as "*correct*" reflects only the timing of the saccade but not the metric characteristics of the saccade, such as amplitude accuracy of the end position. This criterion was chosen because, in contrast to saccade metrics, the timing of the saccade can be measured with a precision, which is independent of the calibration of the IRIS system. Therefore, this criterion can be used to compare controls and patients. It is not sensitive to possible differences in the metric accuracy of the system between patients and controls. If more than one saccade was detected during one trial only the first one was taken into account. The evaluation of this variable was used to confirm the saccade performance under the influences of the different cues. As for the controls, the *proportion of correct saccades* defines a special measure of saccadic performance, different from the variable *saccade* *latency*. Figure 7.2 shows that the latency criterion of one second is long enough to include all saccades within the main population.

For the fixation condition another variable called *proportion of correct fixation* was defined as the number of trials without saccades or with saccades latencies greater than 1000 ms divided by the total number of trials. The proportion of the number of joystick responses was calculated in the same way as with the control subjects.

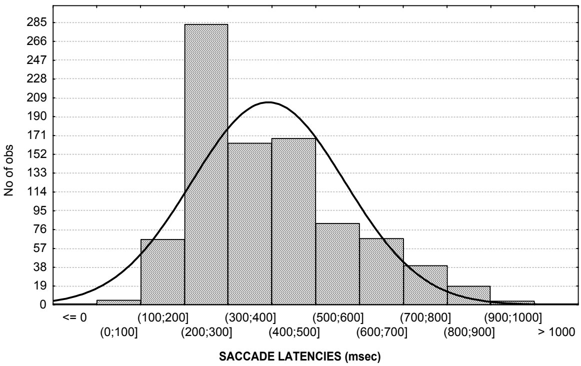

FIGURE 7.2: Histogram showing the distribution of saccade latencies for the Parkinson patients.

The discrimination performance for the Parkinson patients was evaluated only under the fixation condition. Thus, if the patients are not able to complete the saccade task for a particular cue type, but with this cue type they can shift their attention under fixation conditions that would be a good sign for the independence of both systems. If the deficit of the saccade and of control of attention always occurs under the same condition, then the impairments would seem to have a common origin. The discrimination performance was obtained in the same way as with the control subjects.

7.6 Results

7.6.1 Saccade Performance

Prior to statistical analysis the proportion of correct saccades for intentional and reflexive cues was submitted to a rank transformation (Appendix E). To evaluate under which condition the patients performed better, a t-test for dependent samples was applied between both variables. The results (Figure 7.3) show a better saccade performance under the reflexive cue than under the intentional cue with a p<.05.

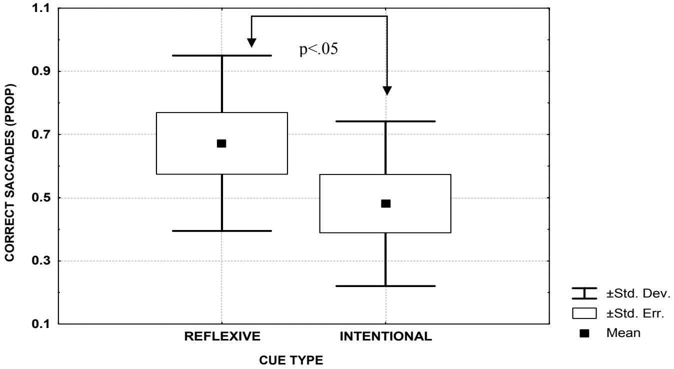

FIGURE 7.3: Results of the t-test. Proportion of correct saccades as a function of the factor cue type is shown. Significant differences between both levels were found. Standard deviation, standard error and mean for the variables are shown.

The comparison with the controls was carried out with repeated measures ANOVA. Again the *proportion of correct saccades* was rank transformed before the statistical analysis. The between factor was the group (control/patient) and the within factor was the cue type (intentional/reflexive). The control subjects performed better than the patients [F (1,16)=10.43; p<.0052]. Under the reflexive cue the saccade performance is better than under the intentional cue [F (1,16)=12.03; p<.0032]. The results of the t-test done for the controls did not show any difference between the saccade performance for the intentional and the reflexive cue. In contrast, the t-test for the patients showed better performance with the reflexive than with the intentional cue. This shows that the patients have a stronger impairment for the intentional cue type, although the interaction between the factors group and cue type did not reach significance [F (1,16)=2.94; p<.1059]. Figure 7.4 presents the data for the factors group (control/patient) and cue type (intentional/reflexive), the difference between controls and patients for the reflexive experiment tend to be smaller than for the intentional experiments. This tendency could become significant if more patients were measured.

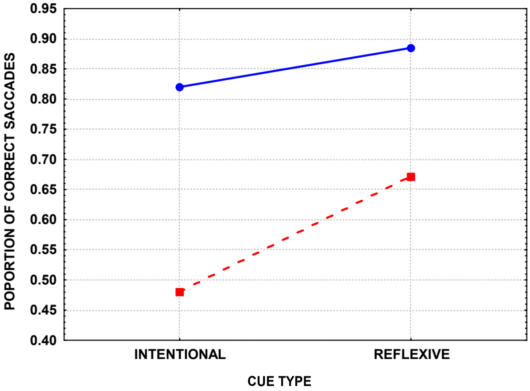

FIGURE 7.4: Proportion of correct saccades as a function of the factor cue type. The solid line indicates the controls and the dash line the patients.

7.6.2 Fixation Performance

After the rank transformation of the *proportion of correct fixation* (Appendix G), a t-test for dependent samples was used to evaluate the capability of the patients for fixating under the intentional and reflexive cue influences. The results did not show any difference in the fixation performance for both cues.

A two factorial RM-ANOVA with the between factor group (controls vs. patients) and within factor cue type (intentional vs. reflexive), showed no differences in the fixation performance for both groups. Figure 7.5 represents the fixation performance as a function of the cue type for controls and patients.

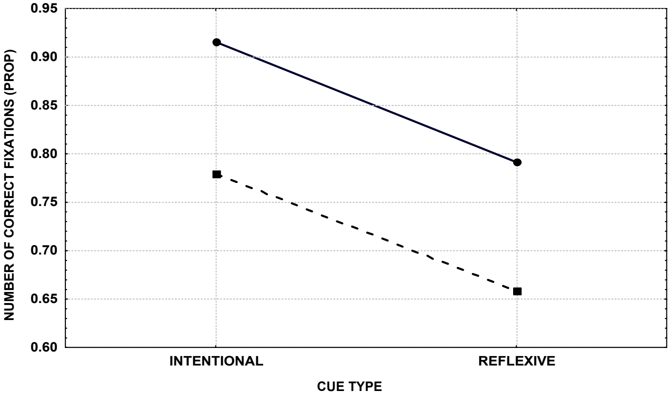

FIGURE 7.5: Proportion of correct fixations as a function of the cue type. Dash line indicates the values for the patients and normal line for controls.

7.6.3 Confidence

After a rank transformation, the *proportion of the number of joystick responses* (Appendix F) was evaluated using a three factorial RM-ANOVA with the factors: cue type (intentional vs. reflexive), eye movement condition (fixation vs. saccade), and trial type (valid vs. invalid). The results showed that the patients confidence was higher for the reflexive cue than for the intentional [F (1,7)=14.09; p<.0071]. Since no interaction between the factors trial type and cue type was observed, the effect of the cue type on the confidence can be considered to be identical for valid and invalid trials.

As with the controls, the PD patients also showed higher confidence for reflexive cues. An additional four factorial RM-ANOVA with the between factor group (controls vs. patients) and the within factors cue type, eye movement condition and trial type was used to evaluate the differences between both groups. The results (Figure 7.6) showed three significant main factors and no significant interactions. The factor group [F (1,16)=20.73; p<.0003] revealed that the control subjects had more joystick responses than the patients. Thus, they were more confident than the patients about their perceptual responses. In the reflexive cue condition both groups were more confident than in the intentional cue condition [F (1,16)=23.31; p<.0002]. The third main significant factor was the eye movement condition, showing more confidence in the fixation condition than in the saccade condition [F (1,16)=5.76; p<.0289]. Figure 7.6 presents the subjects' confidence under the different conditions.

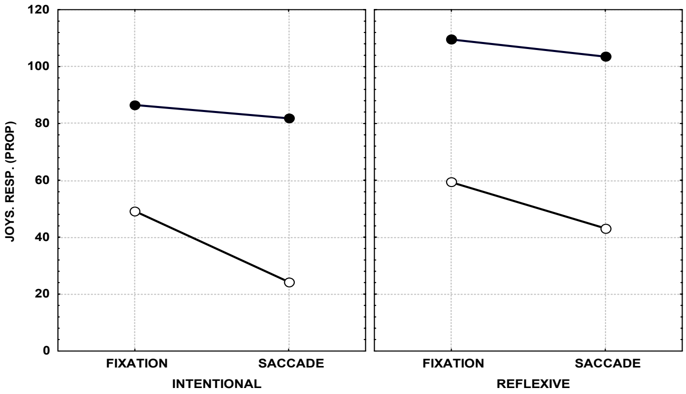

FIGURE 7.6: Subjects confidence showed as the proportion of the number of joystick responses as a function of the eye movement condition for intentional and reflexive cues. Filled circles are used for controls and open circles for patients.

7.6.4 Discrimination Performance

The proportion of correct joystick responses for valid and invalid trials for each fixation experiment was used to evaluate the discrimination performance for the patients group (Appendix H). One patient, who did not have any joystick response for invalid trials, was not included in the analysis. After the rank transformation of the data, a two-way RM-ANOVA was carried out, with the factors: cue type (intentional/reflexive) and trial type (valid/invalid): The results revealed no main effect or interaction of these different conditions on the patients' performances. Figure 7.7 represents the proportion of correct responses as a function of the trial type for intentional and reflexive experiments. Although the difference in the proportion of correct responses between valid and invalid trials was similar for patients and controls, this effect did not reach significance in the patients due to the large between subject variability.

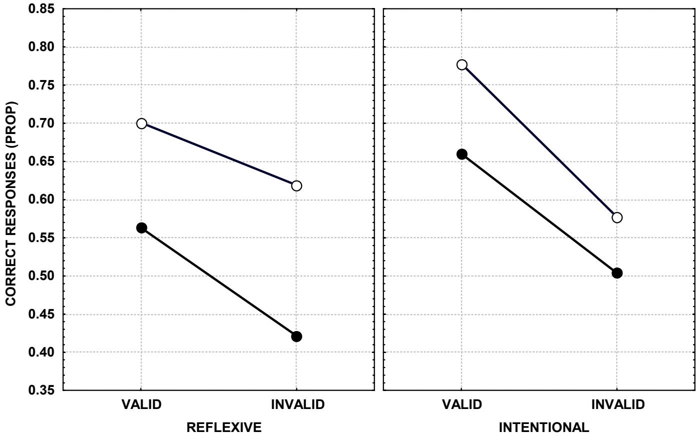

FIGURE 7.7: Discrimination performance as a function of trial type (valid/invalid) for reflexive and intentional cue. Open circles are used for controls and filled for patients.

Another RM-ANOVA (again with rank transformed data) with three factors evaluated the differences in the discrimination performance with the between subjects factor group (controls vs. patients) and the within subjects factors cue type (intentional/reflexive) and trials type (valid/invalid). The controls group has more correct responses than the patient group

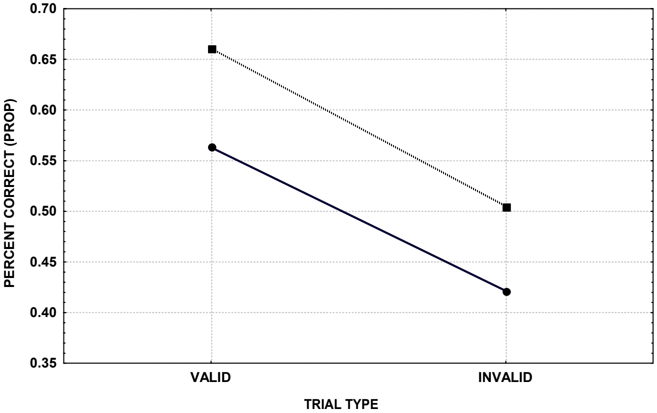

FIGURE 7.8: Proportion of correct responses as a function of the trial type. Dash line indicates discrimination performance for reflexive experiments and solid line for intentional.

(factor group; $p<0.05$). There are more correct responses for valid trials than invalid trials ($p<.01$). No interactions between the factors were found. Figure 7.8 shows the discrimination performance as a function of the trial type for intentional and reflexive cues.

7.7 Discussion

7.7.1 Saccade Performance

Crawford, T.J., et al. 1989, tested seven Parkinson patients in three different eye movement conditions (reflexive random, to remembered targets and temporal overlapped), the results of their study showed that patients with PD have a specific impairment in the generation of saccades to remembered targets. Using a reaction time criterion Briand et al. (1999) demonstrated that their subjects did not differ from controls in latency, error rates, or saccade accuracy when they performed a reflexive eye movement task. Nevertheless, when they performed an intentional task they were slower, made more errors and made saccades, which undershot the target.

According to the criterion used in the present study to classify saccades with correct timing, patients perform fewer correct saccades than controls. This impairment was observed for reflexive and intentional cue types. This criterion differs from other criteria that include latency characteristics (Briand et al., 1999). Moreover, the variable *proportion of correct saccades* was evaluated under a double task condition (motor task + discrimination task). Therefore, this variable cannot be interpreted as a measure of a pure oculomotor performance but must be seen in the context of the double task. The result that this measure was impaired in PD for reflexive and for intentional cues is unexpected on the basis of previous studies showing that reflexive saccades are nearly unaffected in PD. Most probably this difference is caused because we do not measure pure saccade performance but saccade performance in the double task. The attempt to solve the discrimination task does apparently lead to a suppression of the saccadic responses in the patients. This effect occurs for both reflexive and intentional cues. Nevertheless, the finding that the proportion of correct saccades was smaller for the intentional than for the reflexive cue type in PD and that this difference was not observed in the controls is in agreement with the concept of intentional movements being particularly affected in PD.

7.7.2 Fixation Performance

PD patients fixation performance for the intentional and the reflexive task did not differ. Moreover, no differences in the fixation performance were found after the comparison with the control subjects. Thus, PD does not seem to affect the capability of fixation.

The finding that the patients show impaired saccade performance, but good fixation is understandable because of the different mechanisms controlling saccades and fixations. In PD, the programming of the saccade is impaired and an enhancement of the suppression is found.

It is known that the fixation in PD is often disrupted by the increased frequency of square wave jerks, which may indicate a distorted fixation. Thus, the findings of this study point to a profound disturbance in saccade programming, which outlasts the fixation disturbance, resulting in a not-effect with normal fixation.

7.7.3 Confidence

As seen in the control group, PD patients were more confident in responding to the discrimination task with the reflexive cue type (see chapter 6.6.2). Because this effect is the same for valid and invalid cues (see section 7.6.3), it cannot be explained in terms of an effect of the cue type on the efficiency of the attention shift. A shift of the attention should always have the opposite effect on valid and invalid cues. For the controls this finding was interpreted to support the hypothesis that a reflexive activation of the dorsal stream facilitates perceptual processing. Following this argument, the similarity of the effect in PD suggests that such a reflexive activation of the dorsal stream and its facilitating effect on the perceptual processing also occurs in PD. This interpretation is compatible with the finding that in PD the saccade performance was more strongly impaired for the intentional than for the reflexive cue type (see chapter 7.7.1). Taking the saccade performance as a measure of the dorsal activation, one has to conclude that dorsal activation in PD is probably higher in the reflexive than in the intentional task. This explains why the facilitating effect of reflexive dorsal activation on the perceptual response can be observed in PD patents as well as in the control group.

The finding that the patients had significantly fewer joystick responses than the controls irrespective of the cue type shows that the visual perception mechanism in the ventral pathway is affected for both cue types.

Although neither for the patients nor for the controls the factor *eye movement condition* (saccade vs. fixation) showed a significant effect on the proportion of joystick responses. The common ANOVA with the data of both groups revealed that, compared to the saccade condition, the subjective confidence to respond increased significantly under the fixation condition. This main effect was greater for the patients than for the controls (Figure 7.6). Assuming that dorsal activation is higher in the saccade task than in the fixation task, the facilitating effect of dorsal activation on the perceptual processing would predict the opposite result. Based on this concept, better confidence would be expected for the saccade condition than for the fixation condition. However, taking into account that the subjective confidence may also depend on the general difficulty of the task, one can understand why the confidence to respond was less in the double task (discrimination + saccade) than in the single task (discrimination).

7.7.4 Discrimination Performance

Under the fixation condition, PD patients did not show any significant effect or interaction of the different cue types (reflexive/intentional) or trial types (valid/invalid) on the proportion of correct joystick responses. Their general discrimination performance was very close to chance level (0.5). The finding that the discrimination performance of PD patients was significantly smaller than that of the controls suggests that the perceptual mechanism of these patients (ventral pathway) is affected irrespective of the cue type (reflexive/intentional) or trial type (valid/invalid). This general impairment was not due to differences in their fixation ability (Figure 7.5) since the proportion of correct joystick responses was related to the number of trials with good fixations only (see section 6.3.2 and 6.3.4). In agreement with the generally accepted concept that PD mainly affects intentional movements, our PD patients showed a stronger impairment in the saccade performance for the intentional cue than for the reflexive cue (see section 7.6.1). But, contrary to our initial expectation, we did not find a particular impairment of the control of attention (as indicated by the difference of the perceptual performance between valid and invalid trials) for the intentional cue. This result suggests that the saccadic impairment in PD cannot be understood as a consequence of an attentional deficit. In terms of the VAM (Deubel and Schneider, 1996) this means that PD does not specifically affect the common selection mechanism (between the locations 1 and 2 in Figure 5.1). The impairment of the saccades in PD must be due to a lesion in the pathway that is specific for the generation of saccades (position 3 in Figure 5.1). Since this impairment is specific for intentional movements, it cannot explain the weak perceptual performance with both cue types. To explain this we suggest that PD affects not only a single location in the pathways for visual processing for perception and action. At least a second location must be affected too. In terms of the scheme of Figure 5.1, there are two possibilities: The second affected location could be in the common pathway (between locations 1 and 2 in Figure 5.1) or it could be specific to the object recognition (location 4 in Figure 5.1). Based on the findings of previous studies it seems that the target selection mechanism is working for reflexive saccades. Therefore, and because it is believed that the target selection mechanism is common for perception and action (Deubel and Schneider 1996), it seems unlikely that this mechanism is affected (locations between 1 and 2 in Figure 5.1). Thus, it is likely that the second damage affecting the perceptual performance in general concerns the ventral stream (location 4 in Figure 5.1) and is not an indirect consequence of an impaired target selection process. This hypothesis can also explain why the perceptual performance in PD was weak for valid and for invalid trials.

The finding that patients showed significantly more joystick responses for the reflexive task, even though the discrimination performance was not better for the reflexive than for the intentional task is also understandable with this hypothesis, since the higher confidence to give a perceptual response can be due to an activation of the ventral pathway by the reflexive activation of the dorsal pathway. Because the lesion at location 3 (Figure 5.1) does not affect reflexive saccades, this activation through the interactions between dorsal and ventral path (vertical arrow in Figure 5.1) would be possible in PD. However, the visual information necessary for correct discrimination would not reach the areas performing this discrimination because of the second lesion at location 3 (Figure 5.1).

Previous results in covert reflexive orienting in PD patients have reached no consensus (Rafal et al. 1984). Previous studies suggest a unique impairment in reflexive orienting in PD patients. Briand and Hening (2001) found that PD patients made visually-guided saccades faster than control subjects and concluded that automatic orienting processes are not affected in PD. Moreover, they concluded that these orienting processes are more active in PD. Yamaguchi and Kobayashi (1998) investigated reflexive and voluntary orienting in PD patients using different SOAs. They found that voluntary orienting of spatial attention is impaired in PD patients when sustained attention is required, but that the automatic shift of spatial attention is preserved. Brown and Marsden (1988) also support these results. Their theory is that PD patients' cognitive impairment is directly related to a decrement in the cognitive resources that are necessary to perform a given task. This depletion of processing resources is related to a frontal dysfunction, which will result in a deficit in a supervisory attention system (responsible for the modulation of lower cognitive operations, particularly when automatic responding cannot be used to perform a task).

On the other hand, Bennett et al. (1995) assessed covert visuospatial orienting and focusing of attention in PD patients and in controls. They found no differences between both groups in covert orienting, however when more than one attentional task had to be managed, dysfunction in PD became apparent.

Filoteo et al. (1997) found similar results than those of this study. They examined intentional and reflexive shifts of attention in PD patients. They found attentional impairments in both conditions, suggesting that PD patients may experience a rapid decay of the attentional inhibition that usually serves to bias subjects from shifting attention to an uncued location in the endogenous condition, and in returning attention to the cued location in the endogenous condition.

The differences between these results and previous works may be due to different factors: First, the number of patients investigated may not be large enough for statistical analysis of the data. Second, PD is a heterogeneous disease with in many different grades of severity and sometimes the clinical findings do not correspond with the anatomo-pathological findings (postmortem). This can lead to a very heterogenic group of patients with a very high variability.

These results suggest that PD patients have a specific impairment of intentional saccades, but that this impairment does not correlate with their attentional deficits. Deficits of attention in PD seem to be, at least in the population of this study, impaired irrespective of the nature of the cue used (intentional or reflexive). The explanation of these results that is proposed is that, in PD there is an additional general impairment of perception processes beside the impairment of the pathway for saccade generation, which is specific for reflexive saccades. The additional impairment of the perception process is likely to originate from a malfunction in the ventral pathway rather than from a general deficit of the common selection mechanism.

8 Experiment 3: Cerebellar Disorders

8.1 Introduction

The oculomotor vermis is a part of the posterior lobe vermis, which is known to have an important role in the control of eye movements. The oculomotor vermis projects mostly to the caudal part of the ipsilateral fastigial nucleus (FN) that is also important in the control of eye movements. Almost all that we know about the role of the cerebellum in the control of saccades comes from studies of these regions.

The cerebellum plays two important roles in the control of saccadic eye movements. The saccadic eye movements are so fast that there is not time for a visual feedback to direct the eyes to the desired target position. Therefore, the command for a saccade must be generated before the saccade starts. The cerebellum is not essential for the generation of the saccadic command, but once the command is started by the saccade pulse generator, the cerebellum has the capability to change on-line the generated pulse by means of a local, non-visual feedback loop. This correction mechanism helps to improve the accuracy, smoothness, speed, and consistency of the saccade. This is the short-term role of the cerebellum. However, the cerebellum also has a long-term role that adapts for inaccuracies of the motor commands under situations such as age, trauma or physical disability. The long-term adaptation may also be involved in compensating for target motion during the latency period and the saccade duration (Noda H, 1991).

After FN lesion, saccades become slower, inaccurate, and abnormal in size (either hypermetric or hypometric saccades) and speed. Other saccade abnormalities after cerebellar damage include difficulties in fixation, and the necessity of doing multiple saccades to fixate a new relevant target

After unilateral inactivation of FN by means of injection of the GABA-agonist Muscimol in rhesus macaques (Robinson et al 1993) the following saccade changes can be seen: under normal conditions the gain (saccade size/distance to the target) is approximately 1, after the injection of Muscimol in the FN the gain is more variable and depends strongly on the direction (ipsi/contraversive to the lesion side) whereby ipsiversive saccades are too large (hypermetric) and quick, and contraversive saccades too small (hypometric) and slower. The last abnormality refers to the trajectory of vertical saccades, which is usually quite straight. After unilateral injections, the trajectories are strongly curved. After bilateral inactivation both ipsilateral and contralateral saccades are too large and the vertical saccades do not curve.

Previous investigations suggest that patients with cerebellar pathology have difficulty in switching off the attentional set. Courchesne et al (1997) provided evidence that children with cerebellar pathology (autism or neurological insult) are impaired in their ability to rapidly alternate attention between two different sensory channels. The difficulty for these patients in performing the attention shifting task has been hypothesized to reflect a problem in rapidly coordinating mental activity. Ravizza and Ivry (2001) tested adult patients with acquired cerebellar lesions to investigate whether their impairment was similar to that of children. Their results showed that cerebellar patients with cerebellar pathology are impaired in rapidly shifting attention between different perceptual dimensions.

In the next experiments, the hypothesis that cerebellar patients have a specific impairment of reflexive saccades and that this is caused by a specific deficit in reflexive attention shifts will be tested.

8.2 Methods

The subjects were five patients between 40 and 68 years old; none of them had previous experience with oculomotor experiments. All of them were investigated at least 5 days after they arrived in the Neurology Department. All patients were assessed using the Mini Mental State Examination (MMSE). None of them showed any signs of dementia or abnormal cognitive functioning on the MMSE. The clinical ratings of the patients are shown in table 8.1. All the patients were receiving their normal medication at the time of the testing. The vision of those patients, who normally wear glasses, was corrected during the experiments.

Patient	Age/Sex	Diagnosis
1	68/M	Stroke (Left A. Cerebelli Superior)
2	57/F	Stroke (Left A. Cerebelli Superior)
3	44/F	Cerebellar metastases
4	69/F	Cerebellar Atrophy
5	40/M	Stroke (Left A. Cerebelli Superior)

TABLE 8.1. Patient details and diagnosis

8.3 Apparatus

The same procedure as with the control subjects was used with the cerebellar patients. In all patients the eye movements were assessed before the experiments. If calibration was not possible, the patient was not accepted to take part in the experiments. If it was considered that the patient did not understand the task properly, a complete training experiment was run before the beginning of the real experiments to familiarize the subjects with the experimental procedure. If after this training experiment, they still could not perform the task, the patient was not recorded. The results of the training experiments were not used for the final results.

8.4 Experimental Procedures

The same experiments with the same characteristics for the factors cue type (intentional/reflexive), eye movement condition (saccade/fixation) and trial type (valid/invalid trials) were done with the cerebellar patients as with the PD patients. The cue relevance used was 75/25. The cue relevance 50/50 was not used because the experiment requires a lot of concentration and the patients get tired more easily than the control subjects.

For one patient (number 5) one fixation experiment was not done because of time limitations. The data of this patient were used only in the evaluation of the saccades experiments together with the other patients. Therefore, the evaluation of fixation conditions was done with one patient less than in the saccade conditions.

8.5 Data analysis

The data analysis of the cerebellar patients was the same as that of the PD patients. The same variables (proportion of correct saccades, correct fixation, proportion of joystick responses and discrimination performance), with the same calculations were used for both groups of patients. The histogram of the saccade latencies (Figure 8.2) shows that the timing criteria used for the variable proportion of correct saccades was not too short for the cerebellar patients. The figure shows the saccade latencies of all the cerebellar patients for both saccade experiments (intentional and reflexive). The results of the histogram revealed that there are no saccades after one second and that no relevant data were excluded using this timing criterion.

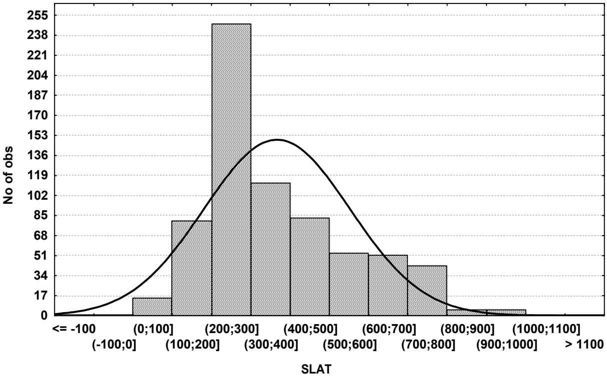

FIGURE 8.2: Histogram showing the distribution of saccade latencies for the cerebellar patients.

8.6 Results

8.6.1 Saccade performance

The proportion of correct saccades for intentional and reflexive cues (Appendix E) was submitted to a rank transformation before statistical analysis. To evaluate under which

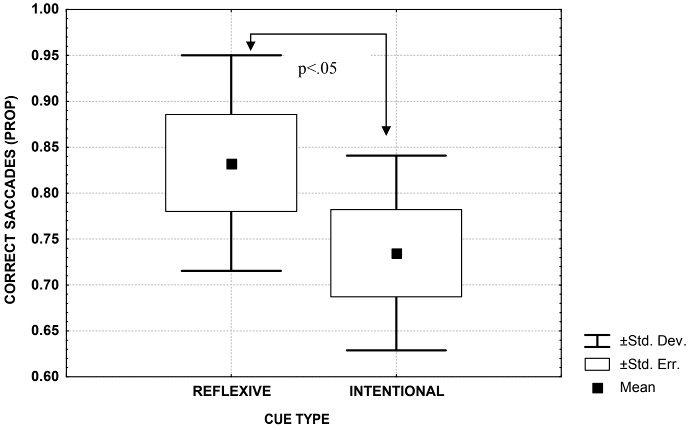

FIGURE 8.3: Results of the t-test. Proportion of correct saccades as a function of the factor cue type is shown. Significant differences between both levels were found. Standard deviation, standard error, and mean for the variables are shown.

condition the patients had better performance a t-test for dependent samples was applied between both variables. The results (Figure 8.3) show a better saccade performance under the reflexive cue than under the intentional cue with a p<.05.

The comparison with the controls and the PD patients was carried out with repeated measures ANOVA on the first rank transformed proportion of correct saccades. The between factor subjects with three levels was the group (control/PD patient/cerebellar patient) and the within factor was the cue type (intentional/reflexive). The control subjects performed better than the patients and the cerebellar patients better than PD patients [F (2,20)=6.17; p<.0082]. Under the reflexive cue the saccade performance is better than under the intentional cue [F (1,20)=14.77; p<.0010]. Although no interaction between the factors group and cue type was found [F (2,20)=.24; p<.7824], the main effect of the factor cue type was mainly due to the patients influence (Figure 8.4). This was confirmed by a t-test showing significant differences in the saccade performance for PD and cerebellar patients, but not for controls.

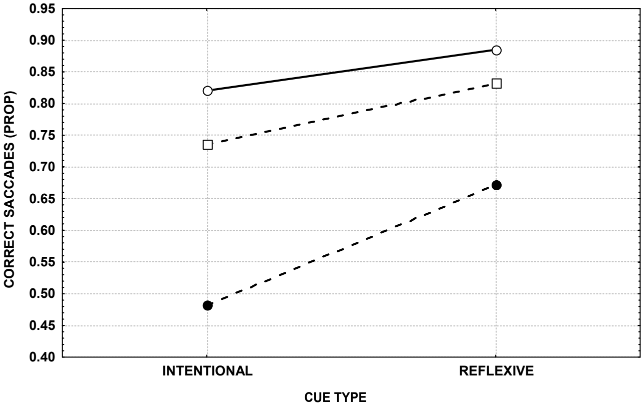

FIGURE 8.4: Proportion of correct saccades as a function of the factor cue type. The solid line indicates the control subjects, the dash line with open ends indicates the cerebellar patients and the dash line with closed ends the PD patients.

8.6.2 Fixation performance

After the rank transformation of the *proportion of correct fixations* (Appendix G), a t-test for dependent samples was used to evaluate the capability of the patients to fixate under the intentional and reflexive cue influences. There was no difference between both cue types (p=.16).

A two factorial RM-ANOVA with the between factor group (controls/ PD patients/ cerebellar patients) and within factor cue type (intentional vs. reflexive), showed no differences in the fixation performance for the main factor group [F (2,19)=2.4; p<.1176]. Nevertheless, the main factor cue type was significant, indicating that overall for the three groups more correct fixations were done for the intentional cue type [F (1,19)=6.31; p<.0212]. The interaction between both factors was not significant [F (2,19)=.87; p<.4352]. Figure 8.5 represents the fixation performance as a function of the cue type for controls and both patients groups.

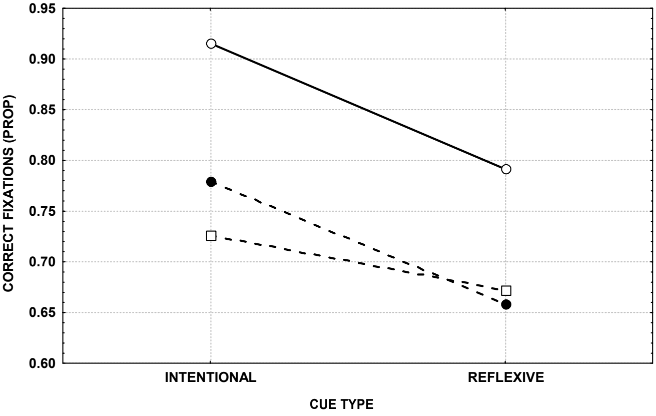

FIGURE 8.5: Proportion of correct fixations as a function of the cue type. The solid line indicates the controls, the dash line with open ends indicate the cerebellar patients and dash line with close ends the PD patients.

8.6.3 Confidence

The *proportion of the number of joystick responses* (Appendix F) was not distributed normally; therefore the data were submitted to a rank transformation before statistical analysis. To compare the confidence of the cerebellar patients with that of the subjects of the two previous experiments a four factorial RM-ANOVA with the between subjects factor group (control/ PD patients/ cerebellar patients) and the within subjects factors cue type (intentional/ reflexive), eye movement condition (fixation/ saccade), and trial type (valid/ invalid) was performed. The results (Figure 8.6) showed two significant main effects and one significant interaction. The factor group [F (2,19)=16.60; p<.0001], revealed that the control subjects had more joystick responses than the patients. The control subjects respond on average in 76%, PD patients in 37% and cerebellar patients in 35% of all trials Thus, the controls were more confident than the patients in pressing the joystick. No differences between both groups of patients were found. In the reflexive cue condition the confidence was higher than in the intentional cue condition [F(1,19)=32.62; p<.0001]. The interaction between the factors eye movement condition and trial type was significant [F (1,19)=5.04; p<.0369]. Figure 8.6 presents the proportion of the number of responses as a function of the cue type for fixation and saccade experiments. The interaction between the factors eye movement condition and trial type was mainly due to the observation that for control subjects and PD patients the eye movement condition did not affect the confidence (control subjects, Scheffé: p<.89; PD patients, Scheffé: p<.99), whereas cerebellar patients, in the saccade condition, were less confident for valid than for invalid trials (cerebellar patients, Scheffé: p<.049).

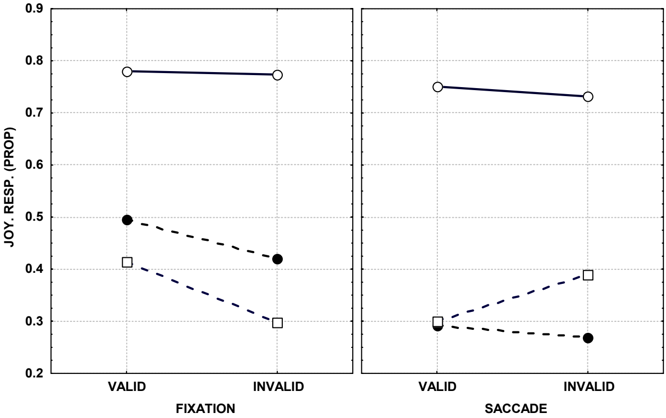

FIGURE 8.6: Proportion of the number of joystick responses as a function of the trial type for the fixation and the saccade eye movement condition. The solid line indicates the controls, the dash line with open ends indicate the cerebellar patients and dash line with closed ends the PD patients.

8.6.4 Discrimination performance

As in the controls and in the PD patients, the proportion of correct joystick responses for valid and invalid trials for each fixation experiment was used to evaluate the discrimination performance for the cerebellar patients (Appendix H). Two patients, who did not have any joystick response for invalid trials, were not included in the analysis. A two-way RM-

ANOVA was carried out on the rank transformation of the proportion of correct joystick responses of the cerebellar patients, with the factors: cue type (intentional/reflexive) and trial type (valid/invalid). Both main effects were not significant, but the interaction was significant [F(1,1)=289.00; p<.0374]. This interaction was due to increased performance in valid trials for the reflexive cue. Figure 8.7 represents the proportion of correct responses as a function of the trial type for intentional and reflexive experiments.

A three-way RM-ANOVA (on the rank transformed proportion of correct joystick responses), was used to compare the perceptual performance under the fixation condition between the groups. The between subjects factor was group (controls / PD patients/ cerebellar patients) and the within subjects factors were cue type (intentional/reflexive) and trial type (valid/invalid). The factor trial type showed a significance [F (1,16)=11.59; p<.0036] with the valid trials having overall a greater proportion of correct responses than the invalid trials. Figure 8.8 shows the discrimination performance as a function of the trial type for intentional and reflexive cues. The mean perceptual performance of the PD patients was impaired with respect to the controls (see section 7.6.4). In contrast, the cerebellar patients did not show such a systematic impairment. Their perceptual performance was even worse than that of the PD patients for the intentional cue (Figure 8.8, left side) but closer to the performance of the controls for the reflexive cue (Figure 8.8, right side). Because of this difference of the performance of the cerebellar patients between the different conditions, the main effect in the

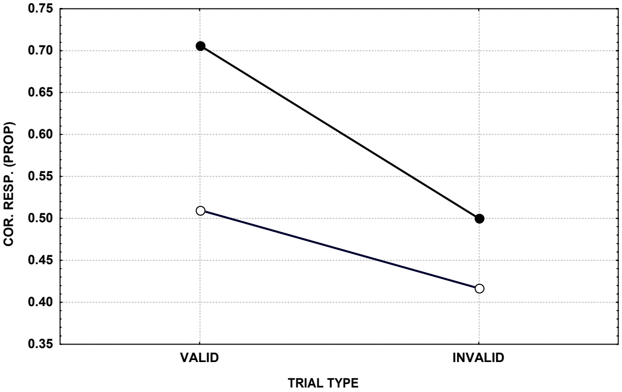

FIGURE 8.7: Proportion of correct responses as a function of the trial type. Open end for intentional and closed end for reflexive are used.

factor group did not reach significance. No interaction between the factor trial type and the other factors was observed, indicating that the cue effect on the perceptual performance was similar for all subjects groups and for the two different cue types.

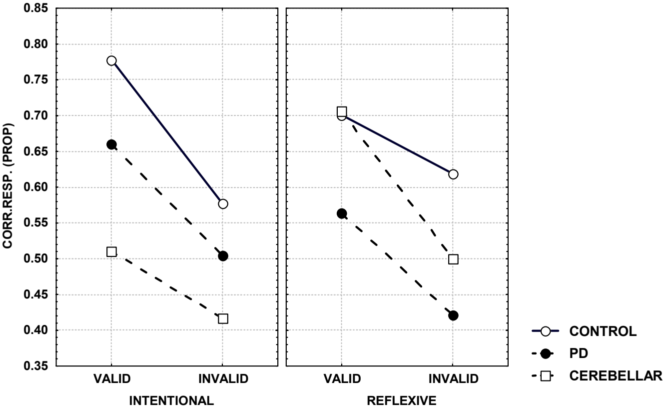

FIGURE 8.8: Discrimination performance as a function of the trial type for intentional and reflexive cue types.

8.7 Discussion

8.7.1 Saccadic Performance

The finding that cerebellar patients' saccadic performance, similar to that of the control group and the PD patients, was better for the reflexive than for the intentional cues differs from the initial expectation that said that cerebellar patients impairment is larger for reflexive cue types.

The finding that cerebellar patients saccadic performance is worse than that of control subjects for both cue types is most probably due to the special measure for evaluating the saccadic performance. As already mentioned in section 7.7.1, this measure evaluates the saccadic performance in a double task (saccade + discrimination) and reflects not only a motor performance, but also the effect of a simultaneous perceptual task on the motor performance. Therefore, the finding that the saccade performance was impaired for both cue types in both patient groups reflects the problems the patients had with the double task.

The finding that cerebellar patients performance is better than that of PD patients can be explained by the hypothesis that the basal ganglia are more important for the correct performance of the double task than the cerebellum. The pattern of attentional deficits does not appear to be associated with the severity of the PD patients' motor disability (Filoteo et al., 1997), but there are no previous studies comparing PD patients and cerebellar patients.

8.7.2 Fixation Performance

The finding that the fixation performance of the cerebellar patients and the PD patients did not differ suggests that neither PD nor cerebellar disease affect the fixation ability. Thus, the parts of the dorsal pathway (see Figure 5.1) responsible for the fixation performance or the suppression of the motor task) seem to be unaffected in PD and in cerebellar disease.

The general better fixation performance for intentional cue type than for reflexive cue type, and the finding that the opposite was true for saccade performance can probably be explained by the hypothesis that for the reflexive cue type the dorsal pathway is activated strongly, a condition that would lead to the more reliable execution of saccades. In contrast, for the intentional cue, this activation is probably weaker. This can explain why under this condition it was easier to suppress erroneous reflexive saccades in the fixation task.

8.7.3 Confidence

The control subjects were more confident than both patient groups. With respect to the difference between reflexive and intentional cues, the confidence of the cerebellar patients to perform discrimination was similar to that of PD patients and controls. All three groups of subjects always showed more joystick responses for the reflexive than for the intentional cue. For the controls as well as for the PD patients this effect was interpreted as an indication that reflexive activation of the dorsal stream facilitates perceptual processing. This could be a possible explanation for the cerebellar patients too.

8.7.4 Discrimination Performance

In the cerebellar patients, under the fixation conditions, the discrimination performance was better for reflexive than for intentional cues This finding parallels our observations concerning the subjective confidence of the perceptual response and suggests (see section 8.7.3) that the object recognition of the ventral pathway works better for reflexive than for intentional cues. This can be explained with the same hypothesis, used in the previous section, arguing that there may be a facilitation of perceptual processes in the ventral stream by reflexive activation of the dorsal stream. This could also explain why the perceptual performance of the cerebellar patients was better for reflexive than for intentional cues.

For the PD patients it has been argued (see section 7.7.4) that the perceptual deficit observed for both cue types is not an indirect consequence of an impaired target selection process, because this target selection process, according to the VAM (Deubel and Schneider, 1996), seems to be common for saccades and perception, and because many previous studies have demonstrated that the target selection mechanism for reflexive saccades works almost perfectly in PD. Thus, the impaired discrimination performance of PD patients cannot be explained by the deficits of the target selection mechanism.

This argument cannot be applied in the same way for the cerebellar patients because the main difference between cerebellar and PD patients was that the cue effect on the perceptual performance (as indicated by the difference between valid and invalid trials) did not depend on the cue type (reflexive/intentional) in PD patients (see Figure 7.7), whereas such interaction was observed for the cerebellar patients, indicating a bigger cue effect for reflexive cues (Figure 8.7). Thus, in contrast to the PD patients, the better discrimination performance with reflexive than with intentional cues seems to be related to a more efficient attention shift with reflexive cues. Under fixation conditions, cerebellar patients had more problems with intentional than with reflexive attention shifts. Although there is no obvious reason why such impairment should occur in cerebellar patients, this hypothesis is compatible with physiological findings. It is known that the cerebellum is connected with the FEF, which plays an important role in intentional attention shifts. The cerebellum is directly connected with the thalamus and a connection between the thalamus and the ventral stream has been proposed (Fukushima, 2003). If a cerebellar disease affects the pathways between the cerebellum and the FEF or between the cerebellum and the thalamus, the object recognition capability of the ventral stream may be impaired.

Both patients showed a larger number of correct saccades with the reflexive cue. Thus, in contrast to PD patients, saccade performance in the cerebellar patients showed a similar dependence on the cue type as the cue effect on the discrimination performance. However, because our measure of saccade performance did not only represent an oculomotor capability of the subjects, but also the interference of perceptual task and motor task, it is not possible to draw the conclusion that (differently from the PD) the saccade deficits of cerebellar patients would be the consequence of the impaired intentional control of attention. This is especially unlikely because, in the oculomotor single task, cerebellar patients do not show a particular impairment of intentional saccades. This result rather suggests that cerebellar patients may have a particular problem with covert attention shifts.

These results are in agreement with previous experiments. Ravizza and Ivry (2001) designed two experiments to investigate in which grade the basal ganglia and cerebellum are implicated in shifting attention, employing an alternating attention task. Their results revealed that the performance of the cerebellar group improved significantly when the motor demands of the attention shifting task were reduced, suggesting that the performance deficit in the cerebellar patients appears to arise from the interaction of the motor and cognitive demands required in the alternating attention task, and that this deficit will be most pronounced when the motor demands are high.

9 General Discussion

The aim of this study was to assess the relationship between covert and overt attention and saccadic eye movements. In the last years, anatomical studies have demonstrated that the output from the basal ganglia and cerebellum project to the frontal cortex, and neuropsychological and neuroimaging studies have implicated the basal ganglia and cerebellum in non-motor aspects of cognition. Moreover, studies investigating saccades in Parkinson's Disease (PD) patients suggest that basal ganglia disorders affect more intentional than reflexive saccades. The second part of the study tested the hypothesis that the impairment saccades in Parkinson's Disease (PD) are a direct consequence of the deficit in control of intentional attention shifts in these patients.

The third part of the study tested the hypothesis that cerebellar patients have a specific impairment of reflexive saccades and that this is caused by a specific deficit in reflexive attention shifts.

In 1995, Schneider proposed the neuro-cognitive Visual Attention Model (VAM). This model is concerned with two main functions of visual attention: selection for object recognition and selection for space based motor action. Schneider proposed that these two functions share a common visual attention mechanism. The main task of this mechanism is to select information from a single object and to send its parameters for an eventual motor action through the dorsal stream ("where"-pathway), and to select important information from this object for recognition in the ventral stream ("what"-pathway). One year later, Deubel and Schneider (1996) investigated the spatial interaction of visual attention and saccadic eye movements in a dual-task paradigm. The results argue for an obligatory and selective coupling of saccade programming and attention to one common target object.

Experiment 1 used a modification of the paradigm used by Deubel and Schneider. Analysis of discrimination performance in this study suggests that this common attentional mechanism is not only valid when the subjects saccade, but also under fixation. Discrimination is always better for valid than for invalid trials irrespective of the eye movement condition. The results of this experiment also suggest that under reflexive conditions the object recognition in the ventral stream is better than under intentional conditions. There are connections between the dorsal and ventral streams (Milner & Goodale; 1993). These results could be interpreted as a facilitation with the reflexive activation of the dorsal stream exerts on the ventral stream. In contrast to this improvement of the discrimination performance in the entire visual field, the attentional effect is bigger for intentional than for reflexive cues, indicated by the bigger difference in the discrimination between valid and invalid trials for intentional cue types. The finding that the discrimination was always better for valid than for invalid trials irrespective of the cue relevance, suggests that the coupling between the selection process and motor action is obligatory and that the decoupling of both tasks is impossible. This supports the results of Deubel and Schneider (1996).

In recent years, anatomical studies have demonstrated that the output from the basal ganglia and cerebellum project to the frontal cortex, and neuropsychological and neuroimaging studies have implicated the basal ganglia and cerebellum in non-motor aspects of cognition. Moreover, studies investigating saccades in Parkinson's Disease (PD) patients suggest that basal ganglia disorders affect more intentional than reflexive saccades. The second part of the study tested the hypothesis that the impairment saccades in Parkinson's Disease (PD) are a direct consequence of the deficit in the control of intentional attention shifts in these patients. The third part of the study tested the hypothesis that cerebellar patients have a specific impairment of reflexive saccades and that this is caused by a specific deficit in reflexive attention shifts.

Previous investigations have failed to reach a consensus about the cognitive deficits in PD and whether these deficits are related to the eye movement disorders associated with the disease or not. The results of Experiment 2 suggest that PD patients have a specific impairment of intentional saccades, but that this impairment does not correlate with their attentional deficits. Deficits of attention in PD seem to be, at least in the population of this study, impaired irrespective of the nature of the cue used (intentional or reflexive). The explanation of these results that is proposed, is that, there is an impairment of perception processes in PD and that this impairment can be due, either to the false output coming from the area V1, or to the ventral pathway information itself. In contrast to these results, previous investigations have found that PD has a specific impairment of reflexive attention shifts (Brown RG, Marsden CD, 1988; Yamaguchi S, Kobayashi S, 1998; Filoteo et al. 1997; Briand et al. 1999, 2001). In contrast to this study, all of these investigations used reaction time paradigms to allocate the attention of their subjects. In this study we do not deny these results, but we argue that when the patients have to perform a dual-task paradigm, their impairment is independent of the cue type.

The results of Experiment 3 suggest that cerebellar patients make better reflexive saccades than intentional saccades, and this saccade impairment is correlated with their better ability to recognize objects under reflexive cue instructions. Thus, the cerebellum plays an important role either in both the cognitive processes and motor task preparation. These results are supported by previous experiments.

Ravizza and Ivry (2001) designed two experiments to investigate in which grade the basal ganglia and cerebellum are implicated in shifting attention. The paradigm used for this end was an alternating attention task. In the first experiment, there were two types of targets presented in two different streams; one was visual and the second auditory, with their respective distractors, one in each stream. Subjects were instructed to switch between the two dimensions, responding to a target in one dimension, then to a target in the other dimension and so forth. In the second experiment, a modification of the alternating attention task, which reduced the motor requirements, was used. The attentional requirements were the same as in the first experiment, but overt responses were only required to targets on one modality. In the first experiment, the performance of both groups was similar. But in the second experiment, when the motor demands were reduced, cerebellar patients showed a significant improvement in the alternating attention task, whereas the Parkinson patients continued to exhibit an impairment. The conclusion of this study was that the performance of the cerebellar group improved significantly when the motor demands of the attention shifting task were reduced, suggesting that the performance deficit in the cerebellar patients appears to arise from the interaction of the motor and cognitive demands required in the alternating attention task, and that this deficit will be most pronounced when the motor demands are high.

10 Summary

The relation between covert and overt spatial attention and saccadic eye movements was investigated in control subjects, Parkinson's Disease (PD) patients, and cerebellar patients in a dual-task paradigm. The main question was how different types of cues (reflexive/intentional) guide the spatial attention during fixation or during the preparation phase of a saccade. The subjects were asked to follow a reflexive or intentional cue, to discriminate a character that appeared either at the cued side (valid trials) or at the non-cued side (invalid trials), and to respond by pressing a joystick. The proportion of valid/invalid trials (cue relevance) was 75/25 and 50/50 for the control subjects, for the patients only the proportion 75/25 was used. All discrimination tasks were performed during the preparation of the saccade to the cued target and also during fixation. The results of the control subjects showed that discrimination of the character is always better at the cued side irrespective of the eye movement condition or the cue relevance, suggesting that spatial attention is engaged at the cued location even under fixation conditions and irrespective of the relevance of the cue. The results of the PD patients point to an intentional saccade impairment that does not correlate with the overall impairment in the attentional control. In the double task, also cerebellar patients showed an intentional saccade impairment that correlates with the deficit in the attentional control. After these experiments further research could investigate the impairment of the patients shown here is true for all cerebellar disorders.

11 Zusammenfassung

In dieser Arbeit wurde der Zusammenhang zwischen sakkadischen Augenbewegungen und der Kontrolle der räumlichen Aufmerksamkeit bei Patienten mit M. Parkinson, mit Erkrankungen des Kleinhirns, und bei einer Kontrollgruppe gesunder Probanden untersucht. Insbesondere interessierte dabei die Frage, wie unterschiedliche Typen von räumlichen Hinweisreizen (reflexiv/intentional) die räumliche Aufmerksamkeit während der Fixation oder in der Vorbereitungsphase einer Augenbewegung bestimmen. Dabei wurde ein Paradigma mit einer Doppelaufgabe verwendet, in dem die Versuchpersonen, einem reflexiven oder intentionalen Hinweisreiz folgend, einerseits eine Sakkade, und andererseits eine Diskriminationsaufgabe (Buchstaben erkennen) ausführen mussten. Der Buchstabe erschien kurze Zeit nach dem Hinweisreiz, wurde jedoch vor dem Sakkadenbeginn bereits wieder ausgeblendet. Der Diskriminationsreiz erschien entweder auf der durch den Hinweisreiz gekennzeichneten (gültiger Hinweisreiz) oder auf der ihr gegenüberliegenden Seite (ungültiger Hinweisreiz). Bei der Kontrollgruppe wurden gültige und ungültige Hinweisreize entweder im Wahrscheinlichkeitsverhältnis drei zu eins (75/25: relevanter Hinweisreiz) oder mit gleicher Wahrscheinlichkeit (50/50 irrelevanter Hinweisreiz) angeboten. Bei den Patientengruppen wurden nur relevante Hinweisreize (75/25) verwendet. Alle Diskriminationsaufgaben wurden sowohl während der Vorbereitungsphase der Sakkade auf das durch den Hinweisreiz gekennzeichnetes Ziel, als auch während stabiler Fixation durchgeführt.

Die Ergebnisse der Kontrollgruppe zeigen, dass bei gültigen Hinweisreizen die Diskriminationsleisung immer besser als bei ungültigen war, und zwar gleichermaßen während der Fixation wie während der Augenbewegungsvorbereitung. Auch die Relevanz des Hinweisreizes hatte kaum Auswirkung auf die aufmerksamkeitsbestimmende Wirkung des Hinweireizes. Dies galt sowohl für reflexive als auch für intentionalle Hinweisreize. Dies zeigt, dass die Effizienz sowohl reflexiv als auch intentional gesteuerte Aufmersamkeitskontrolle weder von der Ausführung der Blickbewegung, noch von der Relevanz des Hinweisreizes notwendig abhängt. Die Patientengruppe mit M. Parkinson zeigte ein spezifisches Defizit bei intentional gesteuerten Sakkaden, ihre Diskriminationsleistung war jedoch sowohl bei intentionalen, wie auch bei reflexiven Hinweisreizen beeinträchtigt. Auch die Gruppe der Kleinhirnpatienten zeigte in der Doppelaufgabe ein ausgeprägtes Defizit der Sakkadensteuerung bei intentionalen Hinweisreizen. Im Unterschied zu den Patienten mit

M. Parkinson, zeigten Kleinhirnpatienten jedoch auch eine Beeinträchtigung der Diskriminationsleistung, die spezifisch für intentionale Hinweisreize war. Inwieweit diese Eigenheit der in dieser Arbeit untersuchten Kleinhirnpatienten allgemein für beliebige Kleinhirnerkrankungen gilt, könnte Gegenstand zukünftiger Studien sein.

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13 Appendix

Appendix A: Proportion of correct responses (control subjects)

C-R	IFS	IFO	ISS	RSO	RFS	RFO	RSS	RSO
50/50	.417	.579	.774	.552	.467	.464	.600	.500
	.870	.654	.952	.652	.931	.630	1.000	.621
	.750	.391	.667	.348	.542	.462	.700	.500
	.762	.450	.500	.400	.546	.542	.756	.625
	.964	1.000	.957	1.000	.900	1.000	.862	1.000
	.786	.813	.964	.897	.893	.704	.938	.719
	.710	.500	.667	.500	.536	.448	.567	.355
	.926	.571	.722	.500	.875	.533	.690	.531
	.385	.500	.565	.455	.531	.571	.600	.643
	.963	.360	.750	.800	.677	.567	1.000	.546
75/25	.606	.364	.773	.467	.342	.625	.914	.400
	.977	.857	.949	.714	.952	.643	.953	.625
	.694	.833	.731	.571	.737	.571	.725	.667
	.790	.286	.909	.286	.629	.556	.727	.667
	.871	.667	1.000	.500	1.000	1.000	.889	.778
	.805	.500	.800	.500	.696	.667	.894	.933
	.657	.667	.688	.364	.667	.333	.598	.643
	.771	.539	.539	.167	.696	.546	.590	.455
	.718	.333	.556	.500	.644	.625	.735	.571
	.892	.727	.875	.667	.646	.625	.729	.667

LEGEND: C-R: Cue Relevance; IFS: Intentional Fixation Valid Trials; IFO: Intentional Fixation Invalid Trials; ISS: Intentional Saccade Valid Trials; ISO: Intentional Saccade Invalid Trials; RFS: Reflexive Fixation Valid Trials; RFO: Reflexive Fixation Invalid Trials; RSS: Reflexive Saccade Valid trials; RSO: Reflexive Saccade Invalid Trials.

Appendix B: Proportion of the number of joystick responses (control subjects)

C_R	IFS	IFO	ISS	ISO	RFS	RFO	RSS	RSO
50/50	.774	.613	.969	.906	.938	.903	.781	.563
	.719	.813	.656	.742	.906	.844	.906	.906
	.750	.719	.553	.605	.750	.813	.625	.625
	.467	.417	.217	.313	.688	.750	.938	1.000
	.875	.844	.719	.469	.938	.968	.906	.875
	.875	1.000	.903	.935	.875	.844	1.000	1.000
	.969	.875	.750	.813	.903	.906	.938	.969
	.844	.656	.581	.452	1.000	.938	.906	1.000
	.813	.875	.719	.688	1.000	.875	.938	.875
	.730	.676	.516	.484	.969	.938	1.000	1.000
75/25	.688	.733	.917	.938	.809	1.000	.729	.625
	.896	.933	.830	.933	.875	.875	.896	1.000
	.766	.400	.591	.500	.844	.933	.833	.800
	.413	.438	.458	.438	.745	.600	.595	.682
	.705	.429	.512	.167	.682	.643	.837	.643
	.872	.875	.851	1.000	.958	.938	.979	.938
	.729	.800	.696	.688	.894	.938	.896	.875
	.729	.813	.646	.563	.479	.688	.875	.938
	.813	.750	.574	.500	.938	1.000	.459	.667
	.771	.688	.833	.800	1.000	1.000	1.000	.938

LEGEND: C-R: Cue Relevance; IFS: Intentional Fixation Valid Trials; IFO: Intentional Fixation Invalid Trials; ISS: Intentional Saccade Valid Trials; ISO: Intentional Saccade Invalid Trials; RFS: Reflexive Fixation Valid Trials; RFO:Reflexive Fixation Invalid Trials; RSS: Reflexive Saccade Valid trials; RSO: Reflexive Saccade Invalid Trials.

Appendix C: Joystick Latencies (control subjects)

C-R	IFS	IFO	ISS	ISO	RFS	RFO	RSS	RSO
50/50	786.458	842.316	1039.419	1155.000	641.333	721.571	879.760	864.611
	525.609	789.077	447.476	561.174	546.276	603.037	491.586	599.069
	841.833	912.522	993.952	1146.478	861.833	886.654	791.300	811.600
	593.333	437.522	800.700	834.933	559.864	506.500	649.178	617.875
	823.714	807.000	784.435	1081.800	740.233	735.833	931.621	912.964
	847.179	905.063	674.857	918.207	697.821	771.148	762.281	807.938
	453.452	456.643	488.250	521.115	351.107	332.207	448.833	430.419
	769.000	959.333	807.889	958.286	782.125	843.167	566.103	611.125
	749.885	701.286	1072.826	1157.955	466.406	484.571	992.933	892.393
	685.000	810.833	837.313	902.400	872.742	861.933	702.188	747.485
75/25	817.030	729.727	893.841	886.000	967.395	1100.500	653.686	610.600
	685.023	802.357	670.077	942.143	498.571	647.500	397.372	456.750
	1020.361	993.833	1400.923	1680.857	829.474	752.929	756.000	674.333
	932.790	722.429	718.227	1083.429	628.629	709.556	501.477	467.333
	827.807	1040.000	998.500	1162.000	994.233	1026.444	1114.528	1134.000
	765.049	983.786	661.800	799.625	934.544	891.200	761.000	865.933
	574.000	544.000	560.313	575.273	851.857	846.200	514.023	556.929
	908.971	1021.077	676.387	659.778	584.304	650.727	720.691	559.600
	722.846	789.417	1018.667	1095.625	800.511	795.938	782.794	1048.929
	653.541	863.545	756.750	770.917	703.729	883.750	690.875	739.400

LEGEND: C-R: Cue Relevance; IFS: Intentional Fixation Valid Trials; IFO: Intentional Fixation Invalid Trials; ISS: Intentional Saccade Valid Trials; ISO: Intentional Saccade Invalid Trials; RFS: Reflexive Fixation Valid Trials; RFO:Reflexive Fixation Invalid Trials; RSS: Reflexive Saccade Valid trials; RSO: Reflexive Saccade Invalid Trials.

Appendix D: Saccade Latencies (control subjects)

C-R	ISS	ISO	RSS	RSO
50/50	275.774	290.035	284.280	289.778
	353.381	419.652	243.552	238.828
	545.333	520.609	288.650	326.600
	627.500	546.467	319.667	294.000
	259.826	281.600	246.517	251.036
	328.750	355.724	348.938	310.094
	387.167	428.154	274.567	258.161
	575.000	680.143	374.069	367.313
	539.304	557.864	364.533	407.071
	647.438	644.600	245.500	239.758
75/25	292.727	304.133	203.971	211.200
	389.590	376.286	248.837	246.563
	559.654	585.857	243.650	259.000
	368.909	445.857	317.159	308.200
	325.227	205.500	243.861	227.778
	351.200	329.625	277.596	276.467
	429.875	436.000	235.977	226.429
	533.032	526.222	382.691	384.333
	586.222	583.125	319.618	318.429
	495.350	410.750	235.708	215.400

LEGEND: C-R: Cue Relevance; ISS: Intentional Saccade Valid Trials; ISO: Intentional Saccade Invalid Trials; RSS: Reflexive Saccade Valid trials; RSO: Reflexive Saccade Invalid Trials.

Appendix E: Proportion of correct saccades (control and patients)

GROUP	INTENTIONAL	REFLEXIVE
PARKINSON	.625	.848
	.663	.938
	.854	.905
	.098	.282
	.200	.658
	.371	.566
	.663	.913
	.375	.269
CEREBELLAR	.738	.911
	.828	.886
	.736	.775
	.561	.654
	.813	.937
CONTROL	.975	.675
	.835	.945
	.753	.788
	.888	.964
	.750	.886
	.926	.949
	.875	.911
	.738	.924
	.563	.820
	.900	.987

LEGEND: INTENTIONAL: Intentional Saccade experiment (Valid and invalid trials together) ; REFLEXIVE: Reflexive Saccade experiment (valid and invalid trials together).

Appendix F: Proportion of joystick responses (patients)

GROUP	IFS	IFO	ISS	ISO	RFS	RFO	RSS	RSO
PARKINSON DISEASE	.327	.222	.216	.182	.480	.438	.703	.769
	.215	.389	.352	.333	.438	.375	.246	.263
	.816	.750	.533	.923	.960	1.000	.705	.737
	1.000	0.000	0.000	.100	.563	.688	.127	.250
	.523	.429	0.000	0.000	.391	.500	.587	.250
	.136	.100	0.000	0.000	.347	.188	.324	.250
	0.000	0.000	.333	0.000	.425	.200	.422	.133
	.688	.813	0.000	0.000	.625	.625	.100	.111
CEREBELLAR	.259	0.000	.467	.667	.563	.563	.311	.400
	.125	.200	0.000	0.000	.468	0.000	.535	.583
	.543	.563	.312	.375	.625	.438	.538	.563
	.130	.125	0.000	0.000	.591	.500	.229	.533

LEGEND: IFS: Intentional Fixation Valid Trials; IFO: Intentional Fixation Invalid Trials; ISS: Intentional Saccade Valid Trials; ISO: Intentional Saccade Invalid Trials; RFS: Reflexive Fixation Valid Trials; RFO: Reflexive Fixation Invalid Trials; RSS: Reflexive Saccade Valid trials; RSO: Reflexive Saccade Invalid Trials.

Appendix G: Proportion of correct fixations (control and patients)

GROUP	INTENTIONAL	REFLEXIVE
CONTROL	.872	.817
	.929	.917
	.840	.753
	.938	.543
	.938	.901
	.988	.852
	.925	.713
	.950	.557
	.838	.863
	.938	.999
PARKINSON DISEASE	.500	.407
	.920	.325
	.925	.939
	.913	.835
	.999	.911
	.488	.571
	.600	.620
	.888	.658
CEREBELLAR	.871	.899
	.513	.519
	.909	.658
	.613	.613

LEGEND: INTENTIONAL: Intentional fixation experiment (For valid and invalid trials together); REFLEXIVE: Reflexive fixation experiment (for valid and invalid trials together).

Appendix H: Proportion of correct responses (patients)

GROUP	IFS	IFO	RFS	RFO
PARKINSON DISEASE	.667	.500	.750	.429
	.929	.571	.905	.667
	.500	.417	.479	.500
	1.000	0.000	.444	.455
	.435	.500	.444	.500
	.667	1.000	.353	0.000
	.424	.538	.567	.400
CEREBELLAR	.520	.333	.567	.286
	.500	.500	.846	.714

LEGEND: IFS: Intentional Fixation Valid Trials; IFO: Intentional Fixation Invalid trials RFS: Reflexive Fixation Valid Trials; RFO: Reflexive Fixation Invalid Trials.

14 Curriculum Vitae

Susana Maria Casaña Pérez
Medical Doctor
24.05.1978 in Valencia (Spain)

Avenida. Cataluña, 20, 23
46021 Valencia (Spain)
Tel: 0034963605106
Marital status: single

EDUCATION:

1983-1992	Primary school Parque Colegio Santa Ana Valencia, Spain
1992-1996	High School Centro de enseñanza preparatoria Garcia-Hernandez Valencia, Spain

STUDIES:

1996-2002	Universidad de Valencia (Spain), Facultad de Medicina Degree: Licenciada en Medicina, General Surgeon
09/99-12/02	Hospital Clinico Universitario. Valencia, Spain Medical practice. Digestive surgery, General surgery, Cardiovascular surgery, Traumatology, psychiatry, Haematology, Gastroenterology, Preventive medicine, Radiology, Oncology, Urology, Endocrinology, Gynaecology and Obstetrics, and Cardiology.
2000-2001	Universitet I Oslo, Det Medisinske Fakultetet, Oslo, Norway Erasmus exchange student, medical studies
08/00-07/01	Rikshospitalet. Oslo, Norway Medical practice. Dermatology, Otorhinolaryngology, Neurology, Paediatrics, Forensic medicine, and Rheumatology.
01/02-02/02	Klinikum Großhadern. Munich, Germany Medical Practice. General Surgery

WORKING EXPERIENCE:

1998-1999	Fons Valencia per la Solidaritat. Xativa, Valencia Social studies of Central American and developing countries
06/99-07/99	Fons Valencia per laSolidaritat. Xativa, Valencia Scholarship and preventive medicine social work in Managua, Nicaragua
07/02-08/02	Johannes Gutenberg-Universität Mainz, Germany Medical practice. Traumatology
11/02-05/04	Research in Neurologische Klinik und Poliklinik am Klinikum Großhadern der Universität München.