THE ROLE OF EYE MOVEMENTS IN THE INVESTIGATION OF VISUAL SELECTIVE ATTENTION IN PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE

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Stefanie Kraft

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1 INTRODUCTION

While considerable evidence suggests that patients with Parkinson's disease (PD) at more severe levels demonstrate a variety of oculomotor symptoms, it is not clear to what extent the oculomotor system is affected by mild to moderate symptoms. The vast majority of published studies investigating eye movements in PD have used well controlled experimental designs (e.g. remembered saccade tasks, anti-saccade tasks, overt orienting tasks) and have found that, among other factors such as the study sample itself, impairment for PD patients seems to be task dependent. Eye movements are tightly related, anatomically and functionally, to mechanisms of visual selective attention. Whether visual selective attention is impaired in patients with PD is still a matter of debate. The fact that patients in later stages of the disease frequently demonstrate deficits in executive functions additionally complicates research. Findings of studies investigating visual selective attention, in particular attentional shifting in patients with mild to moderate PD, are heterogeneous. Similar to oculomotor research in patients with PD, results vary strongly depending on experimental details. Due to the tight coupling between oculomotor control and mechanisms of visual selective attention, studies investigating the latter domain in patients with PD (and in general) should include careful analysis of eye movements. The study presented here is an effort to integrate eye movements into research of visual selective attention in patients with mild to moderate PD. The theoretical part of this study is divided into nine subsections. The first subsection shortly describes Parkinson's disease (PD), pointing out the problems patients encounter during the course of the illness. Because PD is mainly a disorder of the basal ganglia, the second subsection is concerned with the anatomy, connections and pathophysiology of the structures involved. The third subsection outlines the problems researchers generally face when studying cognitive aspects in patients with PD. The fourth subsection introduces the topic of visual selective attention from a cognitive neuroscience perspective, before turning to the difficulties PD patients demonstrate on tasks involving different aspects of visual selective attention. Before discussing the methodology of eye movement studies, a section is devoted to the special relationship between selective attention and eye movements. Impairment of eye movement in patients with PD is described, followed by a short summary and research

questions. The methodological part of this work first describes the study sample, technical settings and data pre-processing. The three experiments: viewing of photographs, visual search and covert attention are described in separate sections. Each section includes the stimuli and procedure used, the hypotheses, a short description of data analyses and the results and discussion with reference to the empirical background. A general discussion follows. Finally, the limitations of the study and implications for future research are expounded.

2 THEORETICAL BACKGROUND

2.1 Parkinson's disease

In 1817, James Parkinson first described Parkinson Disease (PD) in "An Essay on the Shaking Palsy" (J. Parkinson, 1817). Parkinson's disease is a neurodegenerative disorder, which is caused by a progressive degeneration of nigostriatel dopaminergic neurons within the brain.

Prevalence, Incidence

PD causes both motor and non-motor symptoms and is believed to affect between 100.000 and 250.000 people in Germany. The estimated annual incidence rate is between 10.000 and 15.000. The likelihood of developing PD is approximately 1% for people older than 65. Development of PD before the age of 30 is rare, yet up to 10% of all cases begin before the age of 40 (Kompetenznetz-Parkinson, 2003).

Symptoms

PD is characterized by three cardinal motor symptoms, which are: 1) bradykinesia (slowed movements), 2) resting tremor (shaking of an arm or leg when it is not being moved) and 3) muscle rigidity (stiffness). Bradykinesia is often used synonymously with akinesia and hypokinesia. Strictly speaking, akinesia refers to a lack of spontaneous movement (e.g. in facial expression) or associated movement, (e.g. arm swing during walking) and hypokinesia refers to movements which are smaller in size (e.g. micrographia of handwriting). While PD is classified as a movement disorder, there are many non-motor aspects of the disease, including dementia, depression, sleep disorder, gastrointestinal symptoms, autonomic failure, visuospatial deficits, impaired executive functions and memory. The degree to which attentional mechanisms are affected is still under debate.

Causes of Parkinson's disease

PD is idiopathic in 80 –90% of all cases, i.e. symptoms can neither be explained by secondary causes nor hereditary degenerative disorder. The role of genetic factors is controversial. Several genes are known to cause PD. The most important one is parkin. However, genetic factors can account only for a small minority of cases. Another possibility discussed are environmental toxins. Although the exact identity of these

toxins is unknown, their effects are thought to build up over time and eventually lead to disease in genetically predisposed individuals.

Diagnosis

The diagnosis of PD is often difficult, since a specific test or marker does not exist. It depends on the presence of at least one of the three major symptoms, as well as the absence of a secondary cause. The diagnosis of idiopathic PD requires at least three additional criteria, such as for example Levodopa sensitivity, slow progression of illness and asymmetric beginning. Usually a standard neurological examination, involving various simple tests of reactions, reflexes, and movements is performed. The "Unified Parkinson's Disease Rating Scale" (UPDRS) (Fahn & Elton, 1987) is predominantly used as a rating tool to follow the longitudinal course of PD. The severity of the disease is usually determined by the Hoehn and Yahr Staging of PD (Hoehn & Yahr, 1967).

Treatment

PD treatment depends on age, severity, variety of clinical symptoms, and progression of the disease**.** No treatment has yet conclusively shown a slowing or reversal of the disease. A combination of Levodopa (L-Dopa), dopamine agonists, MAO-B-inhibitors, amantadine, and anticholinergics can effectively reduce symptoms. Dopamine agonists directly stimulate dopamine receptors. MAO-B-Inhibitors reduce the degradation rate of dopamine. Amantadine is antiglutaminergic. Anticholinergics are predominantly used in younger patients with tremor. For most patients, drug treatment can provide several years with a reasonable quality of life. However, as PD progresses, it becomes increasingly difficult to bring symptoms under control with medication. Frequent complications, especially under L-Dopa treatment, are motor fluctuations including freezing, wearing-off and dyskinesia, due to a loss of L-Dopa storage capacity in the striatum and pulsatile dopamine receptor stimulation. PD patients who suffer predominately from tremor have an overall better prognosis regarding mobility compared to patients whose main symptoms are bradykinesia and rigidity. For some patients deep brain stimulation (DBS) may be an effective treatment, when long-term medication ceases to show the desired reduction of symptoms. In DBS, electrodes are placed in the brain to deliver continuous stimulation of, most often, the subthalamic nucleus.

2.2 Anatomy, connections and pathophysiology of the basal ganglia

In PD, the main symptoms result from altered dopaminergic neurotransmission in the basal ganglia. Since the basal ganglia play a crucial role in mediating and integrating motor as well as cognitive programs within the brain, the present chapter introduces their basic structure, connections and pathophysiology in Parkinson's disease.

2.2.1 Anatomy of the basal ganglia

In general, there is some disagreement on which structures belong to the basal ganglia. A distinction into dorsal and ventral is common (Ma, 1997). The main components of the dorsal basal ganglia include the globus pallidus, the caudate, and the putamen, the latter two forming the neostriatum. The putamen is separated from the caudate by the anterior limb of the internal capsule. Substantia nigra, subthalamic nucleus and parabrachial pontine reticular formation, including the peduncolopontine nucleus, are also associated with the dorsal area. The lentiform nucleus is formed by the putamen and globus pallidus. The globus pallidus, as the medial part of the lentiform nucleus, is subdivided into an external (GPe) and an internal (GPi) area. The substantia nigra, situated in the rostral part of the midbrain, next to the cerebral peduncles, is divided into two main divisions: the pars compacta (SNc), rich in dopaminergic cells, and the pars reticulata (SNr). The subthalamic nucleus (STN) is situated between the thalamus and the substantia nigra. The vast majority of the neurons in the neostriatum are "medium spiny neurons" (MSN), named after their medium-sized cell bodies and their spiny dendrites. MSN use the inhibitory neurotransmitter GABA and may also contain neuroactive peptides such as substance P and enkephalin. The remaining neostriatal neurons are large, aspiny interneurons, containing acetylcholine. Unlike MSN, these neurons are spontaneously active and are cholinergic (Yelnik, 2002).

Morphologically and chemically, GPi and SNr share many common features. Most of their neurons are large, multipolar projection neurons, containing GABA as a neurotransmitter. Although interneurons have also been described, they are rather infrequent.

The ventral basal ganglia, inferior to the anterior commissure close to the limbic system, include structures involved in cognitive and behavioural functions. They consist of the

substantia innominata, nucleus basalis of Meynert, nucleus accumbens and the olfactory tubercle (the last two forming the ventral striatum). The ventral basal ganglia are closely connected with the amygdala and the ventral tegmental area on a functional level.

2.2.2 Connections of the basal ganglia

The most influential model of basal ganglia circuitry was proposed by Alexander, Delong, and Strick in 1986. It is based on the assumption that the basal ganglia are organized into five structurally and functionally distinct circuits that modulate cortical activity in parallel (Alexander, 1994; Alexander, Crutcher, & DeLong, 1990; Hoover & Strick, 1999): two motor circuits (motor and oculomotor) and three cognitive or behavioural circuits (anterior cingulate, dorsolateral prefrontal, and orbitofrontal) (Zgaljardic, Borod, Foldi, & Mattis, 2003). According to this model, each circuit originates in the frontal cortex and has projections to the striatum. For example, the nuclei involved in the motor circuit include the putamen, globus pallidus, substantia nigra pars compacta, subthalamic nucleus, and the motor nuclei of the thalamus. The model suggests two pathways through the basal ganglia, a direct and an indirect pathway. Whereas the direct pathway is thought to facilitate movement, the indirect pathway is thought to suppress movement (Fig.1) (Albin, Young, & Penney, 1989; DeLong, 1990). Although this model is still popular for a schematic overview, more recent findings suggest that connections and circuit interactions are more complex (for an overview see Saint-Cyr, 2003).

The major input structure of the basal ganglia is the neostriatum, receiving input from the cerebral cortex, thalamus and mesencephalic sites.

Corticostriatal projections can be subdivided according to three functionally different territories (i.e. categories of circuits, rather than circuits). These are: 1) the sensorimotor territory, linking motor cortices (primary motor cortex, SMA, premotor cortex) to the putamen, 2) the associative territory, linking the dorsal caudate nucleus to association cortices, and 3) the limbic territory, linking the ventral striatum to anterior cingulate and medial orbitofrontal cortices. Considerable interaction between these parallel circuits facilitates a high level of integration between different CNS functions (Yelnik, 2002). The neurotransmitter in corticostriate projections is glutamate.

Thalamic projections to the striatum originate primarily from two thalamic nuclei: centromedian and parafascicular. Whereas the former projects to the sensorimotor

(putamen) striatal territory, the latter projects to the associative (caudate) and the limbic (ventral striatum) parts of the striatum. The neurotransmitter in the thalamostriate projections is glutamate.

Mesencephalic projections to the striatum primarily originate from the SNc**.** The neurotransmitter is dopamine, which exerts an excitatory effect on striatal neurons that project to the GPi and SNr and an inhibitory effect on neurons projecting to the GPe.

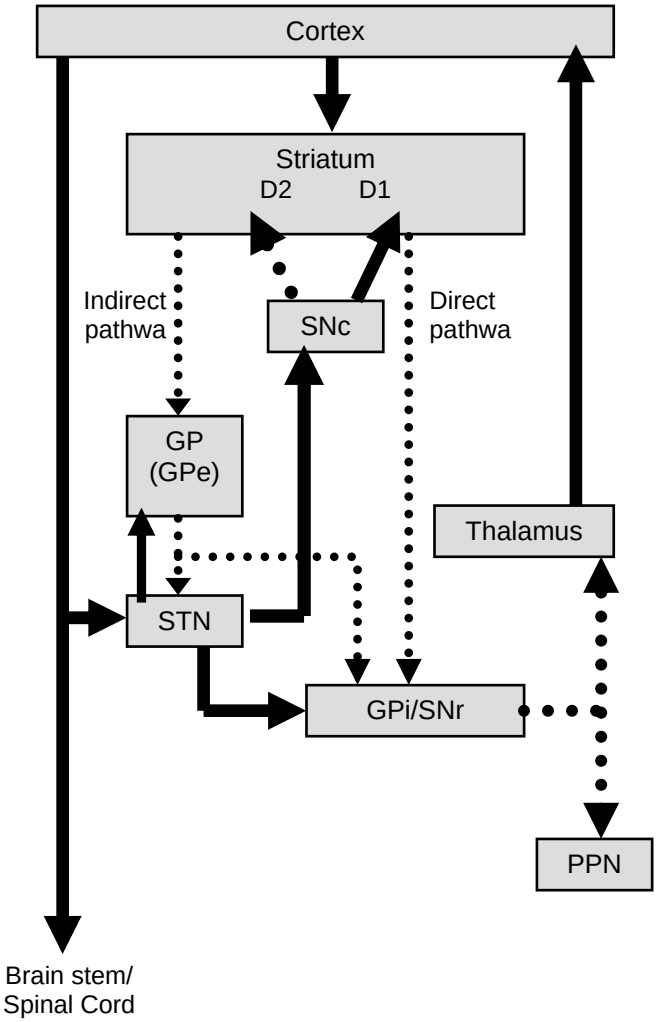

Figure 1: Schematic illustration of basal ganglia anatomy and connections. The dotted arrows mark inhibitory projections, the black arrows mark excitatory projections. The thickness of the arrows illustrates the strength of activity. SNr =Substantia nigra pars reticulata, GPi = internal segment of the Globus pallidus, GP(e) = (external segment of the) Globus pallidus, STN = Subthalamic nucleus, SNc = Substantia nigra pars compacta, PPN = Peduncolopontine nucleus (Rouse, Marino, Bradley, Awad, Wittmann, & Conn, 2000).

2.2.3 Basal ganglia circuitry in PD

In Parkinson's disease, the depletion of dopamine in the striatum results in complex changes of activity in basal ganglia circuits. According to the basal ganglia-thalamocortical model (Alexander et al., 1990), decreased levels of dopamine lead to enhanced activity along the indirect pathway and reduced activity along the direct pathway. In turn, GPi and SNr nuclei receive stronger excitatory input and inhibition of thalamic neurons is increased. Finally, excitatory thalamic output to cortical regions is reduced. Hence, motor symptoms in PD are typically explained by attenuation of activity in motor areas. However, recent evidence from fMRI also suggests overactivity of motor cortical areas in symptomatic PD (Sabatini, Boulanouar, Fabre, Martin, Carel, Colonnese, Bozzao, Berry, Montastruc, Chollet, & Rascol, 2000) and even presymptomatic PD (Buhmann, Binkofski, Klein, Buchel, van Eimeren, Erdmann, Hedrich, Kasten, Hagenah, Deuschl, Pramstaller, & Siebner, 2005). This finding is interpreted as a result of reorganization due to compensatory mechanisms.

According to the response selection theory of the basal ganglia, their primary function is the focused selection of an intended motor program and inhibition of competing responses (Mink, 1996). Focused selection is achieved by context-dependent inhibitory output from the striatum, which focally inhibits activity in the globus pallidus and subtantia nigra pars reticulata, and thus removes inhibition from desired thalamocortical and brainstem programmes. At the same time, competing motor mechanisms are inhibited by subthalamic nucleus activation, leading to increased excitation of the globus pallidus and subtantia nigra pars reticulata and subsequent inhibition of thalamocortical areas and the brainstem. Impairment in patients with PD is therefore thought to be twofold: first, an inability to remove inhibition from an intended program and secondly, an inability to inhibit competing programs.

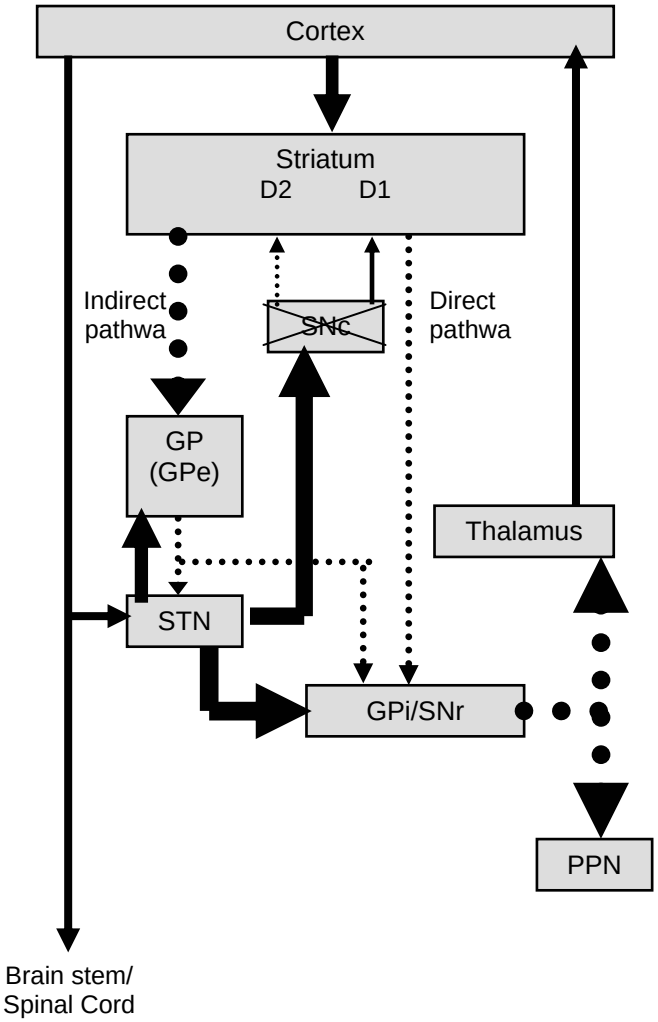

Figure 2: Schematic illustration of basal ganglia anatomy and connections in Parkinson's disease. The dotted arrows mark inhibitory projections, the black arrows mark excitatory projections. The thickness of the arrows illustrates the strength of activity. SNr = Substantia nigra pars reticulata, GPi = internal segment of the Globus pallidus, GP(e) = (external segment of the) Globus pallidus, STN = Subthalamic nucleus, SNc = Substantia nigra pars compacta, PPN = Peduncolopontine nucleus (Rouse et al., 2000).

2.3 Parkinson's disease and cognition- a research dilemma

It was not until the 1980s that researchers began to systematically investigate neuropsychological impairment in Parkinson's disease. Over the past two decades, research has been particularly focused on the domains of memory (Levin, Tomer, & Rey, 1992), visuospatial processing (Waterfall & Crowe, 1995) and executive functions (see Brown & Marsden, 1990). Impairment in PD patients has been found in a variety of different tasks (Dubois & Pillon, 1997). However, it goes beyond the purpose of this study to give a complete review of the literature. Before turning to attention and possible impairment in PD, the present chapter introduces two issues researchers are likely to encounter when studying cognitive functions in patients with PD. First, there is the problem of distinguishing motor from non-motor aspects. Secondly, deficits in primary visual and oculomotor functions are likely to interfere with visual cognitive tasks.

2.3.1 The concept of bradyphrenia

The concept of "bradyphrenia" (Naville, 1922) "implies (1) that increased response latencies are not strictly motoric, but are due to slowed information processing, and (2) that the mental slowing is analogous to the bradykinesia observed in the motor domain, and hence is attributable to dysfunction of dopaminergic basal ganglia mechanisms" (Rafal, Posner, Walker, & Friedrich, 1984). Whether bradyphrenia exists in Parkinson's disease is still a matter of debate. This is mainly due to two reasons: First, PD usually develops late in life and patients often suffer from dementia due to several etiologies. However, there is an association between slowing of thought and aging (Cerella, 1985) and slowing of thought and depression (Cooper, Sagar, Tidswell, & Jordan, 1994). Secondly, many studies employ procedures that require a motor response, so that bradykinesia and bradyphrenia are difficult to separate (Rafal et al., 1984).

2.3.2 Reaction time studies

One line of research has encountered this problem by comparing simple reaction times in (SRT) tasks, where all stimuli require the same response, with choice reaction times (CRT) in tasks, where different stimuli require different responses. Compared to SRT,

CRT involves stimulus analysis and response selection. Conflicting results have been obtained. In some studies, PD patients were slow on SRT tasks, but normal on CRT tasks (Bloxham, Dick, & Moore, 1987; Sheridan, Flowers, & Hurrell, 1987). This finding is interpreted as a failure "to take advantage of the opportunity to program their response fully in advance" (Berardelli, Rothwell, Thompson, & Hallett, 2001). Other studies yielded opposite results, namely the prolongation of CRT relative to SRT (Jahanshahi, Brown, & Marsden, 1992; Lichter, Corbett, Fitzgibbon, Davidson, Hope, Goddard, Sharples, & Pollock, 1988; Reid, Broe, Hely, Morris, Williamson, O'Sullivan, Rail, Genge, & Moss, 1989), suggesting slowing of cognitive processing in PD. A third group of studies found no difference in the extent of slowing between SRT and CRT in PD (Pullman, Watts, Juncos, & Sanes, 1990; Stelmach, Worringham, & Strand, 1986). A review of RT studies emphasizes the relationship between patients' reaction times deficit and the reaction times of controls and concludes that a deficit is more likely to be observed in tasks in which control subjects respond with a fast reaction time than with a slow reaction time (Gauntlett-Gilbert & Brown, 1998). Cooper and colleagues (1994), who measured SRT and CRT under conditions of graded attentional demands, distinguished a "perceptuomotor" factor, probably reflecting a simple altering-arousal deficit, from a "cognitive-analytical" factor, which played a role in more complex tasks only and is likely to reflect impaired inhibitory attentional control processes in PD. Support for these results come from another study, which investigated motor and cognitive processing in PD by measuring lateralized readiness potentials (LRP) (Low, Miller, & Vierck, 2002). This method has the advantage that motor and premotor components can be separated by time-locking the LRP to stimulus onset and response onset. The results indicate that in addition to delayed onset of movement-related potentials, premotor processes are also impaired in PD.

In summary it seems that "the impairment in choice reaction time in patients with Parkinson's Disease is dependent upon the task and the medication status of the patients" (Brown, Jahanshahi, & Marsden, 1993). A rather different and elegantly simple approach separates cognitive and motor speed in PD patients by means of inspection time as an indicator of information processing speed (Johnson, Almeida, Stough, Thomson, Singarayer, & Jog, 2004). Inspection time, in this study, was defined as presentation time at which participants were able to achieve 80% accuracy in

judgement of line length. PD patients required significantly longer stimulus presentation times than healthy controls.

In summary, several attempts have been made to dismantle cognitive and motor processes in patients with PD. However, there is still no clear answer to the question of whether or not bradyphrenia exists in PD.

2.3.3 Preattentive visual dysfunction in patients with Parkinson's disease

Most studies investigating neuropsychological impairment in patients with PD have been conducted in the visual domain. However, primary visual processing deficits, attributed primarily to a dopamine imbalance within the visual system, are frequently observed in patients with PD. The nature of impairment is often unclear. This is because the retina may be directly affected, since retinal amacrine and interplexiform cells contain dopamine (Frederick, Rayborn, Laties, Lam, & Hollyfield, 1982). However, dopaminergic innervation is also found in other structures within the visual system, including the lateral geniculate (Papadopoulos & Parnavelas, 1990) and the visual cortex (D. Parkinson, 1989).

Compared to healthy controls, contrast visual acuity seems to decline in patients with PD and age-matched controls (Repka, Claro, Loupe, & Reich, 1996). This decline was correlated with increasing disease severity. It is not clear whether this decrease in acuity is related to retinal or cortical dysfunction. In addition convergence insufficiency is also frequently observed in patients with PD (Repka, Claro, Loupe, & Reich, 1996). Impaired colour vision, mostly seen in the tritan (blue-yellow) axis has also been reported frequently in PD patients. The abnormality of colour vision can be reversed by treatment with levodopa and other dopaminergic drugs. Contrast sensitivity to visual stimuli defined by luminance (Bodis-Wollner, Marx, Mitra, Bobak, Mylin, & Yahr, 1987; Tebartz van Elst, Greenlee, Foley, & Lucking, 1997) and colour contrast (Haug, Trenkwalder, Arden, Oertel, & Paulus, 1994) has also been found impaired in PD. Whether this impairment of contrast sensitivity in PD resides in the retina or the visual cortex is not yet clear. Other ophthalmologic changes in patients with early untreated PD, such as a reduced eye blink rate, contributing to a tear film dysfunction (dry eyes), are also reported (Biousse, Skibell, Watts, Loupe, Drews-Botsch & Newman, 2004). One-fourth of the patients suffered from visual hallucinations, which are "usually

attributed to decreased visual acuity, cognitive impairment, or medications such as dopaminergics and anticholinergics" (Biousse et al. , 2004).

In summary, patients with PD suffer from a variety of visual problems, which depend on disease severity and medication regimen.

2.4 Theory of visual selective attention

The identification of impairment in selective attention in PD requires an a priori definition of attention. In 1890, William James claimed: "Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or train of thought." More than a century later the function of attention is described as follows: "Regardless of one's methodology, discipline, and intuitions, there is only one core issue that justifies attentional processes: *information reduction*" (Tsotos, Itti, & Rees, 2005).

2.4.1 Selective attention from a cognitive perspective

In natural surroundings and everyday life, we have to cope with a high load of different information simultaneously. Since the capacity of the visual system to process information at any given moment in time is limited (Broadbent, 1958; Schneider & Shiffrin, 1977), information needs to be selected according to priority. Selective attention ensures eefficient and effective cognitive processing by allocating limited processing resources to relevant aspects and, at the same time, relegating other aspects.

Early versus late selection

A central issue in attention research concerns the level of processing at which selection takes place. One of the first so-called "filtering models" was suggested by Donald Broadbent (1958), who postulated that input is filtered right after sensory analysis and before perception. Different sorts of sensory information were thought to correspond to certain neural pathways. However, Broadbent's theory raised some questions, such as why salient information, which is not attended to, can break through this sensory filter. Later models tried to confront these issues by either making the filter more permeable (A. M. Treisman, 1964) or moving the filter further "up" to allow some perceptual and conceptual processing to take place (Deutsch & Deutsch, 1963). A more recent view assumes a flexible locus of selective attention which depends on task demands (Lavie, 1995).

A second major topic in attention research concerns the "units" of selective attention. In a natural situation an object is defined by its features and is located somewhere in space.

Does attention operate on the level of objects, on the level of features of objects or on the level of spatial location?

Object-based attention

How can competition among multiple information sources be resolved?

One of the first prominent models that investigated stimulus salience is the "feature integration theory" (A. M. Treisman & Gelade, 1980). This theory assumes that object features (e.g. colour, motion, orientation) are independently coded by the visual system and that features produce activation on specific retinotopic feature maps. Feature maps contain two kinds of information: the presence of a feature anywhere in the visual field and implicit spatial information about the feature. Attention is thought to bind these features together. Feature integration theory is best explained by visual search. In a visual search task, the efficiency is varied by modifying the difference between a pre-specified target stimulus and the surrounding distracter stimuli. In "simple feature search", the target and distracter stimuli have no features in common, the target appears to automatically "pop-out" and detection is independent of the target's location. In "conjoined feature search", on the other hand, target and distracter stimuli share at least one feature. Participants usually decide as quickly as possible whether a target item is present among a variable number of distracter items or not. With greater similarity of target and distracter stimuli, the search becomes more serial and the time to detect the target increases.

However, more recently the distinction between parallel and serial search has been questioned. Searches for conjunctions were often found more efficient than serial search would predict; that is, more complex targets also seem to "pop out" (Duncan, 1998; Duncan & Humphreys, 1992). The "guided search model" developed by Wolfe and colleagues (Chun & Wolfe, 1996; Wolfe, Cave, & Franzel, 1989) countered this problem by suggesting an interaction between bottom-up, stimulus-driven guidance to salient items and top-down control based on instructions or prior search experience. They argued that rather than initial processing being parallel and subsequent processing being serial, processes are neither purely parallel nor purely serial.

In contrast to the models introduced so far, which describe attention from a more mechanistic point of view, Desimon and Duncan (1995) regard attention as "an emergent property of many neural systems working to resolve competition for visual

processing and control of behavior". According to the biased competition account of attention, information selection depends on both, bottom-up stimulus-driven factors, such as the salience of a stimulus, and top-down processes, such as directing attention to a particular stimulus location. For stimuli occurring at the attended location, processing will be facilitated (Desimone & Duncan, 1995; Duncan, 1998; Kastner & Ungerleider, 2000).

The present study investigates performance of PD patients on a visual search task, which induces competition among multiple information sources.

Spatial attention

In the field of selective attention, a distinction is often drawn between object-based attention, as discussed above, and spatial attention, which occurs when one attends to a particular locus in space at the expense of other loci.

Attention to spatial locations is typically investigated by "covert" attention shifting paradigms (M. I. Posner, 1980b). A symbolic cue (i.e. an arrow) directs attention to the location where the target is most likely to occur. Subjects are required to shift their attention "covertly", that is, without making an eye-movement to the cued location. Manual responses are faster when the cue is valid as compared to conditions where the cue is invalid or neutral. Cueing can be different in nature. Whereas peripheral cues trigger exogenous reflexive shifts of attention with a short latency (ca. 50 ms) and transient activation (50-200 ms), central cues evoke endogenous voluntary shifts of attention with a long latency (> 200 ms) and sustained activation (> 500 ms) (H. J. Müller & Rabbit, 1989). A typical effect observed in covert attention tasks with peripheral primes is "inhibition of return" (IOR). If the stimulus onset asynchrony (SOA) between cue and target stimulus is longer than 300 ms, the reorientation of attention is inhibited for a prior cued location (M.I. Posner & Cohen, 1984). Since the target stimulus does not immediately occur at the cued location, attention is likely to be shifted to another location during the delay and needs to be reoriented to the target stimulus. The facilitatory effect with SOA's below 300 ms is therefore turned into its opposite.

From this line of research, the idea emerged that attention moves like a "spotlight". Information illuminated by this spotlight is processed faster and more in depth than information at other locations. Two controversial assumptions of this theory are that the

diameter of the "spotlight" is constant and that it moves at constant velocity, similar to smooth pursuit eye movements. Contradictory to the notion of a unitary beam, recent findings suggest that for briefly presented stimuli, the spotlight can be divided between spatially separate locations (Awh & Pashler, 2000; M. M. Müller, Malinowski, Gruber, & Hillyard, 2003). In contrast to the idea of a moving spotlight, Eriksen and Eriksen (1974) compared selective attention with a variable "zoomlens". Attention can be focused with high resolution onto a small area or with lower resolution onto a larger area. This model tries to account for the finding, that longer reaction times for incompatible "flanker" stimuli are reduced with increased Stimulus Onset Asynchrony (SOA) between cue and target stimulus. Attention is thought to change from a focused to a more blurred state.

Both theories share the common assumption that selective attention functions in a location- based manner, meaning attention is directed to a region which contains information of interest.

In the present study, the spatial aspect of attention is investigated in PD patients by use of a covert-attention shifting task.

Relationship between object-based and spatial attention

The relationship between location-based and object-based attention is not yet fully resolved. According to the feature integration theory of visual attention (A. M. Treisman & Gelade, 1980), efficient target detection occurs prior to target localization and can even occur independently. Contrary to this notion, Hillyard and Vento (1998) found that the effects of attention to stimulus attributes, such as colour, occur approximately 60 ms later than those reported for selection based on spatial attention. They therefore suggest a hierarchical model of attention, with the selective processing of stimulus attributes dependent on the prior selection of location. An alternative explanation is that selection for location and selection for attributes takes place in parallel (Desimone & Duncan, 1995), but the selection for location is accomplished more rapidly.

Apart from only selecting locations or object features, there is also evidence that attention can select whole objects. If an observer discriminates one feature of an object (e.g. colour), it was shown that other features of the same object (e.g. orientation) can be discriminated efficiently without interference (for a review see Reynolds & Chelazzi,

2004). It therefore seems that if attention is directed to one feature of an object, all other object features are also processed.

In summary, there is an ongoing debate concerning the relationship between object-based and location-based attention and recent theories take into account that a two-fold distinction may be an over-simplified view of how visual information is selected for attention.

2.4.2 Neural correlates of visual selective attention

What happens in the central nervous system if we "pay attention" to a stimulus?

The attentional system is "neither a property of a single brain area nor of the entire brain" (M. I. Posner & Dehaene, 1994). This expression subsumes what different studies of attention have shown, that neural activity during attention demanding tasks was found in corresponding visual, auditory, motor, as well as association areas.

Two processing streams

The visual system enables us to perceive our environment in a three-dimensional way by extracting and analysing different aspects of form, colour, depth, and motion from each retinal image. Its importance is stressed by the fact that approximately 40 percent of all nerve fibres in the brain are involved in some sort of visual process. Until now, approximately thirty visual cortical areas (Felleman & Van Essen, 1991) have been described in the macaque monkey, as opposed to at least ten areas identified in humans. The majority of axons of retinal ganglion cells terminate in the magno- and parvocellular subdivisions of the lateral geniculate nucleus, from where cells project to the primary visual cortex. The discovery of a distinct cytochrome oxidase architecture with blobs and interblobs in the primary visual cortex (V1) and cytochrome oxidase stained pattern sections in V2 led to the assumption, that magnocellular and parvocellular information remains largely segregated up to an early cortical level. A dissociation of visual streams has also been suggested for higher cortical stages. A dorsal "where" stream, involved in the analysis of motion and spatial orientation as well as visual guidance, is assumed to travel from V1 and V2 via V5 to parietal areas, whereas a ventral "what" stream, responsible for colour, form and object identification, travels from V1 and V2 via V4 to inferior-temporal regions (areas TEO, TE) (Mishkin, Ungerleider, & Macko, 1983).

Neurons in the inferior temporal (IT) cortex respond primarily to shape, colour or texture of a stimulus. They have large receptive fields, which predispose them to identify an object regardless of its position in the visual field. In monkeys, recording of neural activity during a delayed match-to-sample task, suggests that cells in this region are strongly involved in the short-term storage of visual object information (Miller, Li, & Desimone, 1993). Neurons in the parietal cortex, on the other hand, are more concerned with the analysis of spatial locations. They are highly sensitive to the direction of stimulus motion and are involved in the control of pursuit and saccadic eye movements.

Bottom-up and top-down modulation

"The distinction between bottom-up and top-down effects continues to be a fundamental guiding principle in account of attention" (Frith, 2005). Sensory-driven, bottom-up mechanisms in the visual cortex seem to be controlled by higher-order areas in frontal and parietal cortex, which generate top-down signals that are transmitted through feedback connections to the visual system (Corbetta & Shulman, 2002; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Kastner & Ungerleider, 2001).

In which regions of the visual system does attention modulate activity?

Numerous studies have shown modulatory activity in extrastriate regions such as V4 (Motter, 1998), as well as specialized cortical areas such as MT, where motion processing is enhanced by attention (Treue & Maunsell, 1996). Modulatory activity, however, was also found in the primary visual cortex (Maunsell & McAdams, 2001), supporting the view that attention operates at multiple stages in the visual system.

How does attention modulate neural processing in visual cortex?

During the past decade, studies using functional imaging techniques, in particular positron-emission-tomography (PET) and functional magnetic resonance imaging (fMRI), have greatly contributed to the understanding of how attention modulates activity in different areas of the brain. In a classical PET study, Corbetta and colleaques (1991) could show that attention modulates the activity of extrastriate cortical areas, specialized for feature dimensions such as colour or motion. Importantly, this modulation depended on which feature was used as a target for selection. For example, if the speed of the motion of the objects was attended to, increased rCBF activity was obtained in motion processing regions (presumed analogues of macaque areas

MT/MST). Several fMRI studies have also shown, that an increase of contralateral activation is particularly found in extrastriate visual areas, which are clearly retinotopically organized (Hopfinger, Buonocore, & Mangun, 2000; Mangun, Buonocore, Girelli, & Jha, 1998; Martinez, Anllo-Vento, Sereno, Frank, Buxton, Dubowitz, Wong, Hinrichs, Heinze, & Hillyard, 1999; Vandenberghe, Duncan, Arnell, Bishop, Herrod, Owen, Minhas, Dupont, Pickard, & Orban, 2000). Attention also modulates visual processing in V1 (Brefczynski & DeYoe, 1999; Gandhi, Heeger, & Boynton, 1999; Tootell, Hadjikhani, Hall, Marrett, Vanduffel, Vaughan, & Dale, 1998). Taken together, these results provide strong support for independent processing of different visual attributes.

When attention is shifted from one location to another, superior parietal and superior frontal regions have been found to be active (Corbetta, Miezin, Shulman, & Petersen, 1993). Recent studies employing "covert" visuospatial attention tasks localize these activations in parietal areas: superior parietal lobule (SPL), inferior parietal sulcus (IPS), and frontal areas: frontal eye field (FEF), supplementary eye field (SEF), supplementary motor area (SMA), inferior frontal cortex (IFC) and anterior cingulate cortex (ACC) (Corbetta, 1998; Nobre, Gitelman, Dias, & Mesulam, 2000; Rosen, Rao, Caffarra, Scaglioni, Bobholz, Woodley, Hammeke, Cunningham, Prieto, & Binder, 1999). In summary, selective attention seems to modulate neural activity at multiple stages in the visual system, yet the source of these attentive signals remains unknown.

Kastner & Ungerleider (2000) suggest several mechanisms responsible for creating top-down signals to both retinotopic cortex and higher visual areas: "a) the enhancement of neural responses to an attended stimulus; b) the filtering of unwanted information by counteracting the suppression induced by nearby distracters; c) the biasing of signals in favour of an attended location by increases of baseline activity in the absence of visual stimulation; and d) the increase of stimulus salience by enhancing the neuron's sensitivity to stimulus contrast." A key factor in favour of the biased competition theory of attention (Desimone & Duncan, 1995; Kastner & Ungerleider, 2000), is the finding that attentional modulation of activity in retinotopic cortex was also found in the absence of visual stimulation (Kastner et al., 1999).

Summary

Despite the, at first glance, simple definition of attention given at the beginning of this chapter, it proves to be difficult to capture attention within a unitary framework. Past decades have put emphasis on differing aspects of attention and the development of modern technologies has brought new insight into old debates.

The idea of a flexible locus of selection, which depends on task demands, gains support by the finding that interacting selection mechanisms influence the allocation of attention. Convergent evidence from single cell studies in monkeys, as well as functional brain imaging data, indicate that "bottom-up", stimulus driven mechanisms, as well as "top-down", goal directed mechanisms facilitate information processing of stimuli at attended locations or of attributes of attended stimuli. The influence of "top-down" mechanisms on "bottom-up" mechanisms is dependent on task demands. The identification of "top-down" areas also has implications for the discussion of whether attention is directed to locations, objects or features of objects. Various studies on spatial attention have found distinct areas to be active, indicating the existence of a frontoparietal network for directing attention.

2.5 Performance of PD patients on tasks involving selective attention

In contrast to well established neuropsychological impairment in memory and executive functions, there is still an ongoing debate as to whether or not attentional processes are affected in PD. Two main streams of research can be distinguished with respect to visual selective attention in patients with PD: 1) tasks which induce response conflict through stimulus-response (in)compatibility and 2) visual search tasks.

2.5.1 Studies inducing response conflict through stimulus-response (in)compatibility

Studies investigating selective attention in PD on the basis of spatial visual cues (see section 2.4.1) have produced inhomogeneous results. On the one hand, the same benefit for PD patients and healthy controls was found when the cue validly predicted the location of the following target. On the other hand, when the cue was invalid, therefore predicting the wrong target location, patients did not demonstrate the same slowing of reaction times as normal controls (Wright, Burns, Geffen, & Geffen, 1990; Wright, Geffen, & Geffen, 1993). Hence, the magnitude of the cueing effect is assumed to be reduced in patients with PD. This finding gains support from two other studies (Filoteo, Williams, Rilling, & Roberts, 1997b; Yamaguchi & Kobayashi, 1998a), suggesting a PD related decrease in reaction time cost. However, this decrease occurred only at cue-target intervals of at least 800 ms. Pollux and Robertson (2001) even report reduced costs of invalid cueing in PD for a cue-target interval of 600 ms. All studies using shorter time intervals between cue and target presentation found no decrease in reaction time cost after invalid cues (Bennett, Waterman, Scarpa, & Castiello, 1995; Filoteo et al., 1997b; Hsieh, Hwang, Tsai, & Tsai, 1996; Hsieh, Lee, Hwang, & Tsai, 1997; Kingstone, Klein, Morein-Zamir, Hunt, Fisk, & Maxner, 2002).

Whereas Pollux and Robinson interpret reduced costs in patients with PD as "a general impairment in maintanance of attention", Fileteo and Delis (1997) argue more specifically "that the basal ganglia may play an important role in inhibitory processes, particularly in maintaining inhibition at unattended spatial locations over extended periods of time."

In an event-related EEG study, response force and EEG potentials were measured during performance of disjunctive (go/no-go) tasks (Wascher, Verleger, Vieregge, Jaskowski, Koch, & Kompf, 1997). This experimental set-up allows the separation of measures of activation and attention-related processes. The authors found for PD patients, as compared to matched controls, a reduction in activation and greater difficulty inhibiting invalidly prepared responses.

A further paradigm, which was used to detangle inhibitory attentional processes in PD, is negative priming (Filoteo, Rilling, & Strayer, 2002). This task requires identifying a target that is presented with a number of irrelevant stimuli. Two stimuli arrays are presented, a prime array and a probe array. The negative priming effect is obtained by contrasting a condition with different stimuli for target and distracters in the prime array and in the probe array with a condition, where an irrelevant stimulus in the prime array becomes the relevant target stimulus in the probe array. Whereas healthy control participants demonstrated prolonged reaction times for the latter condition compared to the former condition, this was not the case for the PD patients. It is suggested that PD patients have greater difficulty inhibiting responses to previously relevant stimuli. Support for disinhibition of response selection in PD also comes from other studies (Hayes, Davidson, Keele, & Rafal, 1998; Praamstra & Plat, 2001).

More recently, Seiss & Praamstra (2004) reported deficient inhibitory control processes in patients with PD as reflected by a failure to show the negative compatibility effect. In this paradigm, an arrow pointing to the right or left side was presented subliminally before the onset of a target arrow, to which participants responded via left or right button press. In the absence of a delay between prime offset and target onset, reaction time is facilitated when prime response and target response are compatible, but slowed when prime and target responses are incompatible. A reversal of prime-target compatibility, the so-called negative compatibility effect, was seen with a delay of 100 ms. The finding that patients with PD failed to show this reversal is interpreted as "impaired control of partial response activation…" (Seiss & Praamstra, 2004).

In summary, different methodological approaches have been applied to investigate response conflict in patients with PD and it was shown that results vary strongly with respect to stimuli, procedures, timing conditions and patient samples, studied at different stages of the disease. Although no universal theoretical framework for these

findings exists, the core of all interpretations is based on deficient inhibitory processes in PD.

2.5.2 Visual search tasks

Another way to investigate selective attention is by visual search tasks (see section 2.4.1) When a target is particularly salient compared to surrounding distractors, visual search can be performed in parallel. Whereas in healthy subjects so-called "pop-out" targets are detected independently of the number of distractors in the display (A. Treisman & Sato, 1990; Wolfe et al., 1989), visual search performance in patients with PD is controversial. On the one hand, it was found that visual search time for simple searches increases in PD patients, when the number of distractors increases, suggesting a deficit in parallel search mechanisms for patients with PD (Troscianko & Calvert, 1993). On the other hand, patients do not seem to show any deficits in deciding whether a target is present or absent while performing simple or conjoined visual search, indicating intact parallel and serial processing, (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999). In this latter study, prolonged response times for simple and conjoined visual search were only found for "frontally impaired" PD patients. The authors suggest that "the frontal lobes may be critical in slowed response latencies in Parkinson's Disease".

A different approach was chosen by Lieb and colleagues (1999), who suggest that the increased reaction times in visual search tasks is due to impaired pre-attentive visual processing. The authors measured visual discrimination thresholds for orientation texture stimuli in patients with PD and a healthy control group and found impaired processing of orientation differences in PD. The findings suggest "that not only the retina but also striate and extrastriate visual cortex are affected by this neurodegenerative disease" (Lieb, Brucker, Bach, Els, Lucking, & Greenlee, 1999).

2.5.3 Pathologic mechanisms

Apart from motor programs, the basal ganglia are also implicated in cognitive and behavioural functions. However, it is still unclear, how frontostriatal circuitry precisely relates to cognitive and behavioural impairments seen in PD. It is well documented that the dorsolateral prefrontal cortex mediates executive functions and impairment on tasks

of executive function in PD is likely to be caused by an imbalance in this circuit. A number of deficits reported in visuospatial tasks and memory tasks have also been attributed to frontal executive impairment (Zgaljardic et al., 2003a).

The striatum, as the major input structure of the basal ganglia, appears to play an important role for shifting visual spatial attention, as Kermadi & Boussaoud (1995) showed using a visuomotor task with monkeys. A visual stimulus either re-oriented attention towards a part of space or instructed a limb movement. They found a population of neurons in the striatum and dorsal premotor area that discharge preferentially in relation to cues which reorient spatial attention. The vast majority of cells, however, were found to be selective for cues instructing a motor act.

Findings with PET (positron emission tomography) suggest the putamen to be a relevant structure, involved in voluntary shifts of attention in humans (Koski, Paus, Hofle, & Petrides, 1999).

Frontostriatal circuits connecting frontal lobe regions with the basal ganglia mediate motor, cognitive and behavioural processes within the brain. The anterior cingulate, one of the frontal cortical regions projecting to the striatum, is associated with response initiation, intention, inhibition and conflict monitoring (for a review see Botvinick, Braver, Barch, Carter, & Cohen, 2001). Imbalance in frontostriatal circuits due to dopamine depletion in PD may thus affect performance on tasks eliciting conflict, such as invalid cueing procedures in visual spatial attention tasks.

Apart from dopaminergic imbalance, noradrenergic, cholinergic and serotonergic systems are also affected by the disease. Hence, non-dopaminergic neurochemical alterations may also contribute to cognitive and behavioural impairment in PD. " While noradrenergic and cholinergic systems are thought to be involved in 'low-level' aspects of attention (e.g. attentional orienting), the dopaminergic system seems to be associated with more 'executive' aspects of attention such as attentional set-shifting or working memory" (Coull, 1998).

Summary

Reaction time studies in PD patients have demonstrated a general slowness in both the initiation and the execution of manual movements. However, it remains unclear, whether this slowness derives from impairment in motor execution or from earlier

processes at the level of perception, stimulus-response translation, movement preparation and/or initiation. Several studies have indicated that PD patients are impaired on tasks of visual selective attention. These findings are consistent with the animal literature that suggests a role of the striatum in attentional processes (Kermadi & Boussaoud, 1995). According to Wylie et al. (2005): ” (1) a fundamental function of the basal ganglia is to coordinate response activation and inhibition to resolve conflict between response alternatives that compete for access to the motor system; and (2) diseases that alter information processing in the basal ganglia interfere with the efficient resolution of response conflict.” However, pathologic mechanisms cannot be solely based on depletion of dopamine in the basal ganglia; non-dopaminergic neurochemical alterations must also be taken into account.

2.6 Relationship between selective attention and eye movements

There is converging evidence from numerous experimental studies that we can covertly direct attention to locations in the periphery. However, scanning a visual scene under natural circumstances is an active process, involving eye movements which bring regions of interest from peripheral retinal locations into the centre of acuity - the fovea. Thus, we can look “from out of the corner of our eye,” but if something suddenly attracts our attention, we usually react by making an eye movement. The allocation of attention in alignment with eye movements is usually referred to as “overt attention shifting” as opposed to “covert attention shifting.” Since the early work of Posner during the 1980‘s, extensive research has been carried out on the processes underlying overt and covert shifts of attention. The exact relationship between selective visuospatial attention and eye movements, however, is still a matter of debate.

Whereas some authors propose covert attention to function as an independent scanning mechanism (R. Klein, Kingstone, & Pontefract, 1992; M. I. Posner, 1980a; M. I. Posner, Snyder, & Davidson, 1980), Findlay and Walker (1999) question the explanatory gain of separate systems, since recent studies have shown that an attentional spotlight does not operate faster than a saccadic eye movement (Findlay, 1997; Findlay & Walker, 1999; Sperling & Weiselgartner, 1995; Ward & Brown, 1996). An intermediate view, the “premotor theory of attention,” allocates attention the role of programming motor

actions which are inhibited in their execution. According to this theory, selective visual attention for spatial locations receives its' activation from the same neural circuits as those in charge of motor programming (Rizzolatti, 1983; Rizzolatti, Riggio, Dascola, & Umilta, 1987; B. Sheliga, Riggio, & Rizzolatti, 1994; B. M. Sheliga, Craighero, Riggio, & Rizzolatti, 1997; Umilta, Riggio, Dascola, & Rizzolatti, 1991). At present, it is mostly accepted that the programming of an voluntary eye movement leads to an obligatory shift of covert attention to the saccade target before the voluntary eye movement is executed (Deubel & Schneider, 1996; Henderson & Hollingworth, 1999; Hoffman & Subramaniam, 1995). Peterson and colleaques (2004) could show that covert attention even precedes involuntary eye movements to an unintended location before switching to the intended location. The authors conclude that since the landing point of a saccade always coincides with an aimed attentional shift, "eye movements are a more powerful measure of covert attention than are manual RTs or error rates."

Findings from neurophysiological studies support this tight coupling between shifts of covert attention and eye movements. Single cell recordings in alert monkeys found an increased firing rate of neurons in the superior colliculus for attentional shifts with eye movements (Kustov & Robinson, 1996; Wurtz & Goldberg, 1989). Visuomotor neurons of collicular layer I, which are known to be involved in the preparation of saccades, even showed sustained activity during covert shifts of attention to a pre-cued target location, although this target was never a saccadic goal (Ignashchenkova, Dicke, Haarmeier, & Thier, 2004). Saccade-related activity is also found in V4 neurons, possibly facilitating the integration of pre- and postsaccadic representations of the target (Moore, Armstrong, & Fallah, 2003).

A large body of recent brain-imaging studies reveals an activation-overlap in frontoparietal regions during tasks involving covert and overt shifts of attention (for a review see Corbetta, 1998). A cortical network active during attention shifting and eye movement tasks was identified. This network comprises the superior temporal sulcus and gyrus, the junction between intraparietal and transverse occipital sulcus, anterior and posterior sectors of the intraparietal sulcus, a large swath of tissue along the precentral sulcus and a region on the medial frontal gyrus. According to Nobre and colleagues (2000), only the levels of activation within some commonly shared areas vary with respect to the type of task employed. They conclude that "visual spatial

orienting tasks may be considered as covert analogous of oculomotor tasks" (Nobre, Gitelman, Dias, & Mesulam, 2000). Moore and colleagues (2003) claim that "the mechanism of covert spatial attention emerges as a consequence of the feedback interactions between circuits primarily involved in specifying the visual properties of potential targets and those involved in specifying the movements needed to fixate them" (Moore, Armstrong, & Fallah, 2003).

Assuming that shifts of attention are a prerequisite for saccade programming, what difference does it make in terms of manual reaction time, whether a saccade is executed or not? Verleger and colleaques (2002) targeted this question by studying the effect of saccades during a simple attentional shifting paradigm on manual response times (Verleger, Heide, & Kömpf, 2002). Subjects in this study were not explicitly told to suppress saccades, neither were they aware that saccades were recorded. Three plausible assumptions were made. First, processing of the target stimulus could be the same, no matter whether it is covertly or overtly attended. Hence manual responses would be of equal speed. Secondly, saccades may facilitate visual processing by bringing the object of interest onto the fovea. Thus manual responses become faster. Last, saccades delay visual processing of the target stimulus and hence manual responses, because they are slower than covert shifts of attention. The authors found evidence for the third alternative. The delay effect was less marked in valid trials, where attention was cued to the correct side, and more pronounced for invalid trials, where saccades had to be made to the opposite side.

So far, the functional relationship between attention and eye movements has been considered on the basis of spatial attention tasks, involving cueing paradigms.

Another approach to study the functional relationship between attention shifts and eye movements is the analysis of scanpaths. In normal viewing, saccades interchange with periods of fixation. This sequence is called a scanpath. Assuming that eye movements are preceded by allocating attention to the saccade's target location (Deubel & Schneider, 1996; Henderson & Hollingworth, 1999; Hoffman & Subramaniam, 1995), fixations can be taken as indicators of attentional allocation.

In the previous chapter, it was suggested that selective attention depends on the interplay of bottom up, stimulus-driven and top down, goal-driven processes. In order to investigate scanpaths, two approaches can be chosen. First, visual search tasks allow us

to study scanpaths by systematically varying bottom-up and top-down influence. Instructions are given with regard to a certain target stimulus, surrounded by distracters. The second approach for investigating scanpaths involves free viewing situations. The work of Yarbus (1967) is famous because it has shown how dramatically verbal instructions influence scanpaths of participants viewing a single photograph (Yarbus, 1967). Most subsequent studies have looked at the relationship between certain stimulus features and eye movements (e.g. scanning of faces).

Free viewing situations minimize the risk of distorting the relationship between attentional shifts and eye movements by using specific instructions. However, control of bottom-up stimulus dependent mechanisms, and top-down influences dependent on observers' goals, experience and expectations, are strongly reduced.

Summary

The allocation of attention in alignment with eye movements is usually referred to as "overt attention shifting" as opposed to "covert attention shifting". In the past, attention was thought to constitute a unitary mechanism, independent of motor programming. This view is challenged by the "pre-motor theory of attention," which assumes that spatial attention derives from activation of the same circuits that are in charge of programming eye movements and other motor activities. This theory gains support from neurophysiological and brain imaging studies, suggesting that the neural mechanisms of visuospatial covert attention largely overlap with those of overt attention shifting. Traditionally, the functional relationship between attention and eye movements has been investigated by means of spatial cueing tasks and visual search tasks. However, both involve experimental manipulations which may lead to a distortion of eye movements and attention. Scanning of natural scenes, on the other hand, allows the analysis of free viewing behaviour, neglecting the control of attentional bottom-up and top-down mechanisms.

2.7 The role of eye movements in vision

Throughout the past few decades, the field of eye movement research has grown immensely. This popularity is mainly based on the following facts: 1) Eye movements are, alongside motor acts and speech-production, the most simple physical acts in humans. Although many areas of the brain contribute to some degree to the control of eye movements, they nevertheless form a closed, well-defined system. 2) Eye movements can be regarded as the link between processes underlying sensory, perceptual and cognitive events, involved in the organisation of complex behaviour. This chapter introduces and defines different kinds of eye movements and outlines the basic neural correlates of the eye movement system.

2.7.1 Types of eye movements

Eye movements comprise movements of the eyeball as well as eyelid closure and pupil motor activity. In the present study, eye movements are always referred to in the context of movements of the eye ball. The human eye is capable of making a large amount of different eye movements, although all of them are accomplished by the same six eye muscles.

Three main classes of eye movements can be distinguished:

1. Eye movements to stabilize information on the retina

There are three compensatory mechanisms for stabalizing information on the retina: 1. Eye movements are accomplished as a reaction to movements of one's own body, e.g. vestibular-ocular reflex. 2. The retinal image motion itself results in gaze-holding movements, which are called optokinetic responses and are, for example, experienced when watching a passing train. 3. Smooth pursuit is a slow movement of the eyes which is made when trying to keep a slowly moving object foveated. It cannot be induced voluntarily.

2. Movements of the eyes to shift gaze to objects of interest.

The entire visual field of one eye encompasses a cone of approximately 100 visual degrees (Schandry, 1989). However, high visual acuity is restricted to the fovea, a small region in the central retina (about 1.5 mm in diameter). Two types of movements can be

distinguished: 1. Conjugate saccadic eye movements either direct the fovea to new objects of interest or correct for movements that cause the fovea to be displaced from a target already being attended to. Since visual processing is disrupted (but not entirely inhibited), during eye movements, saccades shift the gaze rapidly. Saccades can be initiated voluntarily, but are ballistic in nature. Thus once they are initiated, their path of motion and destination cannot be changed. 2. Vergence disconjugate eye movements ensure that an object is still foveated by both eyes when its distance from the observer is changed. Eyes converge to focus on nearer objects and diverge to focus on farther objects. Vergence is normally the result of binocular disparity.

3. Micromovements of the eyes

Even when fixating a stationary object, the eyes are not still, but continually making small movements. These micromovements are composed of three components: 1. Slow drift of the eyes. By shifting the eyes slightly during fixation, stimulation of receptors and neurons is retained**.** 2. High frequency, low amplitude tremor occurs due to instability of muscle control. 3. Micro-saccades, or square wave jerks compensate for 1. and 2. They bring the gaze back when the drift has moved it too far from the target.

2.7.2 Saccades

In the present study saccades and fixations were recorded during free scanning, visual search and covert attention shifting. The following paragraph therefore describes saccadic eye movements, which in natural situations always alternate with fixations.

Saccades are made to bring the fovea onto an object or location of interest. Prior to a saccadic eye movement, the following processes take place: 1) discovery of a potential target, 2) decision to bring the target into the centre of focus, 3) alignment of the retinal coordinates of the target with the actual eye position, 4) disengagement from fixation, 5) transforming the spatial code of the planned eye movement into a time course of neural activity, and 6) execution of a saccade.

Depending on the task to be performed, saccades can be categorized into four main classes:

1. Spontaneous saccades are made at random or incidentally, for example in the dark.

2. Express saccades can be observed when there is a temporal gap between fixation and the presentation of a target stimulus. Latency between the appearance of a target

stimulus and beginning of a saccade can be as short as approximately 100 ms (Fischer & Ramsberger, 1984).

3. Reflex saccades, sometimes also referred to as visually guided saccades, are a typical response to a suddenly appearing peripheral stimulus.

4. Voluntary saccades are generated purposefully, meaning we have conscious access. They are dependent on instructions, experience and motivation. Different paradigms are use to assess voluntary saccades, including predictive, remembered, anti-saccades and purely volitional saccades.

Saccades are categorized based on their velocity, duration, amplitude, accuracy, trajectory, and initiation time (see Leigh & Zee, 1999, chap.3).

Velocity, duration and amplitude

Isolated Saccades show a positive relationship between peak velocity and amplitude. Thus, the larger the amplitude the higher the speed. For example, saccades of 1º have a velocity of approximately 60 deg/sec and saccades of 20º have a velocity of approximately 380 deg/sec.

The relationship between amplitude and peak velocity is called main sequence and can be used to distinguish saccades from other eye movements. Main sequence:

peak velocity = V_{max} * (1 – e $^{-Amplitude/C}$), where V_{max} is the asymptotic peak velocity and C is a constant).

Saccade velocity is independent of its duration (see Wurtz & Goldberg, 1989, p.21). The relationship between amplitude and saccade duration can be expressed as follows (see Carpenter, 1988, p.72):

saccade duration (ms) = 2,2 x saccadic amplitude (°) + 21.

However, "it is important to note, that even the biggest saccades last only ~100ms, which is less than the response time of the visual system. Thus, saccades are ballistic movements - there is no time for visual feedback and accuracy depends on internal monitoring and neural signals" (Leigh & Kennard, 2004). Although we have no voluntary control over saccadic speed and duration, there are some factors which are known to influence saccadic velocity, e.g. the level of illumination and the direction of the movement (centripetally vs. centrifugally directed saccades). It is not yet fully resolved whether saccadic velocity declines with age. Apart from velocity, duration and amplitude the shape of the temporal waveform of the saccade can help to classify

saccades. The ratio of the time to reach maximum velocity (the acceleration phase) to the total duration of the saccade gives an estimation of the skewness, or asymmetry of the waveform. Whereas for smaller saccades acceleration and deceleration phases are equal in duration and the skewness ratio is about 0.5, peak velocity for larger saccades is reached earlier relative to the end of the saccade and the skewness ratio decreases down to 0.2.

Accuracy

Accuracy of a saccade is typically measured by its saccadic gain (saccade amplitude/ target amplitude). If the amplitude is greater than the target distance, we speak of saccadic overshoot (hypermetria). Correspondingly, saccades undershoot a target if their amplitude is too small (hypometria). In the latter case, corrective saccades often compensate for insufficient length.

The eyes do not move together perfectly during saccades. A transient intrasaccadic divergence can be observed due to the fact that for horizontal refixations, the saccades of the abducting eye tend to be larger, faster, and more skewed than the concomitant saccades of the adducting eye.

Saccadic Trajectory

Although horizontal and vertical saccades are generated by separate populations of premotor neurons, in diagonal saccades with 45 degrees inclination the horizontal and vertical components are fairly similar and the trajectory is nearly straight. However, compared with purely vertical or purely horizontal saccades of similar size, the horizontal and vertical components in oblique saccades show minor slowing. Hence, at angles other than 45 degrees inclination, the trajectory would be curved since the main sequences of the two components differ.

Initiation time

The initiation time of a saccade can be defined as the interval between target presentation and onset of movement of a saccade. Often the terms “latency” and “saccadic reaction time” are used instead. The onset of a saccade is conventionally determined by the speed of the eye, exceeding a certain threshold. This threshold is usually task dependent. If a study focuses on micromovements of the eyes, high sensitivity is desired and, hence, low thresholds are typically chosen. On the contrary, if for example the purpose of a study is to measure drivers’ gaze behaviour, microsaccades

will be limited and the threshold is increased. Saccadic initiation time, or latency, is a popular measure in cognitive tasks, since it reflects target processing, target selection and motor programming. It is dependent on stimulus properties, such as luminance, and the nature of the cognitive task. According to Carpenter (1988) "…the greatest changes in latency are caused by providing the subject with prior information about the saccadic target. If the subject knows in advance where the target is going to appear, he or she tends to anticipate and shows shorter latencies than if the target can appear in one of the two possible locations" (Carpenter, 1988). Prior information can be spatial, informing about the position at which a target is likely to appear or temporal, informing about when a target will appear. Similar to manual reaction times, saccadic reaction times often show a skewed distribution to the right side.

2.7.3 Fixation

Processing of the retinal image takes place mainly between the saccades, during the so-called fixations. A fixation is a period of relative stability; the eyes do not remain completely still, but engage in small motions (tremor). Fixations are also regarded as an intersaccadic interval.

2.7.4 Eye blink

A blink is a complete or partial closure of the eye. Three types of eye blinks can be distinguished (Orchard & Stern, 1991): 1) reflex blinks that close and open the eyes rapidly, 2) voluntary blinks that are under conscious control and include squinting and winking and 3) endogenous blinks that occur during reading or speaking and reflect thought processes. Blinks typically occur 20 times per minute. If blinks are made during fixation of a stationary target, the eyes transiently move down and toward the nose. Blinks are often made with saccades; the probability of a blink increases with the size of the gaze shift.

2.7.5 The generation of saccadic eye movements

Extraocular muscles

Nerve impulses and eye muscles control the eye's oculomotor system responsible for eye movement and fixation. Rotation of the eye in various directions is accomplished by six external muscles- two oblique muscles and four straight, or recti, muscles. These are innervated by motoneurons which are found in three of the cranial nerve nuclei. The abducens nucleus (VIth cranial nerve) contains rectus motoneurons that are in charge of horizontal eye movements away from the nose. Superior oblique motoneurons that rotate the eye are found in the trochlear nucleus (IVth cranial nerve). The oculomotor nucleus (IIIrd cranial nerve) contains superior and inferior rectus motoneurons for vertical movement, medial rectus motoneurons for horizontal movement towards the nose and inferior oblique motoneurons for rotation.

Table 1: The six oculomotor muscles

Muscle	Cranial Nerve (CN)	Nucleus
lateral rectus	CN VI	abducens
medial rectus	CN III	oculomotor
superior rectus	CN III	oculomotor
inferior rectus	CN III	oculomotor
inferior oblique	CN III	oculomotor
superior oblique	CN IV	trochlear

Saccadic eye movements are driven by a precisely timed pattern of motoneuron activity. A brief initial burst of activity (the pulse) produces a phasic increase in muscle tension to move the eye at a high velocity. Hence, the height of the pulse determines the speed of the saccade. The pulse gradually decays (the slide) until lower-frequency neural activity (the step) sustains the change in muscle tension, required to overcome the elastic restoring forces of the orbital tissue, and holds the eye in the new position (Sparks & Gandhi, 2003). Thus, the step determines the amplitude of the saccade. Neurons that generate the saccadic pulse are active until the eye reaches the target and then automatically cease discharging. Robinson (1975) was the first to describe motoneuron activity in terms of local feedback mechanisms, which continuously

compare desired- and actual eye position. The difference between these two positions yields a motor error signal that drives the eyes at high velocity until the desired eye position and an estimate of the current eye position match (Robinson, 1975).

2.7.6 The eye movement system

The neural structures that control eye movements form a closed, well-defined system (May & Corbett, 1997).

The motor part of the eye movement system is located within the brain stem. The brainstem circuitry, which determines the direction of saccades by premotor neurons, can be subdivided into two gaze centres: the horizontal and the vertical gaze centre. The paramedian pontine reticular formation is the horizontal gaze centre and contains neurons that project to the extraocular motor nuclei. When gaze shifts to the right, excitatory burst neurons increase the activity of lower motor neurons in the right abducens nucleus and inhibitory burst neurons suppress neurons in the left abducens nucleus. Excitatory burst neurons provide the main source of excitatory drive for the saccade-related pulse of motor neuron activity. The burst of action potentials produced by excitatory and inhibitory burst neurons is gated by inhibition from cells found in the midline of the pontine tegmentum. Omnipause cells, found in the midline of the pontine tegmentum, inhibit burst neurons in the paramedian pontine reticular formation, thereby preventing saccades. They discharge at a relatively constant rate during fixation, but are silent during saccades in all directions**.**

The metrics of saccade movement (amplitude, duration and velocity) are coupled to the number of cells activated, burst duration and peak firing rate of the burst of activity, respectively. Neurons in the nucleus prepositus hypoglossi and the medial vestibular nucleus, in contrast, produce the tonic signal that is required for the step of motor neuron activity.

Compared to horizontal gaze, vertical gaze is less well understood. The rostral interstitial nucleus in the midbrain reticular formation near the oculomotor nucleus is the vertical gaze centre. Vertical gaze depends on input from at least two separate oculomotor nuclei. Whereas one fibre path ascends from the vestibular system through the medial longitudinal fasciculus of both sides, a separate pathway descends, presumably from the cerebral hemispheres, through the pretectum to the 3rd nerve

nuclei. The vertical gaze centre also receives input from omnipause cells and contains burst neurons. Neurons in the nucleus of Cajal presumably produce the tonic signal for step in vertical gaze motoneuron activity. Oblique saccades are produced by the cooperation of vertical and horizontal gaze centres.

The superior colliculus, a multi-layered structure situated on the roof of the midbrain, controls the pulse and the step component of the motor signal by sending projections to both the horizontal and vertical gaze centres. The superior colliculus can be divided into two functional regions: the superficial layers, and the intermediate and deep layers. The former receives input from the retina and the latter is important for the generation of saccades. Thus, the superior colliculus acts as an important intermediary between sensory and motor signals, providing the motor command to the burst neurons in the paramedian pontine reticular formation and the trigger command to the omnipause neurons. Collicular neurons discharge a high frequency burst of action potentials immediately prior to saccades. The saccade-related activity of superior colliculus neurons results from input of the frontal eye fields, the posterior parietal cortex, and the substantia nigra pars reticulata.

The frontal eye field (BA 8) lies in the precentral gyrus and sulcus, close to the intersection with the superior frontal sulcus (Rosano, Krisky, Welling, Eddy, Luna, Thulborn, & Sweeney, 2002). Motor neurons in the frontal eye field control the generation of saccades via their projections to the vertical and horizontal gaze centres and the superior colliculus. The activity of frontal eye field neurons contributes to the "selection of a target to which a saccade will be made, the decision whether to look at it or not, and the process of visual scanning of a complex visual scene" (Leigh & Zee, 1999, p.116).

In addition to the frontal eye field, the supplementary eye field in the dorsal medial portion of the frontal lobe, the dorsolateral convexity of the frontal lobe and the parietal eye field (corresponds to area LIP in monkey) in the lateral bank of the intraparietal sulcus also contain neurons involved in programming saccades to visual targets. Other cortical areas important for the programming of saccades are the dorsolateral prefrontal cortex, lying on the dorsolateral surface of the frontal lobe, anterior to the frontal eye field and the posterior parietal cortex. The posterior parietal cortex plays an important role for shifts of visual attention, which may be accompanied by saccades. The

activation of parietal cortex neurons is particularly sensitive to salient visual stimuli and they respond most when a stimulus within their receptive field is a saccade target. In monkey area 7a of the inferior parietal lobule, neurons are found that discharge mainly after saccades have been made. There is a direct connection from frontal and parietal cortical areas to the superior colliculus. Additionally, frontal areas project indirectly through a second pathway involving structures of the basal ganglia, in particular, the GABAergic substantia nigra pars reticulata and the caudate nucleus. The substantia nigra pars reticulata acts as a gate for the voluntary control of saccades. Neurons in the substantia nigra tonically inhibit the superior colliculus, thereby preventing unwanted saccades. Caudate neurons discharge at a low rate that increases prior to saccades. They project to the substantia nigra pars reticulata, hence reducing tonic inhibition prior to a voluntary saccade. This basal ganglia structure is mainly involved in visually guided- and remembered saccades.

In addition to the regions described so far, there is also evidence for a thalamic contribution to the programming of saccades. Saccade-related properties are found in neurons throughout the intramedullary lamina and in neurons of the pulvinar. Whereas the former neurons play a role in relation to spontaneous and visually guided saccades, the latter are thought to be important for directing visual attention (LaBerge & Buchsbaum, 1990).

A further pathway contributing to the control of saccades connects the cortical eye fields via the pontine nuclei to the cerebellum. The cerebellum, in particular the dorsal vermis (lobule VII) and the caudal part of the fastigial nucleus, are also closely connected to the brain stem. In monitoring a corollary discharge of the saccadic command until the eye reaches the target and then terminating the eye movement, this pathway is assumed to play a role for the accuracy of saccades.

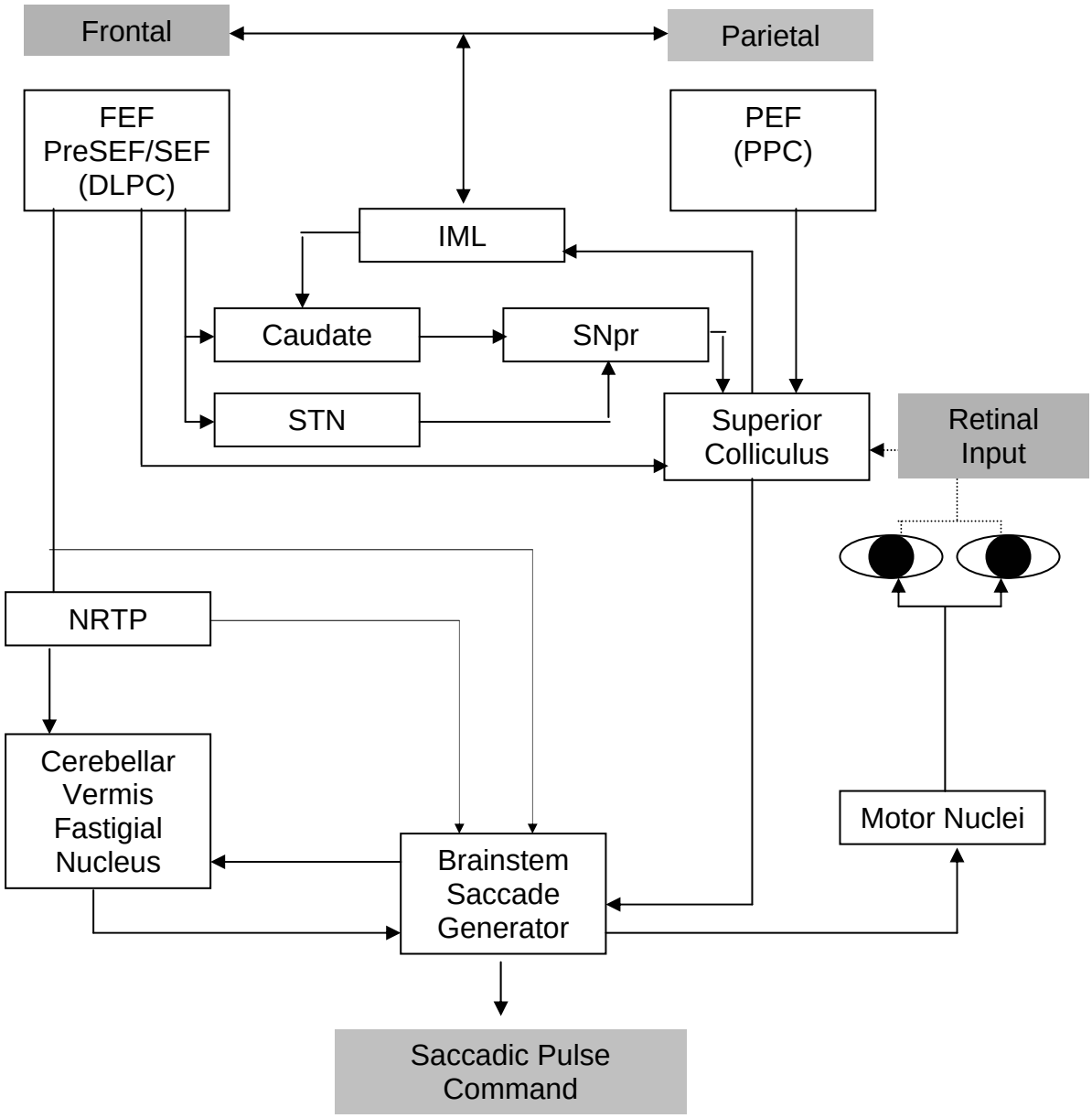

Figure 3: Simplified block diagram of the major structures that projects to the brainstem saccade generator (premotor burst neurons in the paramedian pontine reticular formation and rostral interstitial nucleus of the medial longitudinal fasciculus). Also shown are projections from cortical eye fields to superior colliculus. FEF = frontal eye fields; SEF = supplementary eye fields; DLPC = dorsolateral prefrontal cortex; IML = intramedullary lamina of thalamus; PEF = parietal eye fields (LIP); PPC = posterior parietal cortex; SNpr = substantia nigra pars reticulata; NRTP = nucleus reticularis tegmenti pontis; STN = subthalamic nucleus. Figure adapted and slightly modified from Leigh and Kennard (2004).

Summary

The measurement of eye movements allows the simultaneous investigation of motor, perceptual and cognitive processes. Eye movements can be allocated to three different classes according to their purpose: 1) eye movements that are generated to stabilize visual images on the retina, 2) movements of the eyes that shift the gaze to objects of interest, and 3) micromovements of the eyes. Since the focus of the present study lies within the second class, characteristic saccadic properties such as velocity, duration, amplitude, accuracy, trajectory, and initiation time were described in more detail. Fixations and eye blinks were briefly defined. The gross anatomy of the six eye muscles and their innervations via commands from ocular motorneurons were outlined. Finally, an eye movement system with the interrelated connections between different subcortical and cortical structures was illustrated by a block diagram.

2.8 Eye movements in Parkinson's disease

Impairment of oculomotor control mechanisms in patients with idiopathic Parkinson's disease is well recognised (T. J. Crawford, Henderson, & Kennard, 1989). However, due to the heterogeneity of the disease, results are inconsistent with respect to the nature and extent of oculomotor impairment.

The basal ganglia contribution to the suppression and initiation of saccadic eye movements, through the inhibitory pathway from the substantia nigra pars reticulata (SNr) to the superior colliculus, was briefly described in the previous chapter.

Most studies report normal reflexive saccades in patients with mild to moderate idiopathic Parkinson's Disease (T. J. Crawford et al., 1989; Gibson & Kennard, 1987; Hodgson, Dittrich, Henderson, & Kennard, 1999; Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990, 1992). However, when more severely impaired patients were examined, reflexive saccades where found to be hypometric (Nakamura, Kanayama, Sano, Ohki, Kimura, Aoyagi, & Koike, 1991; Shibasaki, Tsuji, & Kuroiwa, 1979). Hypometria has also been observed for memory guided saccades (T. J. Crawford et al., 1989; Lueck et al., 1990, 1992) and predictive saccades (T. Crawford, Goodrich, Henderson, & Kennard, 1989). Hypometric primary saccades are often followed by correction saccades to a visual target. This frequently observed pattern in PD is referred to as "multi-stepping". The opposite of hypometria, hypermetria relative to the target location, has also been reported for PD patients (O'Sullivan, Shaunak, Henderson, Hawken, Crawford, & Kennard, 1997). Conflicting results have been reported with respect to saccadic latencies in PD. Whereas some authors suggest prolonged latencies in patients with PD (Hikosaka, 1991; Rascol, Clanet, Montastruc, Simonetta, Soulier-Esteve, Doyon, & Rascol, 1989), others found no difference compared to matched controls (Gibson & Kennard, 1987). For reflex saccades, two studies even found faster reaction times for PD patients compared to matched controls (Kingstone et al., 2002; Roll, Wierzbicka, & Wolf, 1996). Mixed results have been obtained for the performance on anti-saccade tasks as well. Some studies have not found any difference compared to matched controls (Lueck et al., 1990; Vidailhet, Rivaud, Gouider-Khouja, Pillon, Bonnet, Gaymard, Agid, & Pierrot-Deseilligny, 1994), others report poorer performance for PD patients (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Crevits & De

Ridder, 1997) and a third finding even suggests superior performance for PD patients (Kingstone et al., 2002).

The velocity of saccades in PD is another area replete with controversy. Whereas some authors suggest that saccadic velocity is preserved (Bronstein & Kennard, 1985; DeJong & Jones, 1971), others found saccadic velocity to be altered in PD (Rascol et al., 1989; Shibasaki et al., 1979; White, Saint-Cyr, Tomlinson, & Sharpe, 1983). Bolger (1999) studied oculomicrotremor, which is constantly present in all humans and occurs when the eye is at rest, in PD patients. Compared with healthy controls, PD patients showed a reduced frequency, as well as an abnormal pattern of oculomicrotremor bursts (Bolger, Bojanic, Sheahan, Coakley, & Malone, 1999).

2.9 Conclusions and research questions

PD is characterized by the three cardinal motor symptoms: bradykinesia, tremor and rigidity. The oculomotor system is also affected by the disease, leading to abnormalities in eye movement parameters. Due to dopamine alterations within the visual system, primary visual processing deficits have also been found. Since the basal ganglia play a crucial role in mediating and integrating motor as well as cognitive programs within the brain, PD is also accompanied by non-motor impairment, including dementia, depression, autonomic failure, visuospatial deficits, impairment in executive functions and memory. The results with regard to attention are ambiguous. For patients with PD, a general slowing of reaction time and a reduced reaction time effect for different cueing conditions, in particular for the difference between invalid and neutral cues, are discussed. However, intact attentional shifting with short (< 800 ms) time intervals between prime and target has also been reported. According to Filoteo and colleagues (1997), altered cueing patterns in patients with PD result from difficulties in inhibiting attentional shifts to other locations.

Disparate findings concerning the extent of impairment are likely to result from differences in experimental design, measurement, and sample populations. In only four of the reported cueing studies involving patients were eye movements recorded via EOG (Bennett et al., 1995; Low, Miller, & Vierck, 2002; Seiss & Praamstra, 2004; Wright, Burns, Geffen, & Geffen, 1990). In these studies, trials in which eye movements were detected were discarded from further analysis.

Patients with PD are known to demonstrate a range of visual and oculomotor impairments. Hence, deficient eye movement control may possibly interfere with performance on tasks of visual selective attention. The intention of the present study is therefore to investigate visual selective attention and to control for possible confounds through the use of basic eye movement parameters. Thus, tasks of visual selective attention are combined with explicit eye movement analysis.

3 METHODS

3.1 Study sample

The study was approved by the local ethics committee. Participation in the study was voluntary and written informed consent was obtained for all subjects after the character of the examination had been explained (see Appendices A and B).

3.1.1 Inclusion/Exclusion criteria

All participants reported having either normal or corrected-to-normal vision and showed right hand dominance. Exclusion criteria were:

- apart from PD, any pre-existing neurological condition
- a pre-existing psychiatric condition
- impaired vision and colour blindness
- substance abuse
- high-dose antiparkinson medication with potentially sedating drugs and /or drug intoxications
- strong head tremor in PD patients
- dyskinesia in PD patients
- patients with Hoehn & Yahr exceeding level three
- diabetes mellitus
- non-idiopthic PD

3.1.2 Classification instruments

MWT-B

Patients and control participants were matched for education using the "Mehrfachwahlwortschatztest" (MWT-B) (Lehrl, Triebig, & Fischer, 1995). The MWT-B (see Appendix C-*I*) provides a measure of verbal intelligence and correlates with more complex intelligence tests fairly well ($r \approx 0.72$). It consists of 37 items, each requesting the participant to select the only meaningful word out of four non-words.

MMSE

The Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) was used as a crude screening device for the current global cognitive state (see Appendix C-*II*). The

MMSE was developed as a "practical method for grading the cognitive state" and has mainly been used by medical clinicians as a bedside test. Although it was never meant to be a diagnostic tool for the diagnosis of dementia, it has frequently been used for that purpose. With a cut-off of 23-24 (max. 30), a sensitivity of 86% and a specificity of 92% is reported (O'Connor, Pollitt, Hyde, Fellows, Miller, Brook, & Reiss, 1989).

UPDRS

Several clinical measures exist to quantify PD symptoms and the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987) is one of the most widely used (see Appendix C-*III*). It was developed for clinicians to monitor impairment and disability caused by PD. The UPDRS is subdivided into four subscales: I) Mentation, Behaviour and Mood, including intellectual impairment, thought disorder and motivation/initiative, II) Activities of Daily Living (ADL), i.e. speech, swallowing, handwriting, dressing and walking, III) Motor, including for example speech, tremor at rest and action or postural tremor, rigidity, finger taps and facial expression and IV) Complications, such as diskinesia and clinical fluctuations. The UPDRS demonstrates high reliability and moderate validity (C.G. Goetz, 2003).

Hoehn & Yahr

The Hoehn and Yahr (H&Y) staging scale is a widely used tool to evaluate disease severity (see Appendix C-*IV*). Whereas the original version (Hoehn & Yahr, 1967) includes five stages of severity, the later version incorporates 0.5 increments for a subtler classification. The stages range from unilateral impairment (Stage 1) to bilateral impairment, postural instabilities, loss of physical independence, and being wheelchair or bed-bound (Stage 5). Although the H&Y scale is a useful tool, especially for evaluating the progression of PD, it has its limitations. First, five stages, which are non-linear, allow only a crude classification. Secondly, postural instability is heavily weighted, neglecting other motor and non-motor factors of PD (C. G. Goetz, Poewe, Rascol, Sampaio, Stebbins, Counsell, Giladi, Holloway, Moore, Wenning, Yahr, & Seidl, 2004).

3.1.3 Patients

Twenty-eight patients, treated for mild to moderate idiopathic PD at the University Hospital Hamburg-Eppendorf, participated in the study. Five patients were not on medication during the time of the study. All other patients were tested during a period of least signs and symptoms, one to two hours after taking medication. Six patients were excluded from the study, one due to impaired colour vision and the other five due to symptom severity. At most one week prior to testing all patients underwent neurological examination, including the MMSE, UPDRS and H&Y scale. Except for one patient (number 2), PD symptoms were rated by means of UPDRS. For all patients, disease severity was estimated by the Hoehn and Yahr staging scale. Duration of illness was estimated from the patients' medical records. The MWTB was administered after the experiments. Because one patient was not a native German speaker and another patient had to leave early for a clinical appointment, scores are missing in two cases.

Due to symptom laterality, two patients responded with their non-dominant hand.

The mean age of the remaining 22 patients was 60.5 years, SD = 9.1 years (range = 37 – 75 years). A description of the patient group is given in Table 2. The results of the group comparisons are presented in Table 4.

Table 2: Description of patients

Patient (number)	Sex (male/female)	Hand tested (left/right)	Handedness (left/right)	Age	Duration of illness (in months)	Hoehn and Yahr (1.0 – 5.0)	MWTB Score (max. 37)	MMSE (1 - 30)
1	f	r	r	67	36	2.0	27	29
2	f	r	r	69	26	2.0	30	30
3	m	r	r	64	40	1.5	34	30
4	f	r	r	64	60	2.0	33	29
5	m	r	r	53	70	2.0	-	30
6	m	r	l	57	34	2.0	32	29
7	m	r	r	59	48	2.0	28	29
8	m	l	r	60	24	2.0	30	30
9	m	r	r	61	48	1.0	32	30
10	f	r	r	56	84	2.0	25	26
11	f	r	r	64	240	2.0	32	28
12	m	r	r	75	156	2.5	31	30
13	m	l	l	37	44	1.0	33	30
14	m	r	r	72	156	2.5	30	30
15	f	r	r	57	24	2.0	35	29
16	m	r	r	41	6	1.0	33	30
17	m	r	r	56	72	3.0	27	28
18	m	r	r	62	56	2.0	23	30
19	f	r	r	60	65	2.0	32	29
20	f	r	r	71	144	2.5	34	30
21	f	r	r	58	22	1.0	-	30
22	f	r	r	69	158	2.5	34	29
				Mean 60.6 SD 9.1	Mean 37.3 SD 59.7	Mean 1.9 SD 0.5	Mean 30.8 SD 3.3	Mean 29.3 SD 1.0

Table 2 (continued): Description of patients

Patient (number)	Medication during testing (yes/no)	Budipin dose	MAO-B Antagonist	L-Dopa dose	Dopamin Agonist	COMT (yes/no)	Anticholinergics (yes/no)
1	y	30 mg		<500mg	Bromocriptinmesilat	n	n
2	y			0	Cabergolin	n	n
3	y		Selegilin	0	Pergolidmesilat	n	n
4	y			<500mg	Pramipexol	n	n
5	y	50 mg		0	Pramipexol	n	n
6	y			0	Ropinirol	n	y (Metixen)
7	n			0		n	n
8	y			0	Dihydroergocryptinmethansulfonat	n	n
9	y			0	Pramipexol	n	n
10	y			0	Pramipexol	n	y (Metixen)
11	y			<500mg	Cabergolin	n	n
12	y			<500mg	Ropinirol	n	-
13	n			0		n	n
14	y			<500mg	Pramipexol	n	n
15	y	35 mg		<500mg	Ropinirol	n	n
16	n			0		n	n
17	y			0	Cabergolin	n	n
18	y			0	Ropinirol	n	n
19	y		Selegilin	<500mg	Pramipexol	n	n
20	y	60 mg		<500mg	Bromocriptinmesilat	n	n
21	n			0		n	-
22	y			<500mg		y	n

Table 2 (continued): Description of patients

Patient (number)	UPDRS 1 Mentation, Behavior, Mood (0 - 16)	UPDRS 2 Activities of daily living (0 - 52)	UPDRS 3 Motor exam (0 - 108)	UPDRS 3 Items 20 -26 L (0 - 28)	UPDRS 3 Items 20 -26 R (0 - 28)	UPDRS 4 A Dyskinesa (0 - 13)	UPDRS 4 B Clinical fluctuations (0 - 7)
1	6	6	17	4	6	0	0
2	-	-	-	-	-	-	-
3	0	3	5	2	2	1	0
4	2	1	3	1	0	0	0
5	1	3	12	4	1	0	0
6	1	6	11	10	5	0	3
7	2	5	28	7	11	2	3
8	0	3	7	1	5	0	0
9	2	5	8	0	8	0	0
10	3	6	14	3	4	0	2
11	4	4	3	0	0	-	-
12	3	6	17	2	7	0	2
13	0	4	16	16	0	0	0
14	6	9	23	8	5	5	3
15	2	3	15	4	6	9	1
16	0	0	13	10	0	2	0
17	6	13	31	12	6	7	4
18	4	15	30	12	7	1	1
19	0	6	25	11	10	0	0
20	2	6	27	10	9	3	2
21	0	5	14	0	9	0	0
22	0	8	36	12	8	0	0
	Mean 2.1 SD 2.1	Mean 5.6 SD 3.5	Mean 16.9 SD 9.6	Mean 6.1 SD 5.0	Mean 5.2 SD 3.5	Mean 1.5 SD 2.6	Mean 1.1 SD 1.4

3.1.4 Controls

25 healthy participants were recruited on a voluntary basis via private contacts. One subject had to be excluded from the experiment due to colour blindness, another subject was not able to participate due to language problems and a third subject was excluded from the analysis because of a psychiatric history. The remaining 22 subjects were selected to achieve parallel groups with respect to age, gender, and education- the latter assessed by the MWTB. The testing situation (experimental procedure, location, equipment and investigator) was identical for control subjects and patients. Two subjects, who were not native German speakers, did not complete the MWTB. The mean age of the control group was 55.2 years, SD = 14.5 years (range = 32 - 77 years). A description of the control group is given in Table 3**.** The results of the group comparisons are presented in Table 4**.**

Table 3: Description of control group

Control Subject (number)	Sex (male/female)	Age	Handedness (left/right)	MWTB Score (max. 37)
1	m	32	r	31
2	m	42	r	36
3	m	68	r	-
4	m	69	r	32
5	f	69	r	35
6	f	50	r	31
7	m	62	r	32
8	m	77	r	36
9	m	65	r	32
10	m	65	r	35
11	m	37	r	33
12	m	77	r	33
13	m	63	l	32
14	m	54	r	34
15	f	55	r	32
16	f	62	r	34
17	f	35	r	30
18	m	37	r	27
19	f	58	r	32
20	f	64	r	30
21	f	37	r	-
22	f	37	l	32

Table 4: T-tests for independent groups - age and education

	PD patient group Mean (SD)	Control group Mean (SD)	T (df)	Significance
Age	60.55 (9.12)	55.23 (14.48)	1.459	$p \leq 0.15$
MWT-B	30.75 (3.26)	32.45 (2.19)	-1.937	$p \leq 0.06$

3.2 Technical setting

The stimuli were presented on a 17 inch colour monitor with a resolution of 800 x 600 pixel and a frequency of 85 Hertz. A constantly dimmed background light illuminated the room apart from the light emitted by the monitor. The display was viewed binocularly at a viewing distance of 57.4 cm. The head was placed in a chin rest and adjusted according to individual height. Manual responses were produced by pressing buttons on a button box, especially developed for clinical studies (Wein, 1996). Four round red buttons with a diameter of 3.5 cm and a height of 1.5 cm were attached to a grey body with a distance of 12 cm between neighbouring buttons. All buttons were sensitive to touch from centre to periphery. Eye movements were recorded using an SMI (Sensori Motor Instruments) "EyeLink" System Type 1, which communicated via a high-speed ethernet connection with the computer that performed the stimulus display. The “EyeLink 1” tracked the pupil and the first Purkinje points. Three cameras were attached to a padded headband (weight 600 g). While two high-speed cameras (CCD sensors) tracked both eyes simultaneously, a third camera (also a CCD sensor) tracked four infrared markers mounted on the visual stimulus display. Thus, head motion was recorded and gaze position was computed. Images were produced at a sampling rate of 250 Hz (4 ms temporal resolution). Spatial resolution was 0.01º of visual angle. Eye movements were detected on-line with a velocity criterion of > 35 °/s, acceleration of > 9500 °/sec/sec and movement of > 0.1°. Despite the high accuracy of the EyeLink system, substantial trial-to-trial variability with respect to absolute gaze position due to slippage of the head-mounted system over time must be considered (Cornelissen, Peters, & Palmer, 2002). Short trial sessions with drift corrections prior to a new session were used to correct the gaze estimate and hence minimize this problem. Additionally, the

EyeLink software includes a calibration procedure which was performed for each subject prior to the first experiment. The investigator sat diagonally behind the participant, running the experiment via the "operator" PC.

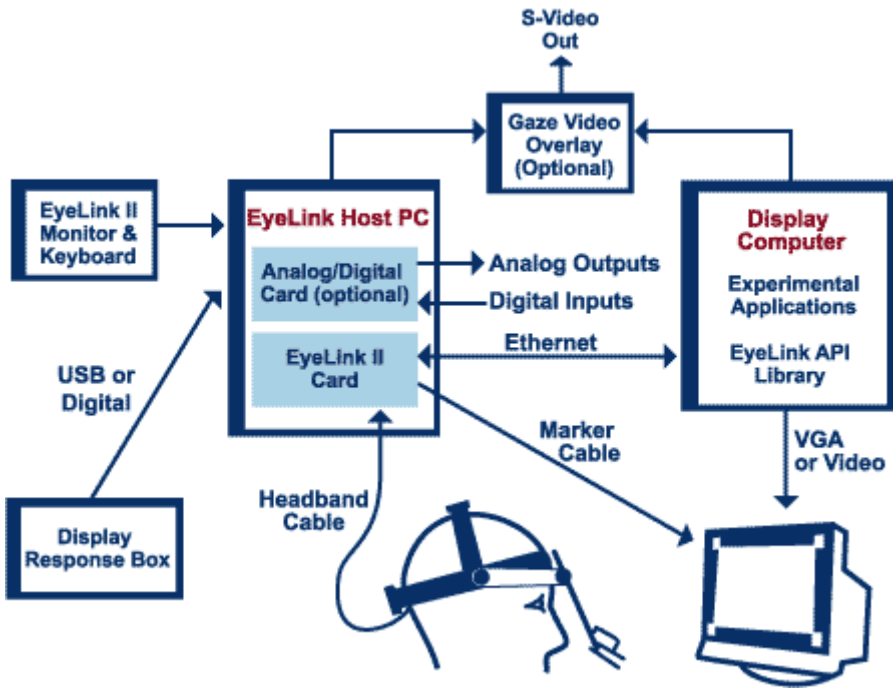

Figure 4: Schematic illustration of the EyeLink I System (SR-Research, 1996).

3.3 Data pre-processing

Binocular vision requires the perfect interplay of all eye muscles. Since binocular control of saccades in PD has been reported to be disturbed (Versino, Zavanone, Colnaghi, Beltrami, Pacchetti, Zangaglia, & Cosi, 2005), only data of one eye (the right eye) was selected for analysis.

The first step consisted of converting binary data (.edf format) into ASCII format for post-processing (see Appendix D for data example visual search). Thereafter, the data was compressed by means of a filter (C+ programming). Since the EyeLink system is prone to artefacts caused by eye-blinks, a filter was implemented which separated real saccades from saccades recorded when the eyelid moved downwards. The remaining events of interest were exported to Excel and sorted into categories (saccades, fixations and eye blinks) by visual basic macros.

The final Excel spreadsheet for fixations contains: temporary position of fixation for each trial (number), spatial coordinates in pixels, the beginning of fixation (absolute), the beginning of fixation in relationship to the last bitmap, and duration of fixation in ms. Correspondingly, the spreadsheet for saccades contains: temporary position of a saccade for each trial (number), the beginning and end of a saccade (absolute), the beginning and end of a saccade in relationship to the last bitmap, spatial coordinates for the beginning and end of a saccade in pixels, duration of a saccade, amplitude of a saccade, saccadic distance on x-axis and maximum velocity of a saccade (see Appendix E for an example).

3.4 Experiments

Altogether, four experiments were carried out within one session. Three experiments are the subject of this study; the fourth experiment was conducted within the scope of an associated "Diplomarbeit" (see Krause, 2003). All participants started out by viewing photographs of natural scenes, continued after a short break with the visual search task and then performed the covert attention paradigm.

The three experiments are separately described. Hypotheses are formulated for each task. A short description of the data analysis for each task precedes the presentation of the statistical results. All analyses were performed with statistical software (SPSS 11.5); a p value of less than 0.05 was considered significant. For all repeated measures analyses of variance (ANOVAs), Greenhouse Geisser correction was used, because the within-subject factors contained more than two levels and correlations between levels were likely. The degrees of freedom were rounded up to whole numbers. For reasons of clarity, the results are discussed separately for each experiment. A general discussion, followed by the study's limitations and implications for future research, is presented at the end.

4 EXPERIMENT 1- VIEWING OF PHOTOGRAPHS

4.1 Stimuli and experimental procedure

The EyeLink system was calibrated for each subject prior to the start of this experiment. Participants were told to relax and look at six photographs (Figure 5), which were presented in consecutive order for 10 seconds each. Apart from that, no instructions were given. The pictures were chosen in an attempt to minimize emotional impact, hence the photographs were considered to be of neutral character. The order of presentation was the same for all participants.

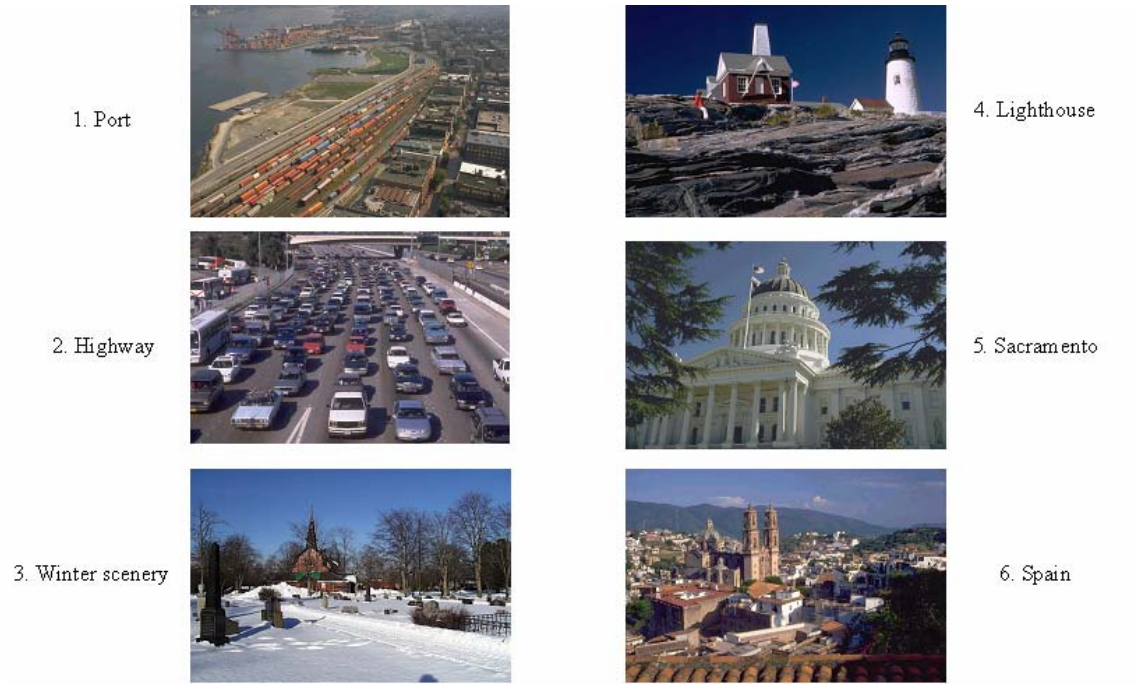

Figure 5: Photographs employed in free viewing

4.2 Variables of interest and hypotheses

Little is known about eye movements in PD when investigated in a free viewing situation. Thus, this first task was mainly explorative, describing fixations and saccades within and between groups.

Since patients with PD suffer from impairment of movement initiation and execution, it is conceivable that "general slowing" (cognitive and/or motor slowing) restricts natural viewing. As a consequence, ***longer fixation periods and hence less saccades in patients with PD compared to healthy controls***, are postulated.

Correlations and group differences of the following saccadic parameters were tested: amplitude, peak velocity and duration.

Saccadic abnormalities and "general slowing" are most profound in severe stages of the disease. It is therefore expected that ***alterations in eye movement parameters are stronger for patients with more progressed stages of the disease (moderate PD) compared to patients with mild PD (see following section 4.3).***

4.3 Statistical analyses

For a preliminary analysis of fixations and saccades, mean number of fixations and mean number of saccades were computed separately for each subject and for each photograph. To ensure valid recording and pre-processing of eye movement parameters, the relationship between these variables was assessed by computing product-moment correlation-coefficients for each group. To compare patients and control participants on these variables, two two-way repeated measures ANOVAs with group (patients vs. controls) as the between subject factor and photograph as the within subject factor, were carried out. A repeated measures ANOVA approach was also used to compare groups on saccadic properties: amplitude, peak velocity and duration. For these three variables, means were computed separately for each subject, pooled across photographs. Three separate repeated measures ANOVAs were then carried out on these variables. In addition, the relationship between peak velocity and amplitude and the relationship between amplitude and duration was examined by computing product-moment correlation-coefficients separately in each group.

In the literature, saccadic abnormalities in PD are mainly reported for patients at more severe stages of the disease. In order to test the effect of disease severity on saccadic parameters, patients with mild PD were distinguished from patients with moderate PD by performing median splits on duration of illness, UPDRS (scale 3) motor exam and Hoehn & Yahr Scale. These grouping factors were then used as between-subject factors in three separate univariate ANOVAs on number of saccades, saccadic duration, amplitude and peak velocity.

Eye position during fixation provides information about locations of interest. To investigate whether attended locations were similar for both groups of subjects, each photograph was split into six regions of interest (Figure 6) and two-way ANOVAs were computed for each photograph separately with position (1-6) and group as factors.

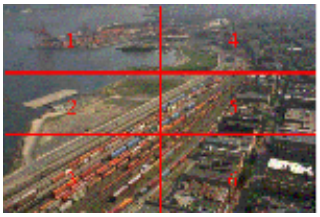

Figure 6: Example of photograph with six regions of interest.

4.4 Results

Due to technical difficulties resulting in an incomplete eye movement script, only 21 patients (nr.1 missing) and 22 control subjects entered the statistical analyses.

4.4.1 Relationship between number of fixations and number of saccades

During natural scanning, saccades and fixations constantly alternate. Thus, in normal scanning behaviour, the number of fixations and saccades is highly correlated. Table 6 presents means, standard deviations and product-moment correlation-coefficients of fixations and saccades, pooled within groups, separately for each photograph. In both groups, the number of fixations and the number of saccades are almost perfectly correlated for all six pictures ($r(12)>.98$, $p<0.001$), indicating valid measurement and data processing. Although on average patients, compared to control subjects, make fewer fixations and fewer saccades for each photograph, this difference did not prove to be significant when tested by two separate analyses of variance (ANOVAs): fixations (ANOVA $F(1,41)=1.88$, $p=0.18$), saccades (ANOVA $F(1,41)=1.88$, $p=0.18$). The main effect of the different photographs was highly significant in both ANOVAs: fixations (ANOVA $F(4,180)=9.90$, $p<0.001$), saccades (ANOVA $F(4,180)=8.41$, $p<0.001$). There was no significant interaction ($p>0.05$).

Table 6: Fixations and saccades for each photograph, averaged within groups (mean ± standard deviation, Pearson product-moment correlation-coefficients (** = $p<0.001$)).

Photograph	Number of Fixations		Number of saccades		Correlation	
	Patient group (n = 21)	Control group (n = 22)	Patient group (n = 21)	Control group (n = 22)	Patient group (n =21)	Control group (n = 22)
Port	31.52±5.40	32.55±5.46	31.57±5.45	32.64±5.44	0.99**	0.99**
Highway	31.29±5.56	33.14±5.97	30.29±5.57	32.36±5.93	0.99**	0.99**
Winter Scene	28.57±4.37	30.14±4.82	28.67±4.35	30.14±4.83	0.99**	0.99**
Lighthouse	29.90±4.55	31.23±6.70	28.95±4.56	30.18±6.70	0.99**	0.99**
Sacramento	26.62±4.94	29.36±6.46	26.67±4.94	29.41±6.53	0.99**	0.99**
Spain	29.05±5.13	32.18±6.58	29.05±4.93	32.63±5.96	0.99**	0.98**

4.4.2 Saccadic metrics

Saccades are, among other properties, defined by their amplitude, peak velocity and duration. Table 7 presents group means and standard deviations for these variables, pooled across photographs.

Three two-way repeated measures analyses of variance were carried out on amplitude, peak velocity and duration with photograph as the within subject factor and group as the between subject factor.

Significant main effects of photograph were found for all three variables: amplitude (ANOVA $F(3,120)=3.73$, $p<0.05$), peak velocity (ANOVA $F(4,166)=10.77$, $p<0.001$) and duration (ANOVA $F(3,120)=3.57$, $p<0.05$). The groups did not differ significantly in amplitude (ANOVA $F(1,41)=0.18$, $p=0.68$), peak velocity (ANOVA $F(4,41)=0.43$, $p=0.52$) or duration (ANOVA $F(1,41)=0.33$, $p=0.86$), nor was there any significant interaction between group and photograph for any of the three variables ($p>0.05$).

Table7: Saccadic metrics for patients and control subjects (mean $\pm$ standard deviation).

Variable	**Patient group (n = 21)**	**Control group (n = 22)**
Amplitude (cm)	6.92 $\pm$ 2.03	7.12 $\pm$ 2.04
Peak Velocity (deg/s)	264.61 $\pm$ 48.72	273.99 $\pm$ 56.63
Duration (ms)	42.50 $\pm$ 13.60	43.06 $\pm$ 11.15

4.4.3 Relationship between peak velocity and amplitude

Saccades show a positive relationship between peak velocity and amplitude, called main sequence:

$$\textbf{peak velocity} = V_{max} * (1 - e^{-Amplitude/C}),$$

where V_{max} is the asymptotic peak velocity and C is a constant (see Wurtz & Goldberg, 1989, p.21).

To assess whether a positive relationship between peak velocity and amplitude exists in patients and control subjects, means were computed for all subjects (pooled across photographs) and correlated separately for each group. The correlations turned out to be significant ($r(43)>0.46$, $p<0.01$). Figure 7 depicts the relationship between peak velocity and amplitude for all subjects, averaged over the six photographs.

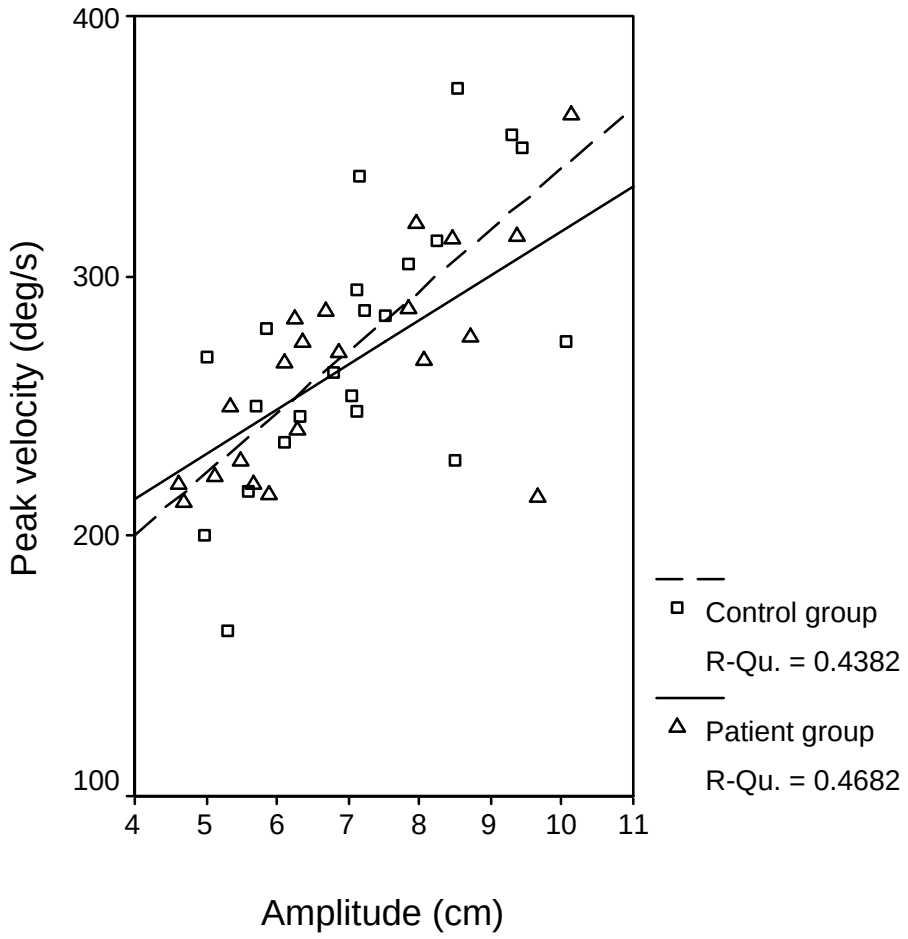

Figure 7: Scatter plot depicting main sequence for patients and control subjects averaged over photographs. The best-fitting regression line is presented for each experimental group. R-squared (R-Qu.) indicates the common variance for the two sets of variables.

4.4.4 Relationship between amplitude and duration

The relationship between amplitude and saccade duration is expressed as:

saccade duration (ms) = 2.2 x saccadic amplitude (°) + 21

(see Carpenter, 1988, p.72).

To assess whether a positive relationship between saccade duration and amplitude exists in patients and control subjects, means (pooled across photographs) were correlated separately for each group. Significant correlations were obtained ($r(43)>0.65$, $p>0.01$). Figure 8 illustrates the relationship between peak velocity and amplitude for all subjects, averaged over six photographs.

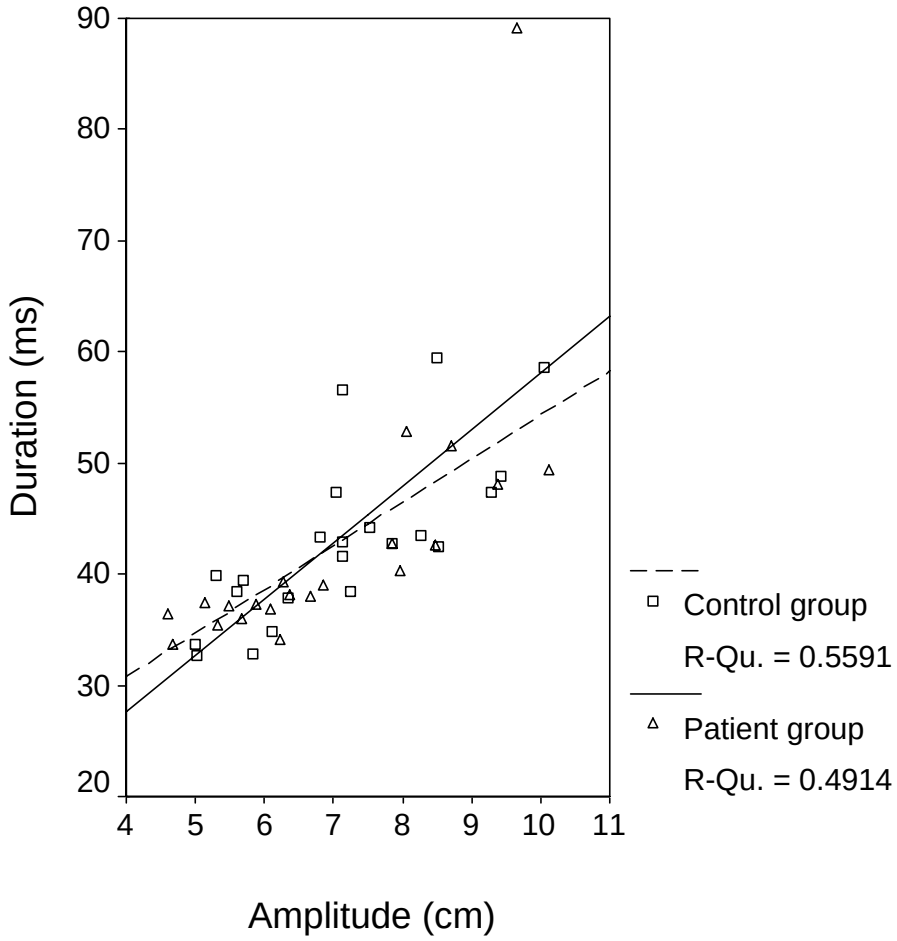

Figure 8: Scatter plot depicting the relationship between amplitude and duration for patients and control subjects averaged over photographs. The best-fitting regression line is presented for each experimental group. R-squared (R-Qu.) indicates the common variance for the two sets of variables.

4.4.5 Association between saccadic velocity and age

It is not yet fully resolved whether saccadic velocity declines with age. The influence of age on saccadic velocity in the present task was assessed by correlating mean saccadic velocity for each subject, pooled across photographs, with age. No significant correlations between age and peak velocity were found in patients ($r=-0.20$, $p>0.05$), or in control participants ($r=-0.00$, $p>0.05$).

4.4.6 Association between saccadic parameters and progression of PD

In order to test whether patients with mild PD differ from patients at moderate stages of PD in saccadic parameters (number of saccades, saccadic duration, amplitude and peak velocity), variable means for each patient, pooled across photographs, were computed and median splits were performed on duration of illness and UPDRS (scale 3) motor exam (Table 8). A median split for the Hoehn & Yahr Scale (median 2) did reveal unequal groups and was therefore dismissed. Univariate ANOVAs on the four saccadic parameters as dependent variables with severity as the between subject factor did not reveal any significant differences between mildly and moderately affected patients (see Table 9 for ANOVA results).

Table 8: Mild versus moderately affected patients, groups distinguished by median splitting

Variable	Median	Mild PD n <= median	Moderate PD n >median
Duration of illness (months)	52	10	11
UPDRS 3 (motor exam)	15	10	10

Table 9: Results of 12 ANOVAs, comparing patients on saccadic parameters. Patient groups are median split according to three variables of disease severity.

	Variable	N (PD mild)	N (PD moderate)	F	df	p
Duration of illness (in months)	**Saccades (number)**	10	11	2.22	1	0.15
	Duration	10	11	0.75	1	0.40
	Amplitude	10	11	0.05	1	0.82
	Peak velocity	10	11	0.83	1	0.38
UPDRS 3 (motor exam)	**Saccades (number)**	10	10	2.50	1	0.13
	Duration	10	10	0.63	1	0.44
	Amplitude	10	10	0.59	1	0.45
	Peak velocity	10	10	0.63	1	0.44

4.4.7 Picture exploration

To investigate whether attended picture segments were similar for both groups of subjects, two-way ANOVAs were computed for each photograph separately with position (1-6) and group as factors.

Regions of interest were very similar for both groups of subjects. A significant difference between the groups was not found for any of the photographs: port (ANOVA $F(1,223)=0.01$, $p=0.91$), highway (ANOVA $F(1,231)=0.01$, $p=0.91$), winter scenery (ANOVA $F(1,179)=0.24$, $p=0.62$), lighthouse (ANOVA $F(1,187)=0.01$, $p=0.91$), Sacramento (ANOVA $F(1,178)=0.39$, $p=0.53$), Spain (ANOVA $F(1,185)=0.01$, $p=0.94$). Obviously, due to picture content, the number of fixations differed significantly for position for both groups. This effect was found for all photographs ($F(6)>13.95$, $p<0.001$).

4.5 Discussion

The first task was mainly explorative, describing fixations and eye movements during viewing photographs of natural scenes. As presumed for normal scanning behaviour, saccades and fixations were found to alternate regularly in both groups of subjects. Although this result is certainly not surprising, it confirms accurate eye movement measurement. Patients and controls did not differ significantly with respect to the number of fixations and saccades made. However, on average, patients made fewer fixations and fewer saccades for each photograph, providing tendential support for the postulated assumption of a "general slowing" deficit.

Saccades are, among other properties, defined by their amplitude, peak velocity and duration. Significant correlations between peak velocity and amplitude and between amplitude and duration have been obtained for both groups. The groups did not differ significantly on amplitude, peak velocity and duration. In the literature, saccadic abnormalities have mostly been described for more severely affected patients. Thus, in tasks with a pre-defined target stimulus, altered saccadic amplitudes (hypometria, hypermetria) are frequently reported in advanced patients. Data about saccadic velocity in PD is less homogeneous. Whereas some authors suggest saccadic velocity to be preserved (Bronstein & Kennard, 1985; DeJong & Jones, 1971), others found slowing of saccades (Rascol et al., 1989; Shibasaki et al., 1979; White et al., 1983).

Since our sample did not include severely affected patients (H&Y score < 4), we examined whether impairment can be observed in moderately affected patients compared to mildly affected patients. For this purpose, median splits were performed on duration of illness and UPDRS (scale 3) motor exam. No significant differences between patient groups were obtained. Thus, for the natural viewing of photographs, no saccadic abnormalities became apparent in our patient sample. In order to investigate age-related lowering of peak saccadic velocities reported in the literature (Wilson, Glue, Ball, & Nutt, 1993), the association between these variables was tested for all subjects. The results do not confirm a negative relationship for the present task and study samples.

Oculomotor abnormalities reported in the literature stem either from clinical bedside testing situations or from highly controlled laboratory settings and results depend

strongly on experimental methodology and patient samples. Thus, the absence of significant eye movement abnormalities in the present task indicates normal scanning behaviour for a free viewing situation for patients with mild to moderate PD. This finding is further underscored by investigating regions of interest for both groups of subjects. Dividing each picture into six regions of interest, we did not find any significant differences between groups. Thus, gaze was attracted by similar visual information in each picture. Overall, the results of the first task suggest, that both groups of subjects demonstrate similar scanning behaviour for natural scenes. However, it must be considered that qualitative visual differences, due to dopamine alterations within the visual system (e.g. impaired colour vision or decreased acuity), convergence insufficiency or even optic hallucinations cannot be excluded.

5 EXPERIMENT 2 - VISUAL SEARCH

5.1 Stimuli

Pictures were composed of the four playing card symbols: diamonds (♦), hearts (♥), spades (♠), and clubs (♣). The symbols (stimuli) were of equal size, measuring 1.5º x 1.5º. Each picture consisted of 40 stimuli, pseudo-randomly distributed over the computer screen. The background was held constant in a neutral grey with a luminance of approximately 25 cd/m². The symbol spades, displayed in the known upright fashion, served as target stimulus and was only present once in each picture. The target stimulus was surrounded by distracting stimuli (distractors). The minimal distance between the stimuli were 4º horizontally and 2º vertically. In some pictures, the distractors were changed according their direction of presentation (upright or upside down) or according to their original colour (red or black). Initially, 30 pictures were designed. In a pilot study, six students rated these pictures according to the level of difficulty of finding the target stimulus. From 30 pictures, 10 pictures (see Table 5) with different levels of difficulty were selected in a consensus procedure (see Figure 9 for an example). These were mirrored across their vertical axis to create ten more pictures of the same level of difficulty. Each picture was presented twice, hence participants saw 40 pictures altogether. The order of presentation was determined by a computerised randomization procedure and was the same for all participants (see Appendix F).

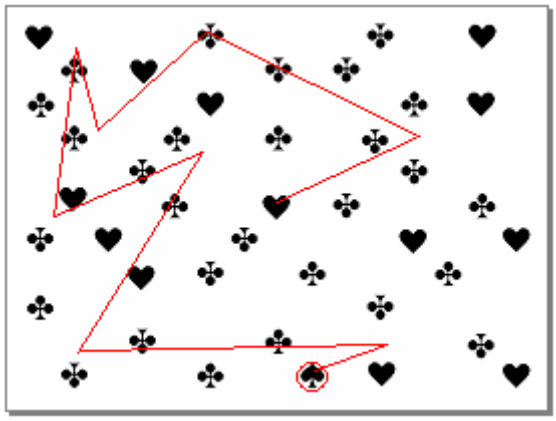

Figure 9: Example of a successful visual search (picture 3). Red line represents saccadic pathway.

Table 5: Overview of distractor characteristics in 10 visual search displays

Picture	Type of distractors	Number of distractors	Orientation of distractors	Colour of distractors
1	♥	19	upside down	black
	♣	20	upside down	black
2	♣	20	upright	black
	♣	19	upside down	black
3	♥	13	upright	black
	♣	13	upright	black
	♣	13	upside down	black
4	♦	19	upright	red
	♣	20	upright	black
5	♦	13	upright	red
	♥	13	upright	red
	♣	13	upright	black
6	♦	8	upright	red
	♥	8	upright	red
	♥	8	upside down	black
	♠	7	upside down	black
	♣	8	upright	black
7	♠	39	upside down	black
8	♠	20	upside down	black
	♠	19	upright	red
9	♠	39	upright	red
10	♣	39	upright	black

5.2 Procedure

In order to make sure that all participants were familiar with playing card symbols, participants were shown real playing cards and asked to name the symbol of a respective card.

Prior to the appearance of a picture, a central fixation cross was shown on the screen. The system was newly calibrated for each picture, to ensure that all participants started searching from the central fixation point. Each picture was presented for 10 sec. The inter-trial-interval was fixed at 3 seconds. Participants were instructed to search each picture overtly, hence moving the eyes directly in the search for the target stimulus. While searching, the lower button of the button box was pushed down. Subjects were instructed to look directly at the target stimulus, release the lower button and press the upper button. They were then asked to return to the lower button and hold it pressed down until the next picture was presented.

5.3 Variables of interest and hypotheses

Visual search tasks can be accomplished in the absence of eye movements, hence covertly. However, in a typical search experiment without explicit instructions, participants nevertheless make eye movements as part of natural search behaviour (Zelinsky & Sheinberg, 1997). Zelinsky and Sheinberg (1997) emphasise the additional information gained by oculomotor measures and even suggest to "redefine search in terms of eye movements rather than RTs".

For the present task, participants were instructed to scan the display overtly. After a stimulus was recognised as the target stimulus and fixated, the successful search was indicated by a manual response. Since saccadic eye movements are very brief, they usually arrive at a target stimulus before the start of a hand movement (Abrams, Meyer, & Kornblum, 1990). The average time interval between the end of a goal-directed eye movement and the end of a goal-directed hand movement is 386 ms across different tasks (Sailer, Eggert, Ditterich, & Straube, 2000).

For the current task, three variables of interest were defined: 1) visual search time (VST – picture presentation onset until end of target saccade), 2) movement initiation time (reaction time (RT) – end of target saccade until lower button release) and movement execution time (movement time (MT) - lower button release until target button press).

According to the response selection theory of the basal ganglia, their primary function is selecting a motor programme by activating and inhibiting competing programes (Mink, 1996). Distractor stimuli in the visual search display are likely to activate irrelevant motor programs, hence increasing the load on response selection mechanisms.

Based on this assumption, it is hypothesised that due to deficient inhibitory mechanisms patients with PD as compared to healthy control subjects are more affected by competing information. In other words, visual search is expected to be less efficient in patients with PD. Hence, activation of irrelevant motor programs by distractor stimuli is assumed to be reflected by an ***increased amount of saccades*** resulting in ***prolonged visual search times.***

With an increase in competing information, impairment is likely to be more apparent. Thus, ***for patients with PD, performance is assumed to be similar to controls on "pop-out" displays but weaker on more competitive searches.***

Even in the early stages of PD, a general slowness in the initiation (Stelmach et al., 1986) and the execution of manual movements is found (e.g. Bekkering, Neggers, Walker, Gleissner, Dittrich, & Kennard, 2001; Isenberg & Conrad, 1994). Hence, ***RT and MT are both hypothesised to be increased in PD.***

5.4 Statistical analyses

Visual search was considered successful when a button press was preceded by a saccade which terminated on the target stimulus or at a maximum distance of 1.5º from the edges of the target stimulus. This tolerance takes measurement uncertainty and imprecise saccades into account and leaves space for saccadic over- or undershoot. Pilot research on six students had shown that a button press did not always immediately follow the target saccade. If more than one saccade during a trial entered the target range, only the last target saccade before button press was considered a hit. Earlier saccades reaching the target range, but not followed by a button press, were treated as undetected targets and therefore neglected. To increase statistical power, mirrored pictures were treated as repetitions of the ten original pictures. Variables of interest were: number of saccades for each picture, saccadic duration, visual search time (VST – time from picture onset until end of target saccade), manual reaction time (RT – time from end of target saccade until lower button release) and movement time (MT – time from lower button release until upper button press). Values, exceeding three standard deviations of the group mean for each picture, were considered outliers and excluded. By histogram inspection, all variables of interest appeared to follow a normal distribution. A search was considered successful when prior to a button press, a saccade hit the target range. Due to the overall fairly small amount of successful searches (see 5.6 for a discussion), pictures could not serve as a within-subject factor of the intended repeated measures analyses of variance**.** Instead, t-tests for independent samples were computed for each picture on variables of interest. To assess the association between VST and RT and the association between RT and MT**,** product-moment correlation-coefficients were computed across all pictures, separately in each group.

5.5 Results

Data from 22 patients and 22 control subjects entered the statistical data analyses for this task.

5.5.1 General search performance

40 pictures were shown. Visual search was considered successful when a button press was directly preceded by a saccade which terminated on the target stimulus or at a maximum distance of 1.5º from the edges of the target stimulus. On average, patients performed 12.41 (SD 6.06) searches correctly, compared to controls with an average of 16.05 successful searches (SD 5.57). This difference proved to be significant (ANOVA, $F(1,43)=4.30$; $p<0.05$). Only a small percentage of incorrect searches can be ascribed to missed target stimuli. Whereas control participants on average, did not detect the target stimulus within the given time in 2.94 (SD 3.75) pictures, PD patients on average missed the target in 3.53 (SD 3.73) pictures. This difference was not significant (ANOVA, $F(1,34)=0.29$; $p=0.60$). Only data from successful searches entered further analyses.

5.5.2 Number of saccades

To investigate whether the two groups differed with respect to the number of saccades made for each of the ten original pictures, t-tests for independent samples were computed. Means and standard deviations are presented in Figure 10. Contrary to expectation, no significant differences were found for any of the pictures ($p>0$ .05).

5.5.3 Duration of saccades

To investigate whether the two groups differed with respect to the duration of saccades made for each of the ten original pictures, t-tests for independent samples were computed. Means and standard deviations are presented in Figure 11. For picture 6, saccade duration was significantly longer in patients than in controls ($t(28) = 2.75$, $p<0.05$). Groups did not differ in saccade duration for any of the other pictures ($p>$ 0.05).

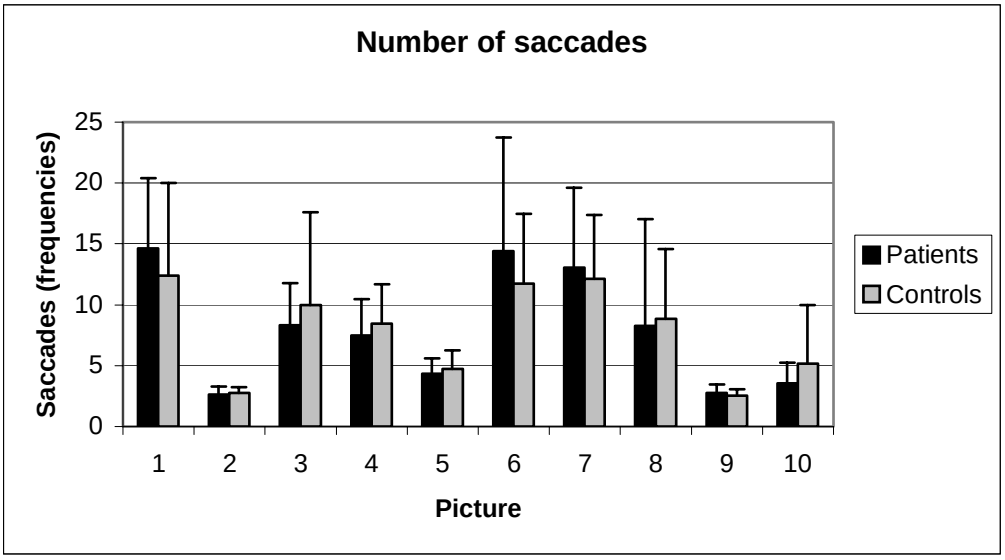

Figure 10: Number of saccades for each picture (mean + standard deviation).

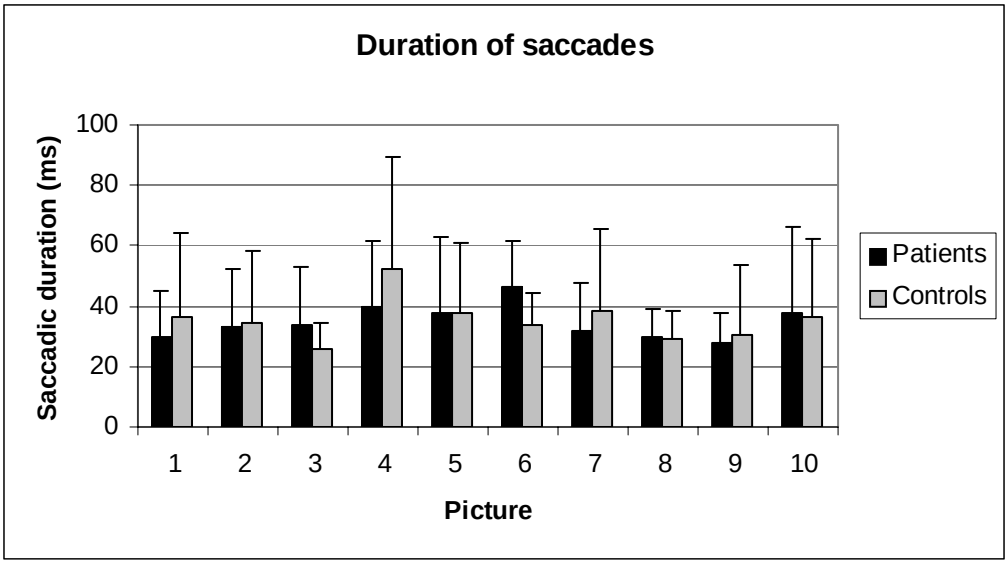

Figure 11: Duration of saccades for each picture (mean + standard deviation).

5.5.4 Visual search time

Visual search time (VST) was defined as the time from picture onset until the end of the target saccade. Table 10 presents means and standard deviations of VST for ten pictures in ascending order for each group. Whereas patients demonstrated the shortest VST for picture 2 followed by picture 9, the opposite is true for control participants. In both

groups, VST increased for pictures 10, 5 and 4, followed by pictures 3 and 8 for patients and the reverse, pictures 8 and 3, by control participants. For both groups of subjects, the longest VST was observed for pictures 6, 7 and 1. T- tests for independent samples did not yield any significant group differences ($p > 0.05$). The relatively small amount of successful searches in both groups and the failure to identify statistically significant group differences for VST precluded any further investigation of the hypothesised stronger impairment of inhibitory mechanisms in patients with progressed stages of the disease.

Table 10: Visual search time for each picture, averaged across groups (mean ± standard deviation). VST is presented in ascending order.

Picture	N	Patient group	Picture	N	Control group
2	13	562.76 ± 165.55	9	18	523.39 ± 181.31
9	18	660.45 ± 533.52	2	19	630.78 ± 140.84
10	16	940.14 ± 698.32	10	14	720.99 ± 169.41
5	15	954.23 ± 262.32	5	16	978.13 ± 460.68
4	11	1582.3 ± 665.94	4	18	2000.47 ± 821.17
3	18	2074.36 ± 1155.47	8	22	2037.77 ± 1469.67
8	17	2153.73 ± 2623.89	3	21	2367.00 ± 1792.19
6	17	2918.32 ± 1770.91	6	16	2489.24 ± 1301.57
7	18	2961.63 ± 1502.09	7	18	2552.99 ± 1026.47
1	17	3299.19 ± 1497.33	1	20	2645.88 ± 1380.42

5.5.5 Reaction time

Manual reaction time (RT) was defined as the time interval from the end of target saccade until button release. Figure 12 presents RT means and standard deviations for ten pictures, pooled across subjects of each group. Significant group differences were obtained for picture 2 ($t(35) = 2.19$, $p<0.05$) and picture 5 ($t(26) = -2.4$, $p<0.05$). Whereas for picture 2 longer RTs were observed for patients, controls exhibited longer RTs for picture 5. To assess the association between VST and RT in patients and control subjects, product-moment correlation-coefficients were computed across

pictures, separately for each group. A positive correlation was obtained for patients ($r(134)=0.28$, $p<0.001$) and control subjects ($r(129)=.44$, $p<0.001$).

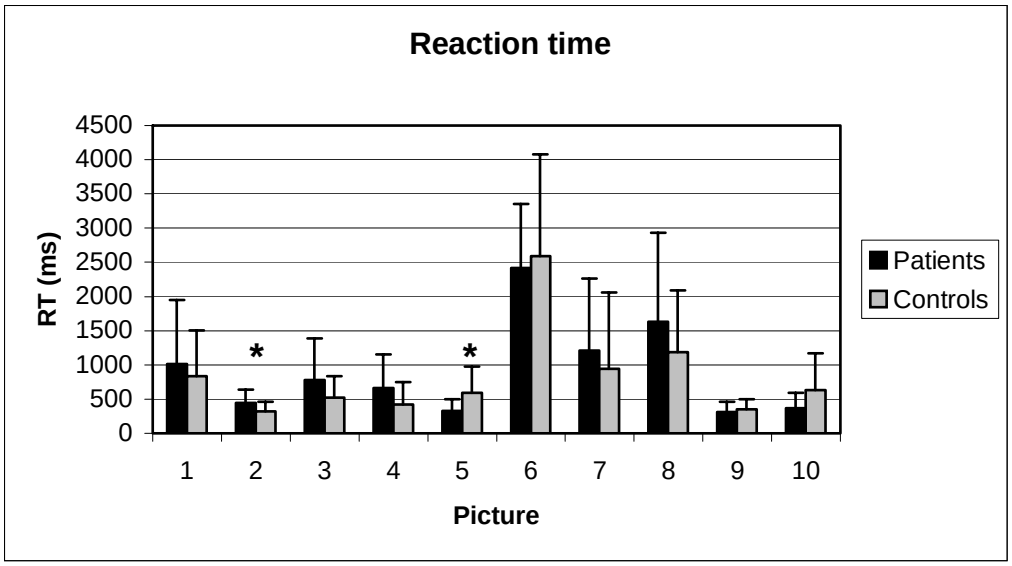

Figure 12: RT for each picture (mean + standard deviation). Asterix indicates significant differences (paired t-tests), * $p<= 0.05$.

5.5.6 Movement time

Movement time was defined as the time interval from lower button release until upper button press. Figure 13 presents means and standard deviations for movement time for ten pictures, pooled across subjects of each group. For all pictures, patients exhibited longer movement times compared to control participants. Independent sample t-tests revealed that the difference in means was significant for picture 2 ($t(32) = 3.16$, $p<0.05$), picture 3 ($t(27) = 3.49$, $p<0.01$), picture 5 ($t(29) = 2.01$, $p=0.05$), picture 7 ($t(36) = 2.18$, $p<0.05$), picture 8 ($t(33) = 3.21$, $p<0.01$), and picture 9 ($t(34) = 2.44$, $p<0.05$).

To assess the association between RT and MT in patients and control subjects, Pearson correlation-coefficients were computed across pictures, separately for each group. A positive correlation was observed for patients ($r(154)=0.37$, $p<0.001$), but not for control subjects ($r(162)=0.06$, $p=0.46$).

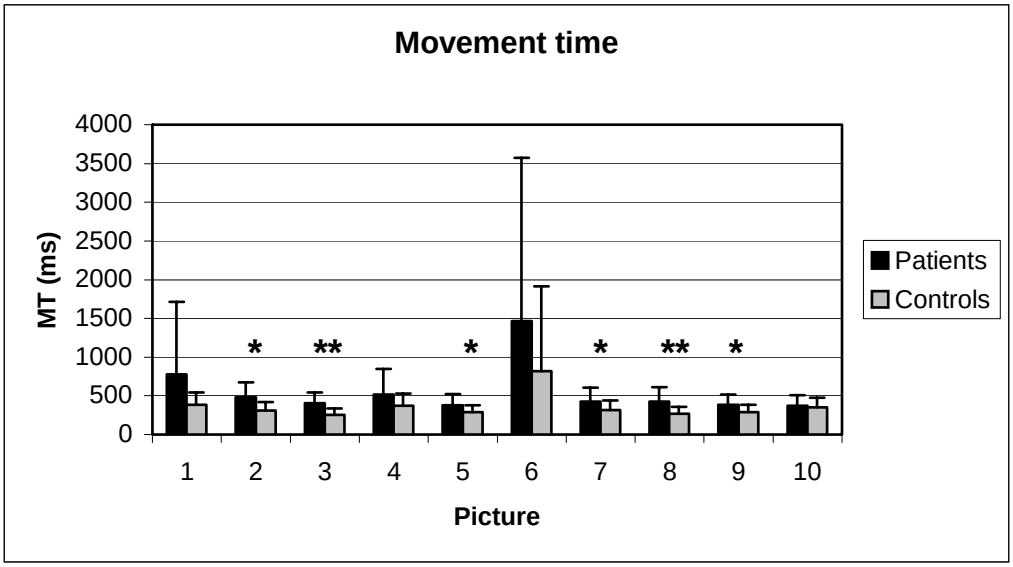

Figure 13: MT for each picture (mean + standard deviation). Asterix indicates significant differences (t-tests), * p<=0.05; ** p<= 0.01.

5.6 Discussion

The effect of interference, induced by target-distractor competition, was investigated in a visual search task. Past research on visual search performance in patients with PD has yielded conflicting results, concerning whether or not parallel and serial search mechanisms are impaired (Troscianko & Calvert, 1993). In a typical search experiment without explicit instructions, participants make eye movements as part of natural search behaviour (Zelinsky & Sheinberg, 1997).

In contrast to earlier studies, visual search performance for this study was split into four components: 1) error rate, 2) visual search time, 3) manual initation time (RT) and 4) manual execution time (MT). This additional information is of particular interest when studying patients with known oculomotor and motor impairment. For example, 1 sec RT can correspond to twenty saccades of approximately 40 ms or two saccades of 40 ms with a long fixation. In addition, RT also includes the motor response of button release.

The general performance of patients and matched control subjects was rather disappointing. Only 30% of searches were successful in patients and 40% of searches in controls. This difference was significant. Since only a small percentage of incorrect searches can be ascribed to missed target stimuli, the amount of successful searches is not considered to be a good indicator for visual search performance in general. It is unlikely that measurement inaccuracy accounts for the poor outcome, because recalibration of the EyeLink system was done prior to each picture and the tolerance of 1.5º degrees should cover technical imprecision. Another possible explanation could be that participants pressed the target button without detection of the target stimulus, thus participants were not compliant. Since subjects were told that due to the recording of eye movements, successful searches could be distinguished from unsuccessful searches, this reasoning does not appear plausible either. Since it is widely agreed that the programming of a voluntary eye movement leads to an obligatory shift of covert attention to the saccade target before an eye movement is executed (Deubel & Schneider, 1996; Henderson & Hollingworth, 1999; Hoffman & Subramaniam, 1995), it is likely that the button release coincided or even preceded the landing of the target saccade in time. However, the relationship between saccades and covert shifts does not

seem to be one-to-one. As Motter and Belky (1998) demonstrated, the number of fixations during active conjunctive search is fewer than the objects in a display, indicating that during each fixation, a covert attentive scan of the surrounding stimuli is made.

Number of saccades and saccadic duration

In line with Mink's response selection theory of the basal ganglia, it was assumed that deficient inhibitory mechanisms would lead to an increased number of saccades to irrelevant stimuli. Contrary to this assumption, for none of the pictures and hence regardless of difficulty, a significant difference between groups was not found for the number of saccades made to reach the target stimulus. This, however, does not necessarily imply intact visual search. It remains possible, that irrelevant saccades were programmed, but not executed. Speaking in terms of the "premotor theory of attention" (Rizzolatti, 1983; Rizzolatti et al., 1987; B. Sheliga et al., 1994; B. M. Sheliga et al., 1997), allocating attention to programming motor actions which are inhibited in their execution, distractors may have increased covert shifts of attention in PD patients. Thus, the number of saccades in and of itself does not supply sufficient information about the actual search pattern. Were the saccades comparable in size? Since there is a consistent relationship between saccadic amplitude and duration (see Carpenter, 1988, p.72), only the latter was explored. For one picture, saccadic duration was longer in patients than in controls, indicating larger saccades. However, considering these two measures together, the number of saccades per picture and the mean saccadic duration suggest that the two groups did not differ with respect to overt search behaviour. If inhibitory deficits in PD were reflected by increased covert shifts of attention, visual search time should have been prolonged.

Visual search time

For none of the pictures was a significant group difference found. With respect to picture difficulty, a similar temporal order for VSTs was found for both groups of subjects. Thus, short VSTs were found for pop-out displays and longer VSTs for displays with stronger distracter interference. It can be concluded that patients and controls did not differ with respect to VST, neither for simple, parallel searches nor for more complex, conjoined searches. This is not to say that inhibitory deficits are not found in more severely impaired patients. Berry et al. (1999) found prolonged response

times for simple and conjoined visual search for only "frontally impaired" PD patients. Frontal impairment is generally seen in patients who are more severely affected.

Reaction time

Gauntlett-Gilbert and Brown (1998) could show in their review of reaction time studies conducted with PD patients that reaction time effects depend strongly on methodology and design. They identified the speed factor in reaction time tasks as a critical parameter for patients to demonstrate deficits on RT tasks. That is, RT differences between control participants and PD patients are most pronounced on tasks where control subjects show fast RTs. This difference is stronger for choice reaction time tasks than simple reaction time tasks. Although the search task required a simple manual reaction, it cannot be compared to a simple reaction time study. For patients, the range of RTs was between 525ms and 4584ms and for control subjects, RTs ranged between 407 ms and 3940ms, depending on the visual search display. Significant group differences were obtained for two pictures, pictures 2 and 5, for which both groups of subjects demonstrated relatively fast RTs. However, whereas for picture 2 longer RTs were observed for patients, controls exhibited longer RTs for picture 5. Hence, for the present task, overall RTs in visual search displays were not found to be prolonged in patients compared to healthy control subjects. A direct comparison of this finding with the results of past reaction time studies in PD patients is, however, not straight forward. In a typical simple reaction time task, RT always includes visual processing of the target stimulus and for serial visual search tasks, the visual processing of distractors adds to that time. Assuming that voluntary (Deubel & Schneider, 1996; Henderson & Hollingworth, 1999; Hoffman & Subramaniam, 1995) and involuntary eye movements (Peterson, Kramer, & Irwin, 2004) are preceded by covert attention, then for the present task, visual processing of distractor and target stimuli fall, at least to a large extent, into VST.

For both groups of subjects, RTs turned out to be significantly correlated to VSTs. This finding does not come as a surprise, considering that although saccadic eye movements typically precede goal-directed hand movements to a visual target stimulus, ocular and manual motor systems are not operating independently (Bekkering, Adam, Kingma, Huson, & Whiting, 1994). Neurons in the superior colliculus are not only involved in the generation of saccadic eye movements, but were also found to be active for a short time during arm movements as well (Stuphorn, Bauswein, & Hoffmann, 2000;

Stuphorn, Hoffmann, & Miller, 1999). It is a striking fact, that in the present task RTs are overall very long, in particular for those search displays with high distractor interference. It therefore seems that although a target stimulus was presented in each display, response uncertainty increased with increasing distractor interference, as captured by VST. Since the target saccade did not necessarily immediately preceded the manual response, intermediate eye movements are unfortunately confounded with this decision process. Another problem in segmenting VST and RT concerns the fact that it cannot be ruled out that some trials were falsely included as hits. The criterion was that a manual response follows a fixation within the target area. However, fixating a stimulus did not necessarily mean detecting that particular stimulus as the relevant target. In summary, although the distinction between VST and RT is not straightforward and must be interpreted with caution, it offers a much more detailed description of search processes compared to simple manual response time.

Movement time

In contrast to VST and RT, MT for six search displays was significantly prolonged in patients compared to controls. For the remaining four pictures, patients also exhibited longer reaction times; however, these differences did not prove to be significant. MT measured the execution of a slight arm movement in combination with stretching the hand and pressing the upper button. The results are in line with Bekkering and colleagues (2001), who found PD patients impaired in the execution of hand movements, as revealed by a lower peak and mean velocity.

A positive relationship between RT and MT was only observed for patients, but not for control participants. The absence of an expected positive correlation between these variables in control subjects is likely to be based on the fact that RT was confounded with eye movements in-between VST and response initiation.

In summary, the number of saccades until target detection, the size of saccades and VST did not differ between groups. Thus, patients, as compared to controls were not effected more by distractor interference, indicating intact inhibitory mechanisms for response selection. RT, or movement initiation, was not found to be prolonged in patients compared to healthy control subjects. However, MT, or movement execution, was found to be impaired in patients.

6 EXPERIMENT 3 - COVERT ATTENTION SHIFTING

6.1 Stimuli

The stimulus display consisted of a black central fixation cross (1ºx1º) and two "place-holder" boxes for the target stimulus (3ºx3º), presented at 8.5º to the left and to the right from the midpoint of the central fixation cross. Small arrows pointing to the left (⊣), to the right (⊢), or to both sides from fixation (⊣⊢) were attached to the fixation cross (1.2º). As in experiment 2, the playing card symbol spades (♠) (1.5ºx1.5º) served as the target stimulus. Correct responses were defined as saccades terminating within the squared place holders for the target stimulus. Termination in any other position on the screen was coded as an error.

6.2 Procedure

Prior to the experiment, each subject performed a sequence of 20 practice trials and it was made sure that all subjects were able to perceive the cues correctly.
Attention was oriented covertly by foveal symbolic cues (arrowheads, 100 ms duration) that indicated the correct location (valid cue) of the upcoming target on 60% of all trials and the incorrect location (invalid cue) on 20% of all trials (Figures 14 and 15). In 10% both directions were indicated (neutral cue) and in 10 % of the trials, the fixation cross remained unchanged, i.e. no cue was presented (baseline condition). There were 60 target trials in the experiment. For half of the trials the inter-stimulus-interval (ISI) between cue-offset and target appearance varied between 300 and 1100 ms (spatial condition – 300 ms, 700 ms, 1100 ms). For the other half of the trials, the cue-lead-time (CLT) between fixation and cue onset varied between 2000 and 2800 ms (2000 ms, 2400 ms, 2800 ms). Since there was added temporal information, this condition was termed temporal-spatial condition. The two conditions were presented successively, without the subjects' conscious knowledge of the paradigm changes. A period of adaptation was accounted for by omitting the first five trials of each condition from the analysis. Trials within each condition were presented randomly. Trials with incorrect, premature key press responses (before the appearance of the target stimulus) were counted as errors and excluded from further analysis.

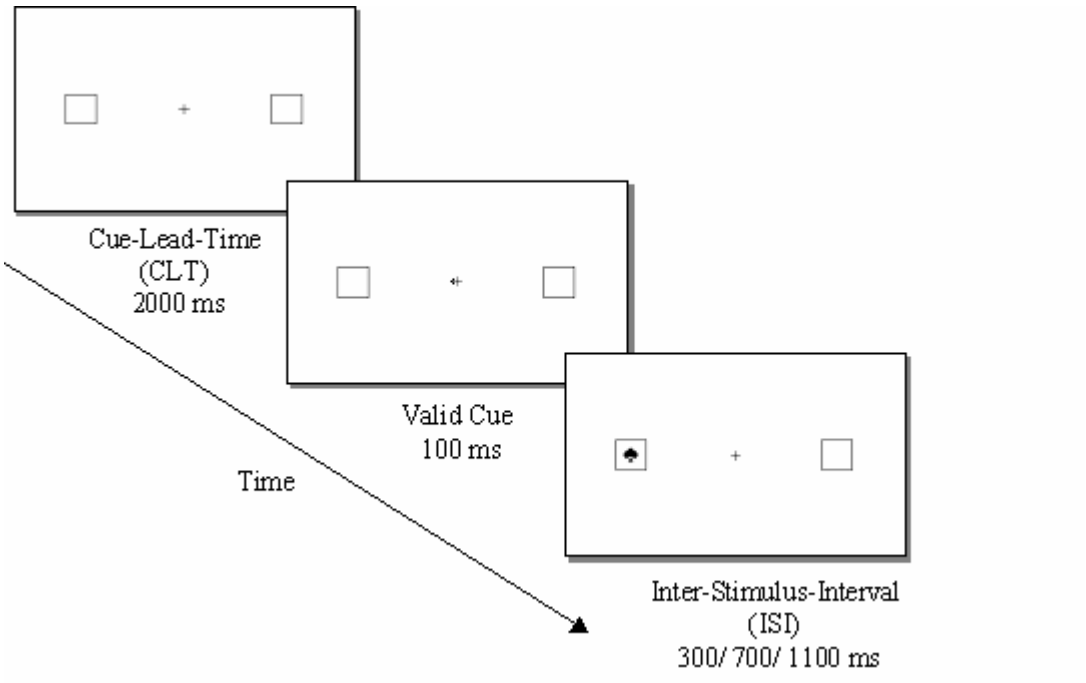

Figure 14: Schematic illustration of a "spatial" trial condition (example with valid cue).

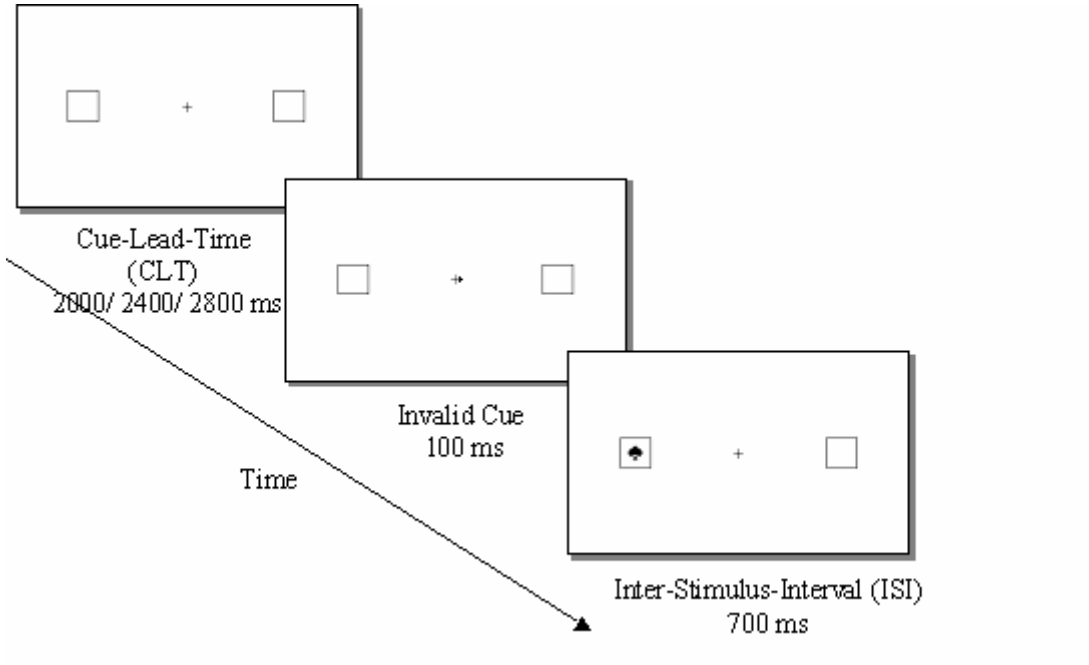

Figure 15: Schematic illustration of a "temporal-spatial" trial (example with invalid cue).

6.3 Variables of interest and hypotheses

PD and control subjects were compared on movement initiation time (reaction time (RT) – time from target onset until lower button release) and movement execution time (movement time (MT) – time from lower button release until target button press) in a covert spatial orienting task, using briefly presented central symbolic cues to direct attention.

Because subjects were instructed not to move their eyes, differences in reaction times are interpreted as a consequence of a correct / incorrect attentional shifts.

For all conditions and both groups of subjects, RT is hypothesised to be faster in the valid condition (attentional 'benefit') and slower in the invalid than in the neutral condition (attentional 'cost'). The longest reaction times are expected for the baseline condition, where no cue is presented.

In the literature, a deficit in reaction time for PD patients has mainly been found in uncued choice reaction time tasks (Gauntlett-Gilbert & Brown, 1998). Thus, compared to the control group, ***reaction times under the baseline condition are hypothesized to be significantly prolonged in patients.***

Reduced RT costs for patients, compared to healthy control participants, are discussed with cue-target intervals of 600-800 ms (Filoteo, Delis, Salmon, Demadura, Roman, & Shults, 1997a; Pollux & Robertson, 2001; Yamaguchi & Kobayashi, 1998b). For shorter time intervals between cue and target presentation, no decrease in reaction time cost after invalid cues is expected

(Bennett et al., 1995; Filoteo et al., 1997a; Hsieh et al., 1996; Hsieh et al., 1997; Kingstone et al., 2002). Following Fileteo and Delis' (1997) argumentation, that reduced costs stem from difficulties in maintaining inhibition at unattended spatial locations over extended periods of time, reduced costs are also expected at longer inter-stimulus-intervals (ISIs), such as 1100 ms. In accordance with the literature, ***reduced costs in patients are conceivable at ISIs of 700 and 1100 ms, but not at 300 ms.***

To investigate whether the expected effect of reduced costs would be influenced by expectation, the ISI was kept constant at 700 ms. Thus, the appearance of the target stimulus was predictable in a temporal sense. In order to maintain alertness during the task, the cue-lead-time (CLT) was varied.

Whereas the effect of a pre-cue on improving movement initiation (i.e RT) has been extensively investigated, its influence on movement execution (i.e. MT) has rarely been examined. Therefore, the effect of spatial and temporal-spatial cueing on MT should be explored. Due to impairment in movement execution, ***patients are expected to show prolonged MTs in all conditions.***

RT and MT are both postulated to increase with the progression of illness.

Although patients with PD are known to demonstrate a range of visual and oculomotor impairments, only four studies recorded eye movements via EOG (Bennett et al., 1995; Low et al., 2002; Seiss & Praamstra, 2004; Wright et al., 1990), but then discarded these from further analysis. Engbert and Kliegel (2003) showed that covert attention is accompanied by tiny eye movements, with an orientation towards the cued direction. Due to degeneration of neurons in the substantia nigra, which prevent unwanted saccades by tonically inhibiting the superior colliculus, ***patients are expected to make more saccades inbetween cue onset and target onset, compared to control participants. Interruptive saccades are expected to be positively correlated with the severity of PD.***

6.4 Statistical analyses

Eye movements before and during shifts of attention were investigated in both groups of subjects. Trials during which saccades were made inbetween cue and target onset were discarded from the analysis when their amplitude exceeded 2.5º degrees from the centre of fixation.

Prior to analysing RT and MT, these variables were checked for having a normal distribution in both groups of subjects (histograms). Data were tested for outliers and values more than three standard deviations from the group mean were excluded. Means were computed for each subject and each condition. Only RT and MT for hits were considered for further analysis, because hits reflect the most successful decision processes. Group differences in errors were tested using Fischer's exact test.

To investigate the association between saccades and RT, and RT and MT, product-moment correlation-coefficients were computed separately for each group, pooled

across conditions. Separate two-way repeated measurement ANOVAs were carried out on RT and MT.

Due to the different time intervals, trials belonging to the spatial condition were analysed separately from trials belonging to the temporal-spatial condition. Four factorial analyses of variance were performed. A repeated measures ANOVA was carried out on RT, with group as the between-subjects factor (PD vs. Control) and cue validity (valid, invalid, neutral, no-cue (baseline) and inter-stimulus-interval (ISI- 300 ms, 700 ms, 1100 ms) as the within-subjects factors. Trials in the temporal-spatial condition were analysed by the same approach; however, ISI was replaced by CLT (2000 ms 2400 ms, 2800 ms) as the within-subjects factor. In order to compare the two timing conditions directly, an additional repeated measures ANOVA, with group as the between-subjects factor (2 levels), cue validity (4 levels) and timing conditions (2 levels: spatial (CLT 2000 ms, ISI 700 ms) and temporal-spatial (CLT 2000, ISI 700 ms)) was performed.

To assess behavioural costs and benefits of visual spatial attention, one-sample t-tests were computed on the size of RT benefits (obtained by subtracting RTs on valid trials from RTs on neutral trials) and costs (obtained by subtracting invalid trial RTs from neutral trial RTs), separately for the two groups of subjects. Groups were then compared via independent t-tests.

MT was also examined by a factorial ANOVA approach, using the same factors and levels as for RT.

Associations between progression of illness and saccades, RT and MT were assessed by correlating the three variables with UPDRS scale 3, MMSE scores, duration of illness (in months) and Hoehn and Yahr scores.

6.5 Results

As was the case for the previous task, data from 22 patients and 22 control subjects entered the statistical data analyses.

6.5.1 Errors

Errors included trials with premature responses, responses to the side opposite the target and responses with RTs exceeding three standard deviations from the mean. Data from these trials was excluded from further analysis. For both groups of subjects, only a relatively small amount of errors was observed. Whereas patients responded in 4.8% of all trials incorrectly, control participants made errors on 2.7% of all trials. The difference between the error rates was significant (Fisher's exact test, $p<0.01$). Comparison of the observed and predicted frequencies in the 2x2 table (Table 11) revealed that this difference is due to the higher error rate in the patient group and the lower error rate for control subjects.

Table 11 2x2 error frequency table

		Patients	Controls
correct	observed	1256	1248
	predicted	1270	1270
errors	observed	64	36
	predicted	50	50

6.5.2 Saccades

In order to control for potential eye movement confounds, saccades during trials were investigated. Table 12 presents means and standard deviations for saccades made before cue onset and after cue onset, pooled across all conditions separately for both groups of subjects. T–tests for independent samples revealed significant group differences. On average, patients as compared to control participants made more saccades both, before cue onset and after cue onset. This difference is apparent for left and right cues, as well as neutral cues and the baseline condition. Overall, however, the number of saccades

made inbetween cue and target, hence during covert attentional shifting, is relatively small (0.7 saccades per trial for patients, compared to 0.35 saccades per trial for control participants). The mean amplitude of saccades was 1.51º (SD 1.05) for patients and 1.44º (SD 1.54) for controls. This difference was not significant ($F(1,43)=0.37$, $p=0.85$). 64% of saccades were oriented towards the cued direction in patients and 61% in controls.

Table 12: Group differences in the number of saccades per trial, made before and after cue onset. Data pooled across all conditions.

Cue	n	Patient group M	SD	n	Control group M	SD	t	df	p
Before cue onset	1380	2.75	1.98	1260	1.71	1.71	14.32	2638	<0.001
After cue onset	1380	0.70	0.98	1260	0.37	0.73	9.67	2638	<0.001
Cue left/right	1104	0.66	0.92	1008	0.35	0.69	8.69	2110	<0.001
Cue neutral	138	0.57	0.90	126	0.36	0.73	2.13	262	<0.05
No cue	138	1.17	1.35	126	0.59	0.98	4.02	262	<0.001

6.5.2.1 Association between saccades and severity of illness

The association between saccades made inbetween cue and target presentation and progression of PD (UPDRS III, MMSE, duration of illness and H&Y) was tested by calculating product-moment correlation-coefficients for PD patients, pooled across conditions. There was a marginally significant negative relationship between saccades made inbetween cue and target, and the Mini-Mental State Examination ($r(21)=-0.42$, $p=0.05$).

6.5.3 Reaction time

6.5.3.1 Association between saccades and RT

Reaction time (RT) was defined as the time from target onset to lower button release. In order to control for potential eye movement confounds, the association between saccades and RT was tested pooled across conditions, separately for each group. Only saccades made after cue onset, hence during attentional shifting, entered the analysis. No significant relationship was found for patients ($r(22)=0.35$, $p=0.11$) or control participants ($r(22)=0.14$, $p=0.55$).

6.5.3.2 RT - Spatial Condition

Overall, no significant group effect for RT ($F(1,42)=1.10$, $p=0.30$) was observed. Whereas control participants exhibited a mean reaction time of 450 ms (SD 12.09), patients, on average, responded with a delay of 468 ms (SD 12.10). As expected, the effect for cue was found to be highly significant ($F(2,85)=62.10$, $p<0.001$). The fastest RTs were observed for valid cues (mean 389.62ms, SD 10.69), followed by invalid cues (mean 440.12ms, SD 12.76), neutral cues (mean 446.91ms, SD 8.85) and the baseline condition (mean 559.14ms, SD 13.56). Bonferroni pairwise comparisons indicated significant differences between all cueing conditions ($p<0.001$), except for the invalid and neutral cueing condition ($p = 1.00$). A significant main effect was also found for ISI ($F(2,81)=8.80$, $p<0.001$). Whereas ISIs of 700 ms (mean 445.01, SD 10.68) and 1100 ms (mean 445.01, SD 10.61) yielded equal RTs, slower RTs were observed for the shortest ISI (300ms) (mean 486.79, SD 11.17). None of the interactions was found to be significant: Cue x Group ($F(2,85)=0.99$, $p=0.40$), Time x Group ($F(2,81)=0.64$, $p=0.53$), Cue x Time ($F(4,149)=1.70$, $p=0.16$), Cue x Time x Group $F(4,149)=1.69$, $p=0.33$) (see Figures 16 and 17).

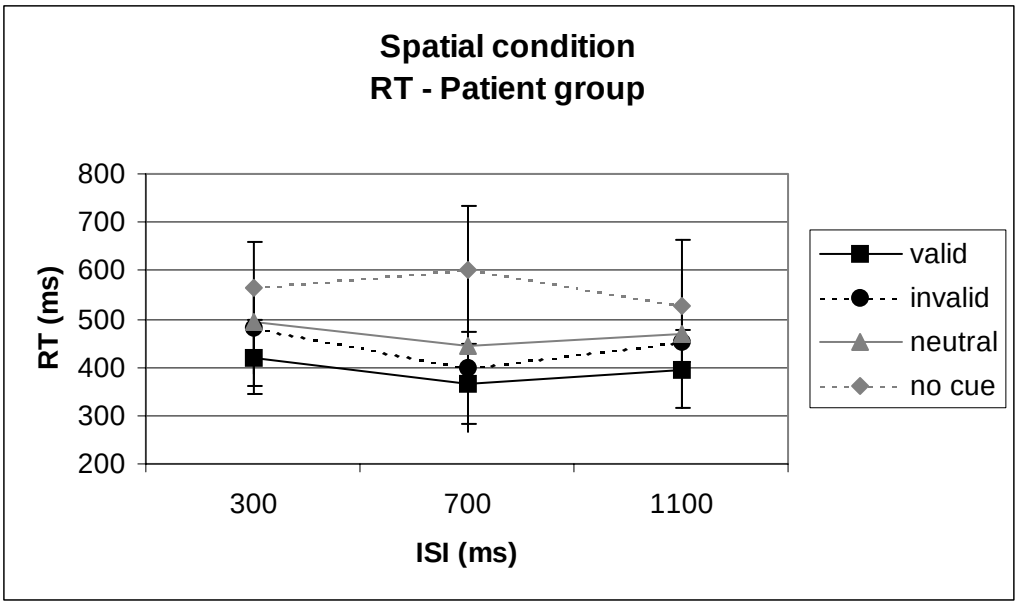

Figure 16: Patients' RTs for trials with four cueing conditions and three ISIs (mean ± standard deviation).

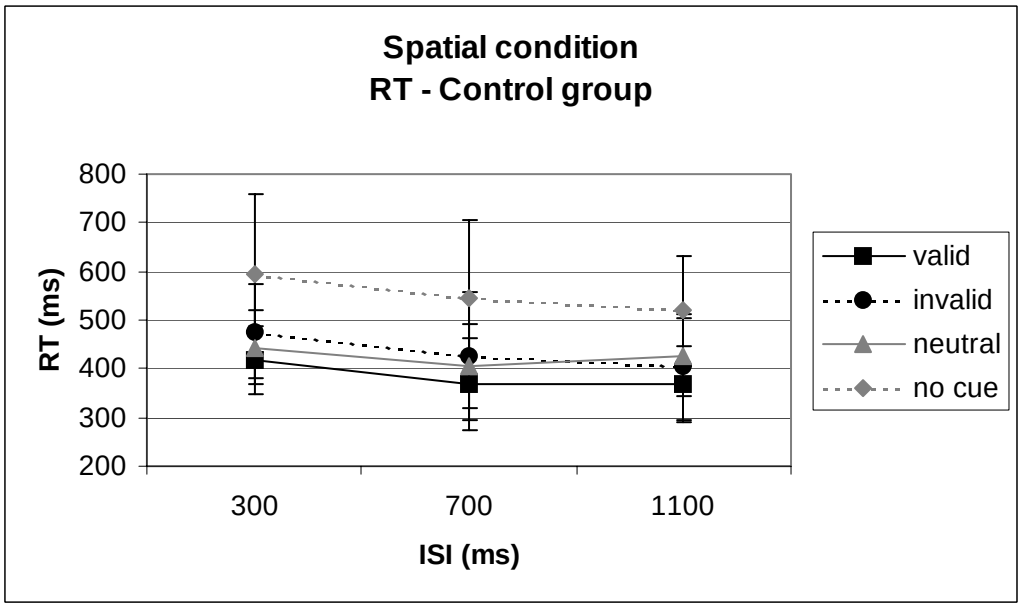

Figure 17: Control participants' RTs for trials with four cueing conditions and three ISIs (mean ± standard deviation).

Supplementary analyses were performed for the size of benefits and costs (Figure 18). For patients, one-sample t-tests (tested against zero) indicated, that the size of benefits differed significantly from zero in all three ISI conditions (300 ms: $t(21) = 4.13$, $p<0.001$; 700 ms: $t(21) = 2.64$, $p<0.05$; 1100 ms: $t(21) = 3.36$, $p<0.01$). The size of costs was not found to be significant for any ISI ($p>0.05$). Figure 18 shows that patients did not demonstrate costs at all for 300 ms and 700 ms ISIs, hence the RTs in the invalid condition were faster than in the neutral condition. For the control group, one-sample t-tests revealed the size of benefits to be significant from zero for the shortest ISI ($t(21) = 2,21$, $p <0.05$, one sample-t-test), but not for the medium and long ISI ($p>0.05$). As for patients, the size of costs was not found to be significant for any ISI ($p>0.05$). Figure 18 shows that for the longest ISI, RTs were shorter in the invalid compared to the neutral condition. Independent t-tests did not reveal any significant group differences for costs nor for benefits for any ISI ($p>0.05$).

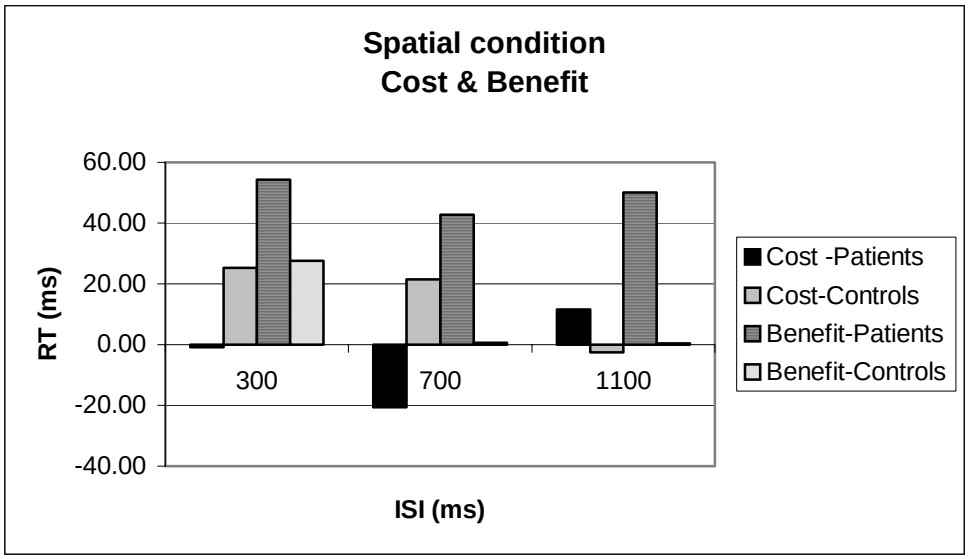

Figure 18: Mean costs and benefits for patients and controls in the spatial condition

6.5.3.3 RT - Temporal Spatial Condition

In the temporal-spatial condition, as in the spatial condition, the two groups did not differ significantly on RT ($F(1,42)=1.99$, $p=0.17$). Whereas the control participants

exhibited a mean reaction time of 431 ms (SD 15.50), the patients responded on average with a delay of 462 ms (SD 15.50). The effect for cue was also found to be highly significant ($F(2,102)=36.29$, $p<0.001$). The fastest RTs were observed for valid cues (mean 403.30 ms, SD 9,81), followed by invalid cues (mean 422.24 ms, SD 13.83), neutral cues (mean 428.86 ms, SD 14.99) and the baseline condition (mean 530.64 ms, SD 15.49). Bonferroni pairwise comparisons indicated significant differences between the baseline condition versus all other conditions ($p<0.001$), and between valid and neutral conditions ($p<0.05$).

The main effect for CLT was not significant ($F(2,82)=2.23$, $p=0.12$). The mean RTs were: 454 ms (SD13.15) for CLT 2000ms, 436 ms (SD 11.76) for CLT 2400 and 449 ms (SD11.41) for CLT 2800 ms.

None of the interactions were found to be significant: Cue x Group ($F(2,102)=0.54$, $p=0.66$), Time x Group ($F(2,82)=0.57$, $p=0.56$), Cue x Time ($F(4,184)=1.69$, $p=0.15$), Cue x Time x Group $F(4,184)=1.82$, $p=0.12$) (Figures 19 and 20).

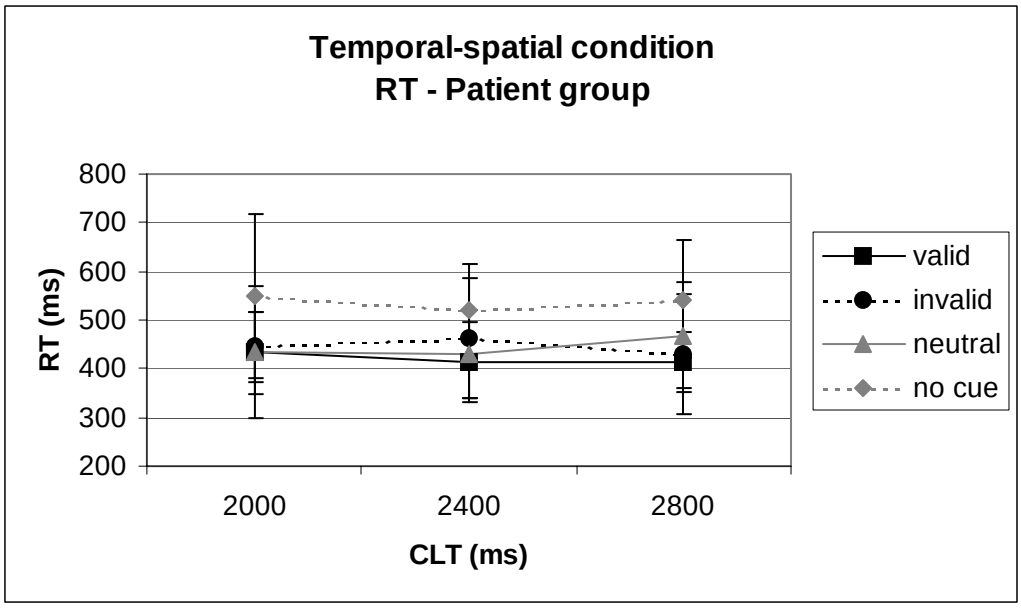

Figure 19: Patients' RTs for trials with four cueing conditions and three CLTs (mean ± standard deviation).

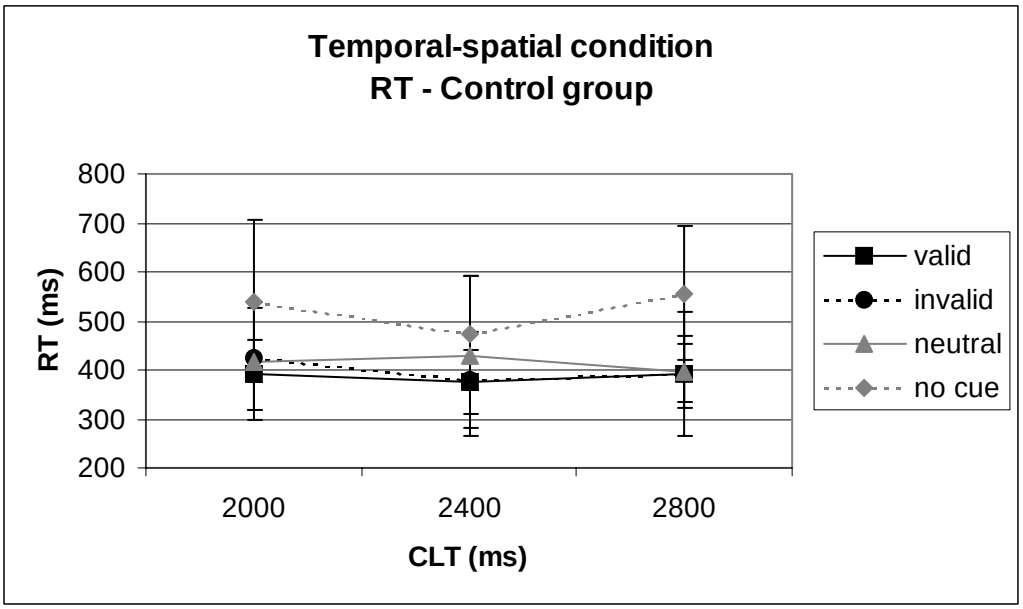

Figure 20: Control participants' RTs for trials with four cueing conditions and three CLTs (mean ± standard deviation).

Figure 21 illustrates supplementary analysis of costs and benefits in the temporal-spatial condition. For patients, one-sample t-tests indicated, that only for the longest CLT did the size of benefit differ significantly from zero (2800 ms: $t(21) = 2.51$, $p<0.05$). The size of costs was found to be significant for CLT 2000 ms ($t(21) = 2.68$, $p<0.05$) and CLT 2800 ms ($t(21) = -2.40$, $p<0.05$). However, as can be seen in Figure 20, this effect was negative for the latter CLT; thus, RTs were shorter in the invalid condition than in the neutral condition. For control participants, the size of benefits and costs were not found to be significant for any of the three CLTs ($p>0.05$). Significant group differences were not found for benefits or costs at any CLT ($p>0.05$, independent t-tests).

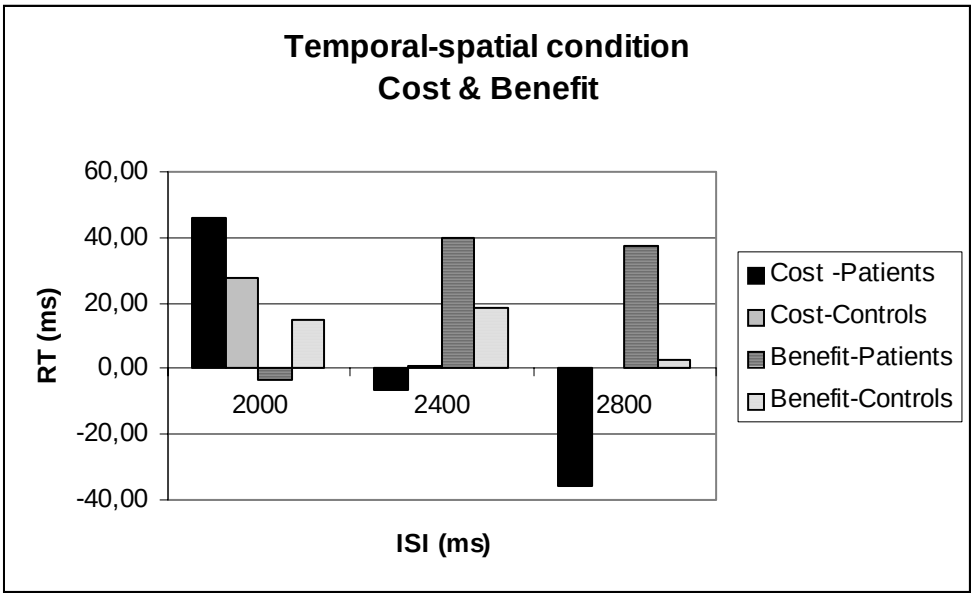

Figure 21: Mean costs and benefits for patients and controls in the temporal-spatial condition

6.5.3.4 Spatial vs. temporal spatial RTs

A direct comparison of RTs in spatial (CLT 2000 ms, ISI 700 ms) and temporal-spatial trials (CLT 2000 ms, ISI 700 ms) did not reveal a significant group effect ($F(1,42)=0.94$, $p=0.34$), nor a significant effect of time ($F(1,42)=0.46$, $p=0.50$). The main effect of cue proved to be significant ($F(2,86)=45.78$, $p<0.001$). No significant interactions were found ($p>0.05$).

6.5.3.5 Association between RT and severity of illness

The association between RT and severity of illness (UPDRS 3, MMSE, duration of illness and H&Y) was tested by calculating product-moment correlation-coefficients for PD patients, pooled across conditions. No significant correlations were obtained ($r(22)>0.05$).

6.5.4 Movement time

6.5.4.1 Association between RT and MT

Movement time (MT) was defined as the time from lower button release until target button press. The association between RT and MT was tested by calculating product-moment correlation-coefficients, pooled across conditions, separately for the two groups. A significant positive relationship between these variables was found for patients ($r(22)=0.42$, $p=0.05$) and controls ($r(22)=0.61$, $p<0.01$).

6.5.4.2 MT - Spatial Condition

Contrary to the postulated hypothesis, there was no significant group effect in MT ($F(1,42)=1.80$, $p=0.19$). On average, MT was 394 ms (SD 26.95) for patients and 343 ms (SD 26.95) for controls. The effect of cue was found to be significant ($F(3,116)=3.19$, $p<0.05$); however, post-hoc (Bonferroni) comparisons did not indicate significant pairwise differences ($p>0.05$). A significant main effect was found for ISI ($F(2,74)=6.01$, $p<0.01$). The longest MT was observed for the longest ISI (mean 389.55, SD 22.14 ms), the shortest MT for the medium ISI (mean 348.69, SD 17.58 ms). Post hoc Bonferroni comparisons confirmed a significant difference for this ISI pair ($p<0.01$), but not for any other combination ($p>0.05$).

Interactions of ISI x Group ($F(2,74)=4.01$, $p<0.05$), as well as Cue x ISI ($F(5,202)=2.7$, $p<0.05$) were significant (see Figures 22 and 23).

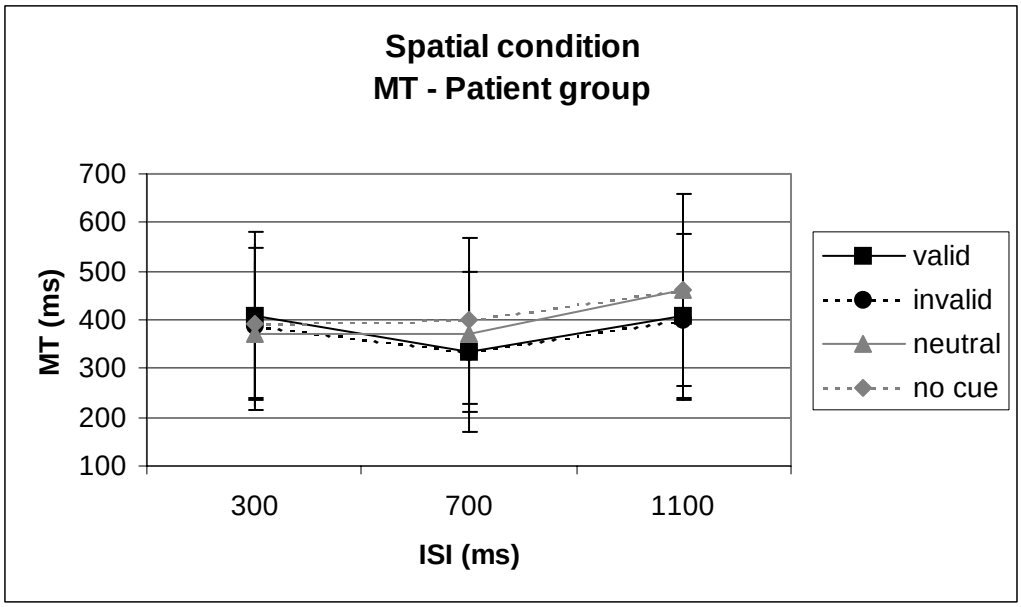

Figure 22: Patients' MTs for trials with four cueing conditions and three ISIs (mean ± standard deviation).

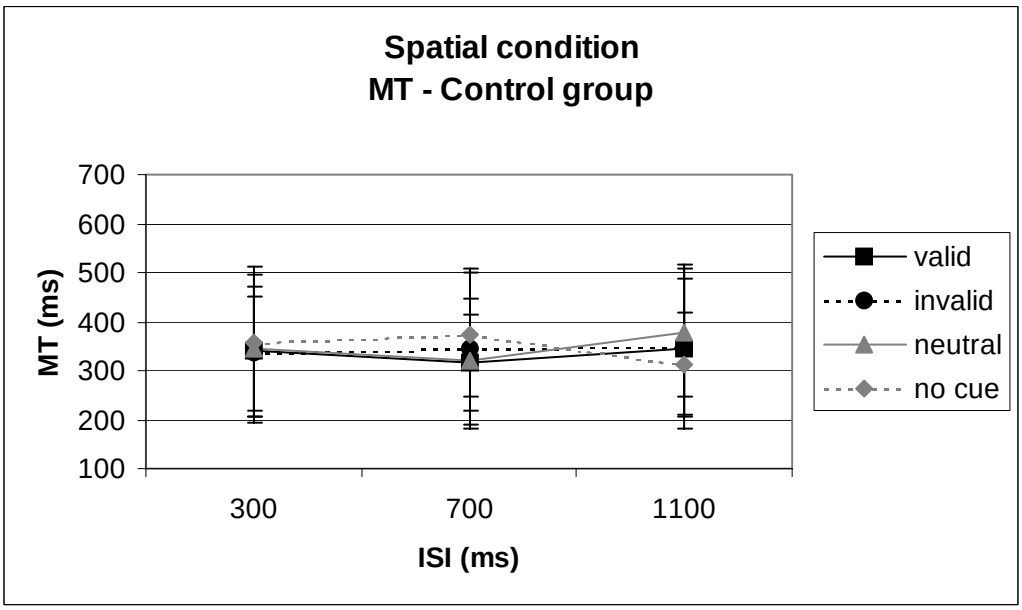

Figure 23: Control participants' RTs for trials with four cueing conditions and three ISIs (mean ± standard deviation).

6.5.4.3 MT – Temporal-spatial Condition

Groups did not differ significantly in terms of MT ($F(1,42)=0.83$, $p=0.37$) for the temporal-spatial condition. On average, MT was 386 ms (SD 29.58) for patients and 348 ms (SD 29.58) for controls. The effect of cue was found to be significant ($F(3,116)=7.39$, $p<0.001$). Post-hoc Bonferroni tests indicated a significant difference for invalid versus neutral cueing ($p<0.01$) and neutral cueing versus the baseline condition ($p<0.001$). The effect of CLT on MT marginally missed significance ($F(2,84)=2.67$, $p=0.07$), but there was a significant interaction between CLT and Cue ($F(4,156)=4.01$, $p<0.01$) (see Figures 24 and 25).

6.5.4.4 Spatial vs. temporal-spatial MTs

A direct comparison of MTs in spatial (CLT 2000 ms, ISI 700 ms) and temporal-spatial trials (CLT 2000 ms, ISI 700 ms) did not reveal a significant group effect ($F(1,42)=0.62$, $p=0.44$). The main effects of time ($F(1,42)=4.72$, $p<0.05$) and cue ($F(2,88)=4.37$, $p<0.05$) were both found to be significant. They were, however, modified by their mutual interaction (Cue x Time, $F(3,110)=7.74$, $p<0.01$).

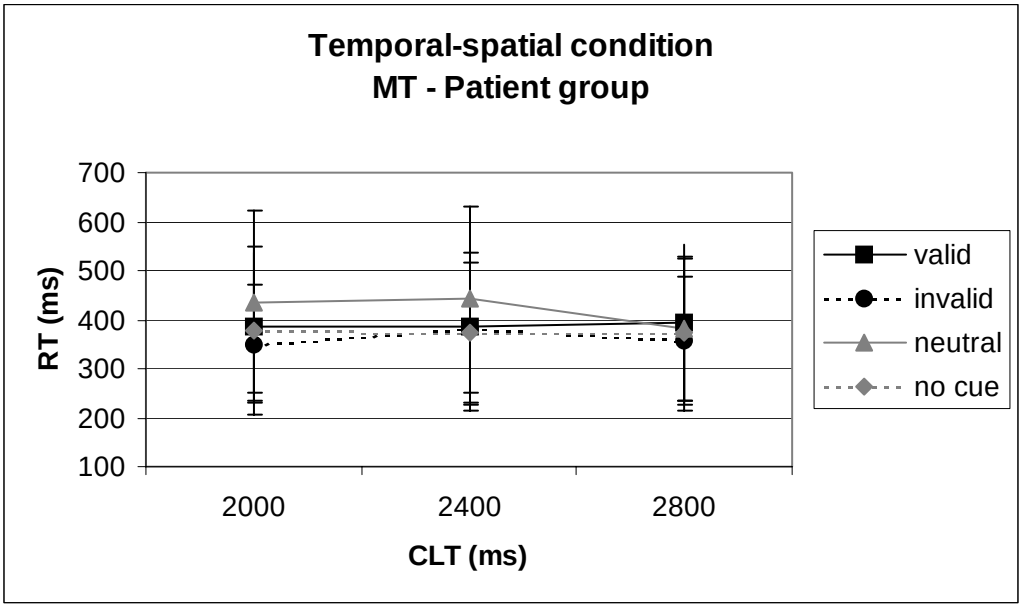

Figure 24: Patients' MTs for trials with four cueing conditions and three CLTs (mean ± standard deviation).

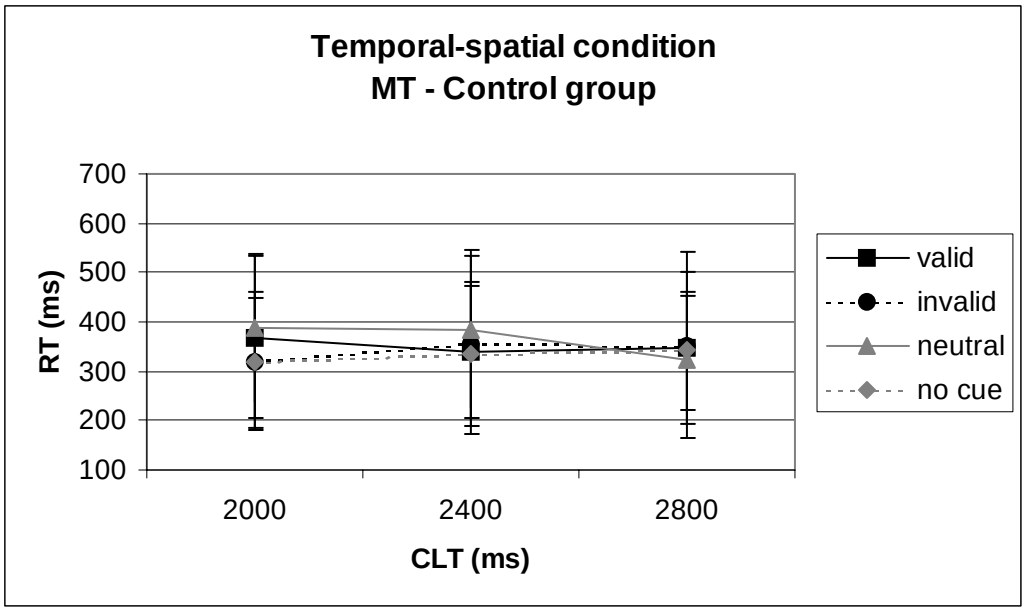

Figure 25: Control participants' RTs for trials with four cueing conditions and three CLTs (mean ± standard deviation).

6.5.4.5 Association between MT and severity of illness

As for saccades and RT, the association between MT and severity of illness (UPDRS III, MMSE, duration of illness and H&Y) was tested by calculating product-moment correlation-coefficients for PD patients, pooled across conditions. A significant negative correlation was found between MT and the MMSE ($r(21)=-0.48$, $p<0.05$). Positive correlations were obtained between MT and duration of illness ($r(22)=0.41$, $p=0.05$) and between MT and H&Y ($r(22)=0.63$, $p<0.01$).

6.6 Discussion

Attention to spatial locations in patients with PD was studied in a covert attention shifting paradigm. Different cueing conditions were compared and conflict was induced by invalid cues. Conflict is typically reflected by the size of costs, which has been found to be reduced in patients with PD in some studies (Filoteo et al., 1997a; Pollux & Robertson, 2001; Wright et al., 1990; Wright, Geffen, & Geffen, 1993; Yamaguchi & Kobayashi, 1998b), but intact in others (Bennett et al., 1995; Hsieh et al., 1996; Hsieh et al., 1997; Kingstone et al., 2002). The results vary strongly with respect to stimuli, procedures, timing conditions and patient samples studied at different stages of the disease and may be confounded by impaired oculomotor control.

Performance, as indicated by error rate, was similar for both groups of subjects. Only a small percentage of trials had to be discarded from the analysis due to response errors.

Saccades

In line with the observation that covert attention is accompanied by small eye movements (Engbert & Kliegl, 2003), small saccades were observed after cue onset for both groups of subjects. These eye movements slightly extended beyond the fixation cross with the arrow and were mainly oriented towards the cued direction. In contrast to Engbert and Kliegel (2003), who used a cueing procedure with an overlap of cue and target, the cue disappeared after 100 ms in the current experiment and the fixation cross remained until target onset. Thus, it cannot be excluded that some of the saccades are reflex movements in reaction to the disappearance of the cue. It was hypothesised that due to degeneration of neurons in the substantia nigra, which prevent unwanted saccades by maintaining the superior colliculus tonically inhibited, patients as compared to controls make more saccades between cue- and target onset. Indeed, it was found that patients made twice as many saccades during this interval compared to controls: 0.7 saccades per trial for patients, compared to 0.35 saccades per trial for control participants. This difference proved to be highly significant.

The ability to maintain fixation during and after cue presentation thus seems to be reduced in patients. It could be argued, that this effect depends on the transformation from the fixation cross into the cue and vice versa. In other words, patients are more likely to make reflexive saccades in reaction to the sudden change of a stimulus. Two

findings contradict that assumption. First, a significant group difference was also found for trials in which the fixation cross did not change (baseline). Secondly, a highly significant group difference was also found for the number of saccades made before cue onset, hence during the interval of pure fixation. Whereas patients, on average, made 2.8 saccades before cue onset, 1.7 saccades were recorded for control participants.

With respect to the saccades made inbetween cue- and target onset, it has to be considered that the data was pooled across all conditions and thus the average ISI was rather long for a covert attention task, making saccades more likely.

Interestingly, impaired saccadic inhibition in patients with PD was also found in the associated overt attention study (Krause, 2003), where saccadic reaction time was measured. Although in that study, saccades were executed as the appropriate response, fixation was disrupted by saccades for PD patients. As in the current study, the majority of disruptive saccades after cue presentation were in the direction of the cue, indicating an effect of spatial information on these saccades.

The number of saccades inbetween cue and target presentation for PD was marginally negatively correlated with the Mini-Mental State Examination. No significant relationship was found between saccades and the other three measures of severity: UPDRS III, duration of illness and Hoehn & Yahr status. This is rather surprising, considering the fact that Martinez-Martin and colleagues (1994) report a substantial correlation between the MMSE and UPDRS. Overall, there was a high group performance for the MMSE with a mean of 29.3 and standard deviation of 1.0 (possible maximum score of 30). Visual inspection of a scatter diagram reveals that the significant correlation is mainly based on one subject, with an average of 1.75 fixation interrupting saccades per trial and a MMSE score of 26. In summary, no association was found between the number of saccades and progression of illness. Three explanations for the lacking association seem plausible. 1) Disinhibition of saccadic execution during fixation had reached its' maximum for disease severity of the present study sample. 2) The selected instruments, or scales, were not sensitive for oculomotor impairment, such as disruptive saccades. 3) The patient sample represents a homogenous group with respect to disease severity.

Reaction time

The magnitude of costs and benefits in covert attention tasks strongly depends on the experimental design, in particular on temporal aspects. Reduced costs for patients are typically observed with cue-target intervals of 600-800 ms (Filoteo et al., 1997a; Pollux & Robertson, 2001; Yamaguchi & Kobayashi, 1998b), suggesting impairment in maintaining inhibition at unattended spatial locations over extended periods of time.

Thus, reduced costs for PD patients were most likely with an ISI of 700 ms. However, previous studies (Filoteo et al., 1997; Pollux & Robertson, 2001; Yamaguchi & Kobayashi, 1998) have used variable ISIs, or stimulus-onset-asynchronies, to identify time intervals at which group differences would occur. One goal of the present task was thereby to investigate whether reduced cost could also be observed when the time interval between cue and target was predictable. In other words, did impairment in maintaining inhibition over extended periods of time in PD patients improve by adding temporal information?

All subjects demonstrated the fastest RTs for valid trials, followed by invalid and neutral trials. The slowest RTs were revealed for trials without cue presentation. Benefits proved to be significant for both groups of subjects. Patients and controls both benefit significantly from valid cues. Interestingly, in contrast to controls, a benefit was observed for patients even for the longest ISI in the spatial condition. Contrary to expectations, slightly faster RTs, although not significant, were observed for invalid compared to neutral cues. Significant costs were only found in the temporal-spatial condition with a CLT of 2000 ms. However, for this condition, no benefits were observed. Considering that in healthy people, full cost-benefit effects are typically found within 200 ms of an arrow cue (e.g. Remington & Pierce, 1984), it can be speculated that the ISIs used here were too long. It is conceivable that a mechanism, called "inhibition of return" (IOR) came into effect (R. M. Klein, 2000, for an overview). For a short time after a cue, responses to targets at the cued location are facilitated relative to those at uncued locations. But as the time interval between the cue and the target increases, responses to targets at the cued location are inhibited relative to those at uncued locations. This inhibitory after-effect (IOR) is thought to encourage subjects to orient to novel stimuli, by preventing them from returning to previously attended locations. In the current study, due to the combination of long ISIs and brief

cue presentations, IOR cannot be fully excluded. However, in the spatial conditions, the slowest RTs were observed for the shortest ISI of 300 ms, arguing against IOR. The distribution of trials across the four cueing conditions may also have contributed to weak cueing effects. In contrast to other studies of covert attention shifting, the baseline condition introduced in the present design left less trials for the other three conditions. Thus, 60% of valid trials and only 20% of invalid trials might not have been sufficient for a full cost and benefit analysis. In other words, too much conflict might have been induced by other conditions, thereby hindering subjects from relying on the (valid) cue. Overall, groups showed similar response patterns with respect to cueing and timing parameters. A direct comparison of spatial and temporal-spatial RTs, including trials with equal CLT and ISI (thus CLT 2000 ms and ISI 700 ms), did not reveal a significant group effect or a significant main effect of time. This result suggests a similar performance for both timing conditions, at least for trials with equal timing parameters, indicating no additional benefit of temporal information for reaction time. It seems that providing subjects with varying CLTs hindered them from developing an internal temporal rhythm of upcoming trials. Thus, although the target was present with a reliable ISI in the temporal-spatial condition, neither controls nor patients could benefit from the temporal information. Whether or not a constant CLT and ISI would have led to the same results, as found for the spatial condition, cannot be confidently answered on the basis of these findings.

No relationship was found between disease severity and RT, supporting the finding that RT was not impaired in the patient sample, neither for mildly nor for moderately impaired patients.

Association between saccades and RT

Unfortunately, there were not enough trials to compare RT on trials with and without saccades. A recent study investigated the effect of saccades during an attention shifting paradigm on manual response times and found that manual responses were delayed in trials with saccades compared to trials without saccades (Verleger, Heide, & Kompf, 2002). The more saccades made by a subject, the slower this subject's manual responses. The delay effect was less marked in valid trials, where attention was cued to the correct side, and more pronounced for invalid trials, where saccades had to be made to the opposite side. This study clearly stresses the importance of measuring eye

movements during covert attention tasks and reveals the susceptibility of reaction time costs and benefits.

In contrast to Verleger and colleagues (2002), subjects in the present study were explicitly instructed to suppress saccades and were aware that eye movements were being recorded. Thus, eye movement confounds were reduced to a minimum and tested by correlating the number of saccades after cue onset with RT across all conditions, separately for each group. There was no significant relationship between the number of saccades and RT for either of the two groups. Although this result indicates independence between saccades and RT, it has to be treated with caution. Since both variables were pooled across all conditions, thus including different ISIs, CLTs and cueing conditions, testing was rather crude. It is likely, that more saccades were made with longer ISIs, possibly showing a positive relationship for these conditions. However, since the amount of trials for each condition was small and the number of trials in which saccades occurred was limited, the association between RT and saccades was not fully resolved by this experiment.

Movement time

The effect of cueing on movement execution (i.e. MT) has, to the best of my knowledge, not yet been examined. Analyses for both timing conditions, spatial and temporal-spatial, indicate a general effect of cue on MT. However, as revealed by post-hoc analyses, these effects were of no systematic cueing order. Thus, costs and benefits were not reflected by MT. Whereas in the temporal-spatial condition MT was not effected by time, time did play a role in the spatial condition with the longest MT observed for the longest ISI and the shortest MT for the medium ISI. Interestingly, this pattern differed from the effect of ISI on RT, where the longest RTs were observed for the shortest ISI. Although cueing and time parameters do seem to exert an influence on movement execution, systematic effects, as observed for RT, were not found.

Since even in early stages of PD, impairment in the execution of manual movements is found (e.g. Bekkering et al., 2001; Isenberg & Conrad, 1994), MT was expected to be increased in PD for all conditions. Although mean MT was reduced in PD patients for spatial and temporal-spatial conditions, differences did not reach statistical significance.

Testing the relationship between disease severity and MT revealed a significant negative relationship between MT and the MMSE. Positive correlations were obtained

between MT and duration of illness and between MT and Hoehn & Yahr status. Surprisingly, MT was not significantly correlated with the UPDRS scale III. It may be speculated that the motor section of the UPDRS is not sensitive enough for specific fine motor movements and hence other tests, such as the nine-hole peg test (9-HTP, Mathiowetz et al., 1985) could have provided additional information. However, overall MT and measures of disease severity exhibit a relationship which suggests a tendency towards manual movement impairment in PD for this task.

Association between RT and MT

MT measured the execution of an arm movement in combination with stretching the hand and pressing the upper button. A significant correlation between RT and MT was found for both groups of subjects, indicating a positive relationship between the initiation and execution of manual movement. Although this result is not surprising, it stresses the fact that whenever RT is assessed, even by means of a very simple response, such as button release, measurement is confounded by movement.

In summary, for the present study and patient sample, deficient inhibitory processes seem to be limited to oculomotor control, as reflected by disruptive saccades made during fixation. Reaction time, or movement initiation time, did not differ for the two groups of subjects in any of the tested conditions. A tendency for impaired motor execution in PD patients was observed.

7 GENERAL DISCUSSION

The purpose of the presented study was to investigate the association between visual selective attention deficits in patients with idiopathic PD and known oculomotor impairment. It was postulated that deficits observed on tasks of visual selective attention in patients with PD are at least partly accounted for by motor and /or oculomor deficits. Whereas there are clinically obvious oculomotor deficits, particularly in later stages of the disease, findings with respect to visual spatial attention strongly vary depending on experimental design. In recent years, the relationship between the programming of saccades and attentional control has been broadly discussed and although anatomical, neuropsychological and neuroimaging studies have provided evidence for a close link between these systems, the extent of dependency is still unclear. Modern eye trackers have facilitated the recording of eye movements during overt and covert attentional tasks and recent results indicate that attentional shifts, without explicit instructions, are accomplished by moving the eyes. For the present study, it was postulated that reported impairment on visuo-spatial attention tasks was a direct consequence of the deficit in motor and/or oculomotor control. The results of the first task indicate intact free scanning of photographs for mildly to moderately affected PD patients, as reflected by scene exploration, duration of fixation and the saccadic parameters amplitude, peak velocity and duration. The second experiment showed that manipulating distractor interference had no greater effect on overt visual search performance for PD patients than for controls. PD patients did not differ from control subjects with respect to saccadic duration and the number of saccades made to reach a target stimulus. Visual search time and reaction time were not found to be prolonged in patients, neither for simple, nor for complex search displays. On the other hand, motor execution, as reflected by movement time, was found to be impaired in PD patients. For the third task, general performance for covertly shifting attention, as indicated by error rate, did not differ between groups. However, the ability to maintain fixation before, during and after cue presentation was found to be reduced in patients. Reaction times did not differ between groups with respect to cueing and timing conditions, indicating intact covert shifting of attention in patients with PD. Movement time for this task was not found to be significantly prolonged in patients, but correlations between movement time and

measures of disease severity indicate an increase of movement time with progression of PD. Normal oculomotor parameters, such as amplitude, duration and velocity on the one hand and prolonged manual movement time on the other hand, indicate that motor and oculomotor systems are differently effected in PD. The results are in line with Bekkering and colleagues (2001), who report intact dynamics of saccades, but a reduced peak velocity of manual pointing responses for PD patients. Patients in that study were also in an early stage of the disease and on medication during the testing period. The authors conclude that "the first sensorimotor deficits in PD patients are likely to occur in the manual execution process but not within oculomotor execution processes."

Although overall findings are in line with the main hypothesis, several confounding factors must be considered.

PD subjects are heterogeneous in many aspects – factors such as different symptoms, duration of illness and the effects of medication all contribute to this diversity. There is converging evidence for differences in cognitive performance between bradykinesia-dominant and tremor-dominant PD patients (Hayes et al., 1998; Wylie & Stout, 2002). However, these differences are rather specific and seem independent of "general motor slowing." Most studies investigating cognitive and motor deficits in PD have looked at severe PD stages. The PD subjects of the current study showed relatively mild clinical signs as indicated by low UPDRS scores on all sub-scales and low Hoehn and Yahr scores. Four patients were newly diagnosed as having PD and had not yet received medication at the time of testing. The remaining patients were all on medication during testing, thus symptoms were reduced and performance was brought into line with healthy controls. Despite medication, the severity of patients' symptoms often fluctuates over short periods of time. In addition, aggravating circumstances in PD research concern the fact that selecting a population of patients with pure idiopathic PD is very difficult, in that several patients may later turn out to be, for example, cases of progressive supranuclear palsy or multisystem-atrophy. The probability of making a false idiopathic PD diagnosis, either falsely including patients without idiopathic PD or falsely excluding patients with idiopathic PD, lies at about ten percent (Hughes, Ben-Shlomo, Daniel, & Lees, 2001; Hughes, Daniel, Blankson, & Lees, 1993; Hughes, Daniel, Kilford, & Lees, 1992). Selection criteria for the present study were very strict to minimize the risk of falsely including patients with other diagnoses. However, when

comparing findings from different studies, it must be considered that often patients were included who did not demonstrate the PD specific dopaminergic deficit or suffered additional structural alterations. It was already mentioned in the theoretical part that apart from dopaminergic imbalance, noradrenergic, cholinergic and serotonergic systems may also be affected by the disease. Therefore, non-dopaminergic neurochemical alterations contribute to cognitive and behavioural impairment in PD as well.

In summary, PD is a heterogeneous disorder, stressing the importance of strict inclusion and exclusion criteria for studies. The present study is, to the best of our knowledge, the first approach which systematically investigates different aspects of visual-spatial attention in a well defined sample of patients with idiopathic PD, considering known deficits in oculomotor control. Overall, the results not only underline the importance of carefully recording eye movements during attentional tasks in patients with oculomotor abnormalities, but also draw attention to the role of motor and oculomotor processes during cognitive visual tasks in general.

8 LIMITATIONS OF THE STUDY AND IMPLICATIONS FOR FUTURE RESEARCH

It is important to note that the study presented here has several limitations. Obviously, the sample of PD patients was small. Therefore, an analysis of subgroups which differ with respect to primary symptoms and level of disease severity was not possible. As discussed in the previous chapter in more detail, PD patients represent a very heterogeneous group and there is considerable evidence from the literature as well as theoretical considerations that such differences may have a strong influence, at least on motor impairment. In this context, it must be pointed out that the distinction between mild to moderate PD is artificial in the sense that it is purely based on a median split for the present sample. Due to the complex diagnostic criteria, there is no general cut-off score to distinguish between mild to moderate disease stages. The patients who participated in the present investigation were chosen within feasible bounds. It is recommended for future studies to broaden the sample in order to explore and refine variables, such as progression of illness, age, main symptoms and dominant side of symptoms, cognitive and emotional status, opthalmolocial parameters (e.g. visual acuity) and medication in more detail within the group of patients.

A clear weakness of the study concerns the limited number of experiments and in particular the restricted amount of trials per experiment. These limitations were necessary due to several factors. First, the majority of patients had been discharged from the hospital at the time of testing. The distance between their home residence and the hospital was often great and they were treated at the neurological outpatients clinic within the scope of a clinical examination. Thus, we had a limited time frame for testing and could not see the patients on more than one occasion. Second, a substantial number of PD patients suffer from fatigue and daytime sleepiness (e.g. Alves, Wentzel-Larsen, & Larsen, 2004; Friedman & Chou, 2004), so the duration of experiments requiring a rather monotonous response pattern (such as covert attention shifting) cannot be too long. To increase the amount of trials and circumvent confounds of fatigue and sleepiness, repeated measurements at different days could be carried out. Alternatively, task conditions within a single experiment could be reduced. In the present study, this is

particularly relevant for the covert attention task, because the small amount of trials in each condition results in limited data variance.

Correct performance for visual search, within the defined criteria, was weak overall. Despite the fact that no button press was observed in only a small number of searches, the overall performance could have been slightly increased by making the task self-paced, thus presenting the next picture after the upper button was pressed. However, the aim of the fixed 10 sec picture presentation was to minimize the "speed factor" of the task, or in other words, to detain subjects from rushing through the experiment. Prior pilot data had indicated that healthy subjects were able to detect the target stimulus in all pictures within at most 6 seconds.

Future research aimed at the association between attentional and oculomotor aspects in PD has the potential to generalize the present findings into a broader line of investigation. Thus, other experimental paradigms could be used to study overt and covert aspects of attention and response selection (e.g. the flanker task, Eriksen & Eriksen, 1974). Further, the temporal dynamics of visual attention, often investigated in the attentional blink paradigm (Raymond, Shapiro, & Arnell, 1992), may be a promising line of inquiry. Finally, the combination of visual attentional tasks, eye movement recording and measures of online brain activity, such as ERPs and neuroimaging, may additionally contribute to the understanding of attention processing and oculomotor impairment in PD patients.

9 SUMMARY

Introduction Previous research has yielded heterogeneous results with respect to visuo-spatial selective attention in PD. The aim of the present study was to investigate whether these deficits are related to the oculomotor deficits associated with the disease or not.

Methods The study sample included 22 patients with idiopathic Parkinson's disease and 22 healthy control participants. Performance between groups was compared on three experimental tasks: 1) viewing of photographs, 2) visual search and 3) covert attention shifting. Stimuli were presented on a computer screen. Eye movements were recorded by the EyeLink I system. Manual responses were accomplished via a button box.

Results For the present study, it was postulated that reported impairment on visuo-spatial attention tasks is confounded by deficits in motor and/or oculomotor control. Patients and controls did not differ with respect to basic saccadic parameters recorded during viewing of photographs. For visual search, the number of saccades until target detection, the size of saccades and visual search time did not differ between groups. Thus, patients were not effected more by distractor interference as controls, indicating intact inhibitory mechanisms for response selection. Reaction time (movement initiation) was not found to be prolonged in patients compared to healthy control subjects. However, movement time (movement execution) was found to be impaired in patients. For covert attention shifting, deficient inhibitory processes were limited to oculomotor control, as reflected by disruptive saccades made during fixation. RT did not differ for the two groups of subjects in any of the tested conditions. However, a tendency for impaired motor execution in PD patients was observed. Contrary to expectation movement time, but not reaction time, increased with an increasing number of fixation disrupting eye movements.

Conclusion Overall findings suggest intact inhibitory mechanisms with respect to response selection and covert attention shifting. However, the suppression of eye movements during fixation seems to be impaired. Whereas movement initiation time (RT) was found to be the same for both groups, movement execution time was found to be prolonged in PD patients.

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11 APPENDIX

Sehr geehrte Damen und Herren, liebe Patienten,

Das Universitätskrankenhaus Eppendorf versucht durch Initiierung und Durchführung klinischer Studien, einen Beitrag für den medizinischen Fortschritt zu leisten, von dem die jeweils betroffenen Patienten profitieren sollen.

In der Medizinischen Psychologie des UKE führen wir zur Zeit ein neuropsychologisches Projekt durch, d.h. es werden Veränderungen von Hirnfunktionen wie Wahrnehmung, Gedächtnis und Aufmerksamkeit als mögliche Komplikationen verschiedener Grunderkrankungen untersucht. Obwohl die idiopathische Parkinson Krankheit im fortgeschrittenen Stadium primär motorische Symptome hervorruft, gibt es in der Literatur auch Hinweise auf Beeinträchtigungen kognitiver Funktionen, insbesondere der Aufmerksamkeit. Die Ergebnisse solcher Studien sind jedoch uneindeutig und führen häufig zu einer großen Verunsicherung bei den betroffenen Patienten.

Die Untersuchung, für die wir Sie als Teilnehmer gewinnen möchten, beschäftigt sich mit einem wichtigen Teilaspekt der Aufmerksamkeit: der gerichteten Aufmerksamkeit. Darunter versteht man die Fähigkeit, seine Aufmerksamkeit trotz einer Vielzahl von ablenkenden Faktoren (z.B. anderen Personen und Objekten) auf immer neue Gegebenheiten lenken zu können.

Prozesse der visuellen Aufmerksamkeit stehen in engem Zusammenhang zu unseren Augenbewegungen. In der Regel richten wir sowohl die Aufmerksamkeit als auch die Augen auf ein Objekt unseres Interesses. Große Ermüdung kann unter Umständen zu einer Beeinträchtigung der Aufmerksamkeit und der Blickmotorik führen und somit im Alltag eine Einschränkung der Lebensqualität bedeuten.

Mit Hilfe einer Blickbewegungskamera wollen wir die gerichtete Aufmerksamkeit anhand von Augenbewegungen beim Anschauen verschiedener Bilder auf einem Computerbildschirm untersuchen.
Ihre Aufgabe besteht allein darin, verschiedene Symbole und Bilder mit den Augen auf dem Monitor zu verfolgen und das Erkennen bestimmter Bilder mit Hilfe eines Tastendrucks zu signalisieren. Das Tragen einer Brille stellt dabei überhaupt kein Problem dar.

Die Untersuchung findet im Universitätskrankenhaus Eppendorf, in der Medizinischen Psychologie (S 30) in Raum 113 im ersten Stock statt und dauert ca. eine Stunde.

Nach Beendigung der Studie erhalten Sie, wenn Sie es wünschen, natürlich auch eine Rückmeldung über die Ergebnisse.

Wir wären Ihnen für Ihre Teilnahme sehr dankbar, und möchten Sie bitten, einen Termin mit Stefanie Kraft oder Sven Krause (Tel.: 42803-4166 oder 42803-8258) zu vereinbaren.

Aufklärungsgespräch

Mein Name ist Stefanie Kraft. Ich bin Dipl. Psychologin. In Zusammenarbeit zwischen der neurologischen Klinik und Poliklinik und des Instituts und Poliklinik für Medizinische Psychologie des Universitätsklinikums Hamburg-Eppendorf, führen wir eine Studie mit dem Titel „Selektive visuelle Aufmerksamkeit und sakkadische Augenbewegungen beim idiopathischen Parkinson Syndrom“ durch. Ich werde Ihnen jetzt erklären, um was es sich dabei handelt und warum wir Sie angesprochen haben. Machen Sie sich gerne Notizen und unterbrechen Sie mich, wenn Sie Fragen haben, oder etwas nicht verstanden haben.

Die Hauptbeschwerden bei der Parkinsonschen Erkrankung sind die motorischen Symptome, wie das Zittern und die Muskelsteifheit. Auch die Bewegung der Augen kann dabei beeinträchtigt sein. Über diese motorischen Symptome hinaus, kann es aber auch im Verlauf der Erkrankung zu Veränderungen von Hirnfunktionen wie z.B. den Gedächtnisleistungen kommen. Unsicher ist bislang, ob auch die Konzentrationsfähigkeit von der Erkrankung betroffen ist.

Die Untersuchung, für die wir Sie als Teilnehmer gewinnen möchten, beschäftigt sich mit diesem Bereich der Aufmerksamkeit, d.h. der Konzentrationsfähigkeit oder gerichteten Aufmerksamkeit. Unter der gerichteten Aufmerksamkeit versteht man die Fähigkeit, seine Aufmerksamkeit trotz einer Vielzahl von ablenkenden Faktoren (z.B. anderen Personen und Objekten) auf immer neue Gegebenheiten lenken zu können. Sie ist daher in unserem Alltag, beim Autofahren oder im Gespräch mit mehreren Menschen von großer Bedeutung.

Die gerichtete Aufmerksamkeit steht in engem Zusammenhang zu unseren Augenbewegungen. In der Regel richten wir sowohl die Aufmerksamkeit als auch die Augen auf ein Objekt unseres Interesses.

Mit Hilfe einer Blickbewegungskamera wollen wir die gerichtete Aufmerksamkeit beim Anschauen verschiedener Bilder auf einem Computerbildschirm untersuchen.

Ich zeige Ihnen jetzt erst mal das Kopfteil mit den kleinen Kameras, die Ihre Augenbewegungen aufzeichnen werden. Das Tragen einer Brille stellt dabei kein Problem dar.

Die Untersuchung besteht aus drei Aufgaben am Computer. In allen Aufgaben sollen Sie verschiedene Symbole und Bilder mit den Augen auf dem Monitor zu verfolgen und das Erkennen bestimmter Bilder mit Hilfe eines Tastendrucks zu signalisieren. Jede Aufgabe wird vorher genau am Bildschirm erklärt und in einem Probedurchgang geübt. Sie können mich aber auch jederzeit fragen, wenn irgendetwas unklar ist. Ich zeige Ihnen jetzt Beispiele für die Aufgaben.

Während die Aufgaben laufen, möchte ich Sie dann bitten den Kopf auf die Kinnstütze vor Ihnen zu legen. Jede Aufgabe wird von mehreren Pausen unterbrochen und auch zwischen den Aufgaben sind Pausen in denen Sie den Kopf zurück lehnen können und die Augen ausruhen können.

Die Untersuchung wird insgesamt ungefähr eine Stunde dauern.

Die Teilnahme an der Studie ist vollkommen freiwillig. Ob Sie teilnehmen oder nicht, hat keinerlei Einfluss auf Ihre weitere Behandlung. Das gleiche gilt - falls Sie teilnehmen wollen -

für alle Ergebnisse der Untersuchungen im Rahmen der Studie. Sie dürfen auch während jeder Untersuchung oder zwischen den Untersuchungsterminen jederzeit aus der Studie aussteigen. Sie brauchen sich dafür weder zu rechtfertigen, noch haben Sie irgendwelche Konsequenzen zu befürchten. Ihre bereits erhobenen Daten werden dann gelöscht. Im Rahmen dieser Untersuchung anfallende Ergebnisse und Daten werden nur in anonymisierter Form zur elektronischen Datenspeicherung und -verarbeitung verwendet.

Falls Sie persönlich Interesse an den Ergebnissen haben, werden wir Sie nach Abschluss der Studie darüber informieren.

Falls Sie an der Studie teilnehmen wollen, bitte ich Sie die folgende Erklärung zu unterschreiben.

Einverständniserklärung

Thema der Studie:
Selektive visuelle Aufmerksamkeit und sakkadische Augenbewegungen beim idiopathischen Parkinson Syndrom

Frau Dipl. Psych. Stefanie Kraft hat mich vollständig über das Wesen und die Bedeutung der geplanten Studie aufgeklärt. Ich konnte dabei alle mich interessierenden Fragen stellen. Ferner hatte ich Gelegenheit, das Aufklärungsblatt genau durch zu lesen und auch dazu Fragen zu stellen. Ein Exemplar der Aufklärung ist mir zum Verbleib ausgehändigt worden.

Ich weiß, dass ich meine Einwilligung ohne Angabe von Gründen widerrufen kann, ohne dass mir daraus Nachteile bezüglich einer laufenden oder zukünftigen Behandlung entstehen.

Ich weiß, dass die im Rahmen dieser Studie erhobenen Daten und persönlichen Mitteilungen der ärztlichen Schweigepflicht unterliegen und zur Auswertung nur ohne meinen Namen (anonymisiert) zusammengeführt werden.

Ich bestätige durch meine Unterschrift, dass ich die Aufklärung verstanden habe und mich mit der Durchführung der vorgenannten Studie einverstanden erkläre.

Hamburg, den.....

Unterschrift des aufklärenden Arztes/Dipl. Psychologin

Unterschrift der Versuchsperson

....

MWT-B

Name _____ Punkte _____

Beruf _____ Alter _____

Untersuchungsdatum _____ männlich – weiblich ____

Sonstiges _____

_____

Anweisung:

Sie sehen hier mehrere Reihen mit Wörtern. In jeder Reihe steht **höchstens ein Wort,** das Ihnen vielleicht bekannt ist. Wenn Sie es gefunden haben, streichen Sie es bitte durch.

---

1. Nale – Sahe – Nase – Nesa – Sehna
2. Funktion – Kuntion – Finzahm – Tuntion – Tunkion
3. Struk – Streik – Sturk – Strek – Kreik
4. Kulinse – Kulerane – Kulisse – Klubihle – Kubistane
5. Kenekel – Gesonk – Kelume – Gelenk – Gelerge
6. siziol – salzahl – sozihl – sziam – sozial
7. Sympasie – Symmofeltrie – Symmantrie – Symphonie – Symplanie
8. Umma – Pamme – Nelle – Ampe – Amme
9. Krusse – Surke – Krustelle – Kruste – Struke
10. Kirse – Sirke – Krise – Krospe – Serise
11. Tinxur – Kukutur – Fraktan – Tinktur – Rimsuhr
12. Unfision – Fudision – Infusion – Syntusion – Nuridion
13. Feudasmus – Fonderismus – Föderalismus – Födismus – Föderasmus
14. Redor – Radium – Terion – Dramin – Orakium

bitte wenden

15. kentern – knerte – kanzen – kretern – trekern
16. Kantate – Rakante – Kenture – Krutehne – Kallara
17. schalieren – waschieren – wakieren – schackieren – kaschieren
18. Tuhl – Lar – Lest – Dall – Lid
19. Dissonanz – Diskrisanz – Distranz – Dinotanz – Siodenz
20. Ferindo – Inferno – Orfina – Firanetto – Imfindio
21. Rilkiase – Kilister – Riliker – Klistier – Linkure
22. kurinesisch – kulinarisch – kumensisch – kulissarisch – kannastrisch
23. Rosto – Torso – Soro – Torgos – Tosor
24. Kleiber – Beikel – Keibel – Reikler – Biekerl
25. Ralke – Korre – Ruckse – Recke – Ulte
26. Lamone – Talane – Matrone – Tarone – Malonte
27. Tuma – Umat – Maut – Taum – Muta
28. Sorekin – Sarowin – Rosakin – Narosin – Kerosin
29. beralen – gerältet – anälteren – untären – verbrämen
30. Kapaun – Paukan – Naupack – Aupeck – Ankepran
31. Sickaber – Bassiker – Kassiber – Sassiker – Askiber
32. Pucker – Keuper – Eucker – Reuspeck – Urkane
33. Spirine – Saprin – Parsin – Purin – Asprint
34. Kulon – Solgun – Koskan – Soran – Klonus
35. Adept – Padet – Edapt – Epatt – Taped
36. Gindelat – Tingerat – Indigenat – Nitgesaar – Ringelaar
37. Berkizia – Brekzie – Birakize – Brikazie – Bakiria

INSTRUCTIONS FOR ADMINISTRATION OF
MINI MENTAL STATUS EXAMINATION

ORIENTATION

1. Ask for the date. Then ask specifically for parts omitted.
   i.e., "Can you also tell me what season it is?" One point for each correct.
2. Ask in turn, "Can you tell me the name of this place?", town, county, etc.
   One point for each correct.

REGISTRATION

Tell the person you are going to test their memory. Then say the names of three unrelated objects, clearly and slowly, about one second for each. After you have said all three, ask him to repeat them. This first repetition determines his score (0-3) but keep saying them until he can repeat all three, up to six trials. If the subject does not eventually learn all three, recall cannot be meaningfully tested.

ATTENTION AND CALCULATION

Ask the subject to begin with 100 and count backwards by 7. Stop after five subtractions. Score the total number of correct answers.

If the subject cannot or will not perform this task, ask him to spell the word "world" backwards. The score is the number of letters in correct order.
i.e., dlrow = 5 points, dlorw = 3 points.

RECALL

Ask the patient if he can recall the three words you previously asked him to remember. One point for each correctly recalled.

LANGUAGE

Naming: Show the subject a wristwatch and ask her what it is.
Repeat with a pencil. One point for each named correctly.
Repetition: Ask the patient to repeat the sentence after you. Allow only one trial.
3 Stage Command: give the verbal instructions, then present the subject a sheet of paper. One point for each part of the command that is correctly executed.
Reading: Have the subject read the phrase "CLOSE YOUR EYES". The letters should be large and dark enough for the subject to read. Ask him to "Read the sentence and do what it says." Score correctly only if they read and the phrase and close their eyes.
Writing: Give the subject a blank piece of paper and ask her write a sentence for you. Do not dictate a sentence, it is to be written by the subject spontaneously. To score correctly, it must contain a subject and verb and be sensible. It should be a complete thought. Correct grammar and punctuation are NOT necessary.
Copying: On a piece of paper, draw intersecting pentagons, each side about one inch and ask him to copy it exactly as it is. To score correctly, all ten angles must be present AND two must intersect. Tremor and rotation are ignored.

Estimate the subject's level of sensorium along a continuum, from alert to coma.

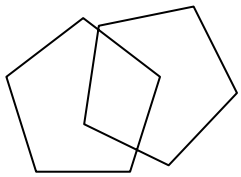
TOTAL SCORE POSSIBLE = 30
23 OR LESS: HIGH LIKELIHOOD OF DEMENTIA
25-30: NORMAL AGING OR BORDERLINE DEMENTIA

MINI MENTAL STATUS EXAM

PATEINT'S NAME: _____ _____

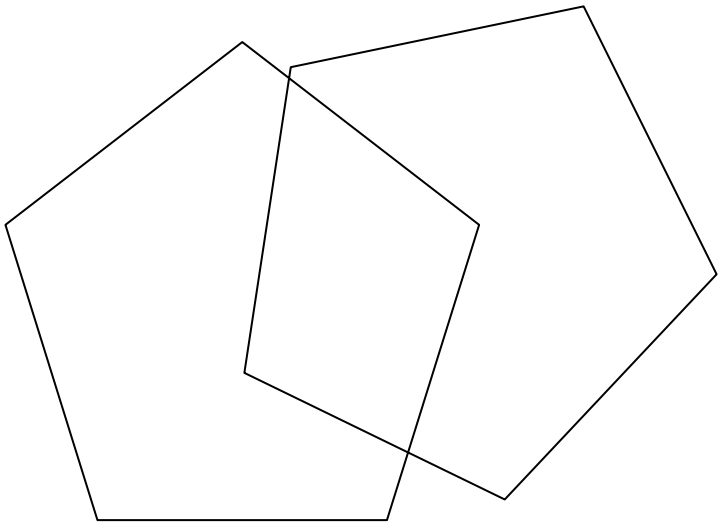
Date: _____ Client's Highest Level of Education: _____

Maximum Score	Score	ORIENTATION
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	where are we: (state) (county) (town) (hospital (floor)?
		REGISTRATION
3	( )	Name 3 objects: One syllable words, 1 second to say each. Then ask the patient all 3 after you have said them.
		Give 1 point for each correct answer. Then repeat them until he learns all 3. Count trials and record. Trials _____
		ATTENTION AND CALCULATION _____
5	( )	Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world" backwards. 100 – 93 – 86 – 79 – 72 – 65 – 58
		RECALL
3	( )	Ask for 3 objects repeated above. Give 1 point for each correct.
		LANGUAGE
9	( )	Name a pencil, and watch (2 points)
	( )	Repeat the following: "No ifs, and or buts." (1 point)
	( )	Follow a 3-stage command: "Take this paper in your right hand, fold it in half, and put it on the floor." (3 points)
	( )	Read and obey the following: "Close your eyes" (1 point)
	( )	Write a sentence. (1 point)
	( )	Copy design. (1 point)



_____
Total Score

Assess level of consciousness along a continuum. _____
(Alert) (Drowsy) (Stupor) (Coma)



Close your eyes.

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

-> 20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

-> 21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

-> 22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

-> 23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

-> 24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

-> 25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

-> 26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes
37. Are "off" periods unpredictable?
0 = No
1 = Yes
38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes
39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes
41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes
42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)

0 = No
1 = Yes

Die mit "->" gekennzeichneten Skalen (20-26) werden für die Patientenübersicht gesondert nach Links und Rechts aufgeführt.

MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

Erläuterung zu ESACC

Beispiel
ESACC R 2359264 2359284 24 511.8 387.3 490.9 313.1 2.97 193.7

(Event) (Auge) (Zeitstempel Anfang) (Zeitstempel Ende) (Dauer) (Anfang Horizontal) (Anfang Vertikal) (Ende Horizontal) (Ende Vertikal) (Amplitude (in Grad)) (Peak Velocity)

MSG 2122467 DISPLAY_COORDS 0 0 799 599
MSG 2133806 TRIALID C:\multi\SUCH.ini BLOCK 1/1
MSG 2139811 DRIFTCORRECT LR REPEATING due to large error...
MSG 2142023 DRIFTCORRECT LR LEFT at 400,300 OFFSET 3.03 deg. 7.0,69.0 pix.
MSG 2142023 DRIFTCORRECT LR RIGHT at 320,40 OFFSET 1.58 deg. -16.0,33.0 pix.
START 2142032 LEFT RIGHT SAMPLES EVENTS
PRESCALER 1
VPRESCALER 1
PUPIL AREA
EVENTS GAZE LEFT RIGHT
SAMPLES GAZE LEFT RIGHT RATE 250.00
SFIX L 2142032
SFIX R 2142032
MSG 2142143 SYNCTIME
MSG 2142155 INSTRUKTIONII.BMP
EFIX L 2142032 2142320 292 400.0 300.2 747
SSACC L 2142324
EFIX R 2142032 2142324 296 402.7 303.9 864
SSACC R 2142328
ESACC L 2142324 2142360 40 399.5 301.3 254.6 347.9 6.42 293.1
ESACC R 2142328 2142360 36 399.0 308.8 241.9 331.2 6.61 308.9
SFIX L 2142364
SFIX R 2142364
EFIX L 2142364 2142480 120 262.7 342.7 768
EFIX R 2142364 2142480 120 252.2 330.4 851
SSACC L 2142484
SSACC R 2142484
ESACC L 2142484 2142516 36 260.9 341.3 158.2 364.8 4.33 219.2
ESACC R 2142484 2142516 36 251.6 329.9 138.9 338.1 4.53 217.7
SFIX L 2142520
SFIX R 2142520
EFIX L 2142520 2142672 156 162.3 359.2 794
EFIX R 2142520 2142672 156 147.3 337.1 865
SSACC L 2142676
SSACC R 2142676
ESACC L 2142676 2142720 48 161.4 357.5 486.9 356.7 13.22 460.3
ESACC R 2142676 2142720 48 149.6 337.2 474.1 362.9 13.29 450.3
SFIX L 2142724
SFIX R 2142724
EFIX L 2142724 2142868 148 480.6 355.9 722
EFIX R 2142724 2142868 148 469.8 359.4 848

SSACC L 2142872								
SSACC R 2142872								
ESACC L 2142872	2142908	40	478.7	353.6	648.8	349.8	6.67	305.1
ESACC R 2142872	2142908	40	471.5	356.6	635.8	356.0	6.49	284.7
SFIX L 2142912								
SFIX R 2142912								
EFIX L 2142912	2143100	192	640.5	349.4	708			
EFIX R 2142912	2143100	192	631.4	354.2	834			
SSACC L 2143104								
SSACC R 2143104								
ESACC L 2143104	2143144	44	637.8	347.1	409.6	247.1	10.32	419.8
SFIX L 2143148								
ESACC R 2143104	2143148	48	631.9	350.7	372.0	246.0	11.64	408.1
SFIX R 2143152								
EFIX L 2143148	2143480	336	409.9	245.4	753			
EFIX R 2143152	2143480	332	388.5	245.1	821			
SSACC L 2143484								
SSACC R 2143484								
ESACC R 2143484	2143488	8	392.1	241.2	393.9	237.6	0.36	46.3
SFIX R 2143492								
ESACC L 2143484	2143492	12	413.3	242.2	417.8	236.0	0.48	46.5
SFIX L 2143496								
EFIX L 2143496	2143724	232	418.3	237.4	726			
EFIX R 2143492	2143724	236	395.1	234.3	790			
SSACC L 2143728								
SSACC R 2143728								
ESACC L 2143728	2143768	44	415.0	244.9	352.4	383.5	7.04	272.1
ESACC R 2143728	2143768	44	393.6	241.6	301.9	376.9	7.40	291.6
SFIX L 2143772								
SFIX R 2143772								
EFIX R 2143772	2144104	336	312.7	371.7	779			
SSACC R 2144108								
EFIX L 2143772	2144108	340	335.8	377.6	685			
SSACC L 2144112								
ESACC L 2144112	2144152	44	338.6	372.5	539.4	369.1	8.25	274.4
ESACC R 2144108	2144152	48	317.5	368.9	524.9	377.8	8.41	268.0
SFIX L 2144156								
SFIX R 2144156								
EFIX L 2144156	2144316	164	537.2	366.5	689			
EFIX R 2144156	2144316	164	525.3	373.1	811			
SSACC L 2144320								
SSACC R 2144320								
ESACC L 2144320	2144352	36	540.3	366.0	673.6	350.5	5.32	240.5
ESACC R 2144320	2144352	36	532.0	372.8	656.7	359.6	5.00	217.7
SFIX L 2144356								
SFIX R 2144356								
EFIX L 2144356	2144604	252	665.7	353.4	669			
SSACC L 2144608								
EFIX R 2144356	2144608	256	654.0	359.1	774			
SSACC R 2144612								
ESACC L 2144608	2144628	24	668.2	357.7	711.9	363.2	1.80	116.2

ESACC	R	2144612	2144628	20	661.4	361.4	697.5	364.6	1.51	104.2
SFIX	L	2144632								
SFIX	R	2144632								
EFIX	L	2144632	2144808	180	707.6	363.5	618			
SSACC	L	2144812								
EFIX	R	2144632	2144812	184	698.1	363.6	723			
SSACC	R	2144816								
ESACC	L	2144812	2144856	48	707.5	365.2	461.7	403.2	10.05	358.7
ESACC	R	2144816	2144856	44	692.5	366.4	445.4	391.2	10.07	368.5
……..										
SSACC	R	2718844								
ESACC	L	2718840	2718880	44	329.0	618.8	414.0	371.2	11.38	471.3
SFIX	L	2718884								
ESACC	R	2718844	2718884	44	308.3	571.3	376.4	358.1	10.08	449.2
SFIX	R	2718888								
EFIX	L	2718884	2719524	644	394.0	373.9	938			
EFIX	R	2718888	2719524	640	388.4	362.2	1048			
SSACC	L	2719528								
SSACC	R	2719528								
ESACC	L	2719528	2719548	24	388.5	374.6	435.1	423.4	2.96	196.8
ESACC	R	2719528	2719548	24	392.5	365.2	430.8	412.8	2.71	174.0
SFIX	L	2719552								
SFIX	R	2719552								
EFIX	L	2719552	2719904	356	436.8	430.2	969			
EFIX	R	2719552	2719904	356	439.8	419.1	1116			
SSACC	L	2719908								
SSACC	R	2719908								
ESACC	L	2719908	2719916	12	441.7	431.3	454.8	429.4	0.64	61.8
ESACC	R	2719908	2719916	12	448.9	419.3	459.9	417.2	0.57	56.4
SFIX	L	2719920								
SFIX	R	2719920								
EFIX	L	2719920	2720296	380	451.9	425.6	957			
EFIX	R	2719920	2720296	380	458.4	415.8	1104			
SSACC	L	2720300								
SSACC	R	2720300								
ESACC	L	2720300	2720336	40	447.7	422.2	341.4	362.6	4.99	225.7
ESACC	R	2720300	2720336	40	454.4	411.3	333.3	346.7	5.48	219.8
SFIX	L	2720340								
SFIX	R	2720340								
EFIX	L	2720340	2720936	600	343.4	361.9	960			
EFIX	R	2720340	2720936	600	342.7	346.1	1043			
SSACC	L	2720940								
SSACC	R	2720940								
ESACC	R	2720940	2720972	36	337.3	343.0	248.5	260.3	5.37	234.8
SFIX	R	2720976								
ESACC	L	2720940	2720976	40	336.1	357.4	262.6	246.3	6.00	293.3
SFIX	L	2720980								
EFIX	L	2720980	2721184	208	257.6	248.7	950			
EFIX	R	2720976	2721184	212	251.0	254.2	1036			
SSACC	L	2721188								
SSACC	R	2721188								

ESACC L	2721188	2721200	16	252.9	239.7	254.5	215.6	1.26	107.0
ESACC R	2721188	2721200	16	250.8	248.7	248.1	229.7	1.05	77.2
SFIX L	2721204								
SFIX R	2721204								
EFIX R	2721204	2721404	204	250.4	227.3	1029			
SSACC R	2721408								
EFIX L	2721204	2721408	208	254.6	216.0	959			
SSACC L	2721412								
ESACC L	2721412	2721456	48	255.9	222.5	486.4	401.5	12.04	410.1
ESACC R	2721408	2721456	52	251.3	230.1	465.6	394.6	11.06	357.5
SFIX L	2721460								
SFIX R	2721460								
EFIX L	2721460	2721752	296	475.0	399.6	915			
SSACC L	2721756								
EFIX R	2721460	2721756	300	472.9	386.1	1002			
SSACC R	2721760								
ESACC R	2721760	2721788	32	477.9	383.5	593.1	352.6	4.69	202.1
SFIX R	2721792								
ESACC L	2721756	2721792	40	474.5	399.5	605.4	357.5	5.43	208.2
SFIX L	2721796								
EFIX L	2721796	2722644	852	599.7	359.9	863			
SSACC L	2722648								
EFIX R	2721792	2722648	860	601.9	353.6	980			
SSACC R	2722652								
ESACC L	2722648	2722712	68	601.6	362.6	165.2	573.0	18.36	414.1
SFIX L	2722716								
ESACC R	2722652	2722716	68	601.3	357.8	117.2	518.0	19.25	483.3
SFIX R	2722720								
EFIX L	2722716	2723068	356	155.2	566.7	974			
EFIX R	2722720	2723068	352	126.5	512.2	1000			
SSACC L	2723072								
SSACC R	2723072								
ESACC L	2723072	2723128	60	147.6	564.4	542.1	394.0	16.59	426.5
ESACC R	2723072	2723128	60	123.6	512.7	533.5	378.2	16.31	434.0
SFIX L	2723132								
SFIX R	2723132								
EFIX L	2723132	2723336	208	527.7	390.6	835			
EFIX R	2723132	2723336	208	529.7	376.7	908			
SSACC L	2723340								
SSACC R	2723340								
ESACC L	2723340	2723364	28	530.6	386.7	608.2	346.8	3.60	194.2
ESACC R	2723340	2723364	28	537.8	373.1	607.7	353.0	2.90	152.9
SFIX L	2723368								
SFIX R	2723368								
EFIX L	2723368	2723648	284	608.1	351.2	810			
SSACC L	2723652								
EFIX R	2723368	2723652	288	612.1	355.4	923			
SSACC R	2723656								
ESACC L	2723652	2723664	16	608.4	355.4	596.2	374.4	1.09	85.6
ESACC R	2723656	2723664	12	609.8	356.8	601.5	364.4	0.55	56.1
SFIX L	2723668								

```
SFIX R   2723668
EFIX L   2723668     2724128        464       601.9   373.1    835
SSACC L  2724132
ESACC L  2724132   2724136        8         597.6   364.6   594.8   358.6   0.40    58.9
SFIX L   2724140
EFIX L   2724140     2724440        304       597.4   357.8    862
SSACC L  2724444
EFIX R   2723668     2724444        780       602.4   361.8    988
SSACC R  2724448
ESACC L  2724444   2724472        32        593.8   358.6   489.4   323.2   4.25    240.9
SFIX L   2724476
ESACC R  2724448   2724476        32        595.6   353.3   490.0   314.6   4.42    223.6
SFIX R   2724480
EFIX L   2724476     2724660        188       496.0   322.3    913
EFIX R   2724480     2724660        184       495.4   316.2   1039
END    2724670       SAMPLES     EVENTS        RES     26.80   22.68
MSG    2724681 TRIAL_RESULT 0
MSG    2724684 TRIAL OK
```

```
Attribute VB_Name = "Modul12"
Sub Aufgabe_3_Basisauswertung_Blickbewegungsdaten_ASC_to_EXCEL()

Dim Leer As Boolean
Dim Eyeblink_anfang
' Datei konvertieren

    ChDir "C:\blicktst"
    Workbooks.OpenText Filename:="C:\blicktst\*_3.txt", Origin:= _
        xlWindows, StartRow:=1, DataType:=xlDelimited, TextQualifier:= _
        xlDoubleQuote, ConsecutiveDelimiter:=True, Tab:=True,
Semicolon:=False, _
        Comma:=False, Space:=True, Other:=False, FieldInfo:=Array(Array(1,
1), _
        Array(2, 1), Array(3, 1), Array(4, 1), Array(5, 1), Array(6, 1),
Array(7, 1), Array(8, 1), _
        Array(9, 1), Array(10, 1), Array(11, 1))
      ', DecimalSeparator:="."

' DecimalSeparator:="." ist ganz wichtig, weil sonst einige Zahlen als
Datum konvertiert werden!

'''
' Arbeitsblätter für linkes Auge und für rechtes Auge erstellen
'''


Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add
Worksheets.Add

Worksheets(14).Name = "Rechtes Auge"
Worksheets(13).Name = "Linkes Auge"
Worksheets(12).Name = "Sakkaden Rechts"
Worksheets(11).Name = "Fixationen Rechts"
Worksheets(10).Name = "Eyeblinks Rechts"
Worksheets(9).Name = "Sakkaden Links"
Worksheets(8).Name = "Fixationen Links"
Worksheets(7).Name = "Eyeblinks Links"
Worksheets(1).Name = "MSG"


Worksheets(14).Activate

' Für MSG Zeilen Zeitstempel (für das Sortieren) verschieben

Range("a1").Select

Leer = False

    Do Until Leer = True

        gelöscht = False
```

```
        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        If ActiveCell.Value = "MSG" Or ActiveCell.Value = "START" Or
ActiveCell.Value = "END" Or ActiveCell.Value = "BUTTON" Then

                ActiveCell.Offset(0, 1).Select
                Selection.Insert Shift:=xlToRight
                ActiveCell.Offset(0, -1).Select

        End If
        If ActiveCell.Value = "PRESCALER" Or ActiveCell.Value =
"VPRESCALER" Or ActiveCell.Value = "PUPIL" Or ActiveCell.Value = "EVENTS"
Or ActiveCell.Value = "SAMPLES" Then

            ActiveCell.EntireRow.Select
            Selection.Delete
            gelöscht = True

        End If

        If ActiveCell.Value = "MSG" Then

            ActiveCell.Offset(0, 3).Select

            If ActiveCell.Value = "SYNCTIME" Or ActiveCell.Value =
"DRIFTCORRECT" Or ActiveCell.Value = "TRIAL_RESULT" Or ActiveCell.Value =
"TRIAL" Or ActiveCell.Value = "TRIALID" Then

                ActiveCell.EntireRow.Delete
                gelöscht = True

            End If

            ActiveCell.Offset(0, -3).Select

        End If

        If Not gelöscht Then ActiveCell.Offset(1, 0).Select

    Loop

'Instruktionen und Probedurchgang löschen

Worksheets(14).Activate
Range("a1").Select

Start = 0

    Do Until Start = 2

        If ActiveCell.Value = "START" Then

            Start = Start + 1
            ActiveCell.Offset(1, 0).Select

            Else: ActiveCell.EntireRow.Delete

        End If

    Loop

 ' Löschen vom "START" des ersten Blocks
```

```
    ActiveCell.Offset(-2, 0).Select
    ActiveCell.EntireRow.Delete


' Probedurchgang des getakteten Durchgangs löschen (Block 4)

Worksheets(14).Activate
Range("a1").Select

Start = 0

    Do Until Start = 3

        If ActiveCell.Value = "START" Then Start = Start + 1

        ActiveCell.Offset(1, 0).Select

    Loop

    ActiveCell.Offset(-1, 0).Select

    ActiveCell.EntireRow.Delete

    Do Until ActiveCell.Value = "START"

        ActiveCell.EntireRow.Delete

    Loop

' Alles MSG Zeilen aus dem Arbeitsblatt "Rechtes Auge" in extra
Arbeitsblatt kopieren

    Worksheets(14).Activate

    Range("a1").Select
    Leer = False
    gelöscht = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "MSG" Or ActiveCell.Value = "START" Or
ActiveCell.Value = "END" Or ActiveCell.Value = "BUTTON" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            gelöscht = True
            Worksheets(1).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(14).Activate
            ActiveCell.EntireRow.Delete


        End If

        If Not gelöscht Then

            ActiveCell.Offset(1, 0).Select
            gelöscht = False

        End If
```

```
        If ActiveCell.Value <> "MSG" And ActiveCell.Value <> "START" And
ActiveCell.Value <> "END" And ActiveCell.Value <> "BUTTON" Then
ActiveCell.Offset(1, 0).Select


    Loop



' Den gesammten Datensatz nach Eventart sortieren
    Worksheets(1).Activate
    Range("a1").Select
    Columns("A:M").Select
    Selection.Sort Key1:=Range("A1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom


' Die MSG Zeilen mit Eventart und Interstimulusintervall codieren (Block 2)

Worksheets(1).Activate
Range("a1").Select


    Do Until ActiveCell.Value = "MSG"

        ActiveCell.Offset(1, 0).Select

    Loop

    ActiveCell.Offset(0, 1).Select


    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "O_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_700"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
```

```
    ActiveCell.Value = "V_1100"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_300"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_300"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "N_1100"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "IV_1100"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
```

```
        ActiveCell.Value = "IV_700"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

' Die MSG Zeilen mit Eventart und Interstimulusintervall codieren (Block 3)

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_700"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "N_700"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0
```

```
Do Until Zähler = 5
    ActiveCell.Value = "V_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_1100"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "IV_300"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "IV_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_300"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "O_700"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0
```

```
    Do Until Zähler = 5
        ActiveCell.Value = "IV_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "O_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_1100"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "IV_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "N_300"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

' Die MSG Zeilen mit Eventart und Interstimulusintervall codieren (Block 5)
(Mit Warnfunktion)

    Zähler = 0

    Do Until Zähler = 6
        ActiveCell.Value = "V_W_2800"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select
```

```
Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "IV_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "IV_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2400"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "IV_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select
```

```
Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "IV_W_2400"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "O_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "N_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "IV_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select
```

```
    Loop

' Die MSG Zeilen mit Eventart und Interstimulusintervall codieren (Block 6)
(Mit Warnfunktion)

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_W_2000"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 6
        ActiveCell.Value = "V_W_2400"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "V_W_2000"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "N_W_2000"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 6
        ActiveCell.Value = "V_W_2400"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 6
        ActiveCell.Value = "V_W_2400"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 5
        ActiveCell.Value = "O_W_2000"
```

```
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2800"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "O_W_2400"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2400"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "V_W_2400"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 5
    ActiveCell.Value = "V_W_2000"
    Zähler = Zähler + 1
    ActiveCell.Offset(1, 0).Select

Loop

Zähler = 0

Do Until Zähler = 6
    ActiveCell.Value = "IV_W_2400"
```

```
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

    Zähler = 0

    Do Until Zähler = 6
        ActiveCell.Value = "N_W_2400"
        Zähler = Zähler + 1
        ActiveCell.Offset(1, 0).Select

    Loop

' Den gesammten Datensatz nach Links / Rechts sortieren

'    Columns("A:M").Select
'    Selection.Sort Key1:=Range("B1"), Order1:=xlAscending,
Header:=xlGuess, _
'        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

' Alle Daten für das linke Auge ins Arbeitsblatt "Linkes Auge" kopieren

    Worksheets(14).Activate
    Range("b1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "L" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(13).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(14).Activate
            ActiveCell.Offset(0, 1).Select


        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' Alle Daten für das linke Auge aus dem Arbeitsblatt "Rechtes Auge" löschen

    Worksheets(14).Activate
    Range("b1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "L" Then

            ActiveCell.EntireRow.Delete

        End If

        If Not ActiveCell.Value = "L" Then ActiveCell.Offset(1, 0).Select

    Loop
```

```
' Eyeblinks filtern



' 1. Spalte umgekehr alphabetisch sortieren, damit nicht bei gleichem
Zeitstempel EBLINK vor SBLINK steht - RECHTS

 '   Worksheets(14).Activate
 '   Columns("A:M").Select
 '   Selection.Sort Key1:=Range("A1"), Order1:=xlDescending,
Header:=xlGuess, _
 '       OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom



' Eigentliches sortieren nach Zeit - RECHTS

'    Worksheets(14).Activate
'    Columns("A:M").Select
'    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending,
Header:=xlGuess, _
'        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom


' 1. Spalte umgekehr alphabetisch sortieren, damit nicht bei gleichem
Zeitstempel EBLINK vor SBLINK steht - LINKS

'    Worksheets(13).Activate
'    Columns("A:M").Select
'    Selection.Sort Key1:=Range("A1"), Order1:=xlDescending,
Header:=xlGuess, _
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom



' Eigentliches sortieren nach Zeit - LINKS

'    Worksheets(13).Activate
'    Columns("A:M").Select
'    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending,
Header:=xlGuess, _
'        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

'End Sub
'Sub eye_dateikonvertierung_II()


' Eyeblinks rechtes Auge auf Fehler (kein Einschluß durch eine Sakkade)
prüfen

    Worksheets(14).Activate
    Range("a1").Select
    Leer = False
    Zähler = 0

    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Then
```

```
            ActiveCell.Offset(-1, 0).Select

                If ActiveCell.Value <> "SSACC" Then

                    ActiveCell.Offset(1, 0).Select
                    ActiveCell.EntireRow.Delete
                    ActiveCell.EntireRow.Delete

'                    ActiveCell.Value = "--- SBLINK"
'                    ActiveCell.Offset(1, 0).Select
'                    ActiveCell.Value = "--- EBLINK"
                    Zähler = Zähler + 1

                Else: ActiveCell.Offset(1, 0).Select

                End If

        End If

        ActiveCell.Offset(1, 0).Select

    Loop

    ActiveCell.Offset(1, 1).Select
    ActiveCell.Value = Zähler



' Eyeblinks linkes Auge auf Fehler (kein Einschluß durch eine Sakkade)
prüfen

    Worksheets(13).Activate
    Range("a1").Select
    Leer = False
    Zähler = 0

    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Then

            ActiveCell.Offset(-1, 0).Select

                If ActiveCell.Value <> "SSACC" Then

                    ActiveCell.Offset(1, 0).Select
                    ActiveCell.EntireRow.Delete
                    ActiveCell.EntireRow.Delete

'                    ActiveCell.Value = "--- SBLINK"
'                    ActiveCell.Offset(1, 0).Select
'                    ActiveCell.Value = "--- EBLINK"
                    Zähler = Zähler + 1

                Else: ActiveCell.Offset(1, 0).Select

                End If

        End If

        ActiveCell.Offset(1, 0).Select

    Loop
```

```
    ActiveCell.Offset(1, 1).Select
    ActiveCell.Value = Zähler


' Eyeblinks für das rechte Auge filtern

    Worksheets(14).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Then

        ' Abfangen des Fehlers "Zwei Eyeblinks direkt hintereinander"
        ' durch Aufsummieren der beiden Blinks

            ActiveCell.Offset(2, 0).Select

            If ActiveCell.Value = "SBLINK" Then

                ActiveCell.EntireRow.Delete

                If ActiveCell.Value = "EBLINK" Then

                    ActiveCell.Offset(0, 3).Select
                    Blinkende = ActiveCell.Value
                    ActiveCell.EntireRow.Delete
                    ActiveCell.Offset(-1, 0).Select
                    ActiveCell.Value = Blinkende
                    ActiveCell.Offset(0, -1).Select
                    Blinkanfang = ActiveCell.Value
                    Summe = Blinkende - Blinkanfang
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Summe
                    ActiveCell.Offset(-1, -4).Select

                End If ' If ActiveCell.Value = "EBLINK" Then

            End If 'ActiveCell.Value = "SBLINK" Then

            ActiveCell.Offset(-2, 0).Select

            ActiveCell.Offset(-1, 0).Select

                If ActiveCell.Value = "SSACC" Then

                    ActiveCell.Offset(0, 2).Select
                    sakkade_anfang = ActiveCell.Value
                    ActiveCell.EntireRow.Delete
                    Eyeblink_anfang = ActiveCell.Value
                    Dauer_SSACC_SBLINK = Eyeblink_anfang - sakkade_anfang
                    ActiveCell.Offset(1, 1).Select
                    eyeblink_ende = ActiveCell.Value

                    ActiveCell.Offset(1, -3).Select
                    If ActiveCell.Value = "ESACC" Then

                        ActiveCell.Offset(0, 3).Select
                        sakkade_Ende = ActiveCell.Value
                        Dauer_EBLINK_ESACC = sakkade_Ende - eyeblink_ende
                        ActiveCell.Offset(0, 1).Select
```

```
                        Eyeblink_dauer = ActiveCell.Value
                        ActiveCell.EntireRow.Delete
                    End If

                    ActiveCell.Offset(-1, 2).Select
                    ActiveCell.Value = Dauer_SSACC_SBLINK
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Dauer_EBLINK_ESACC
                    Dauer_EBLINK_ESACC = sakkade_Ende - eyeblink_ende
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Eyeblink_dauer
                    ActiveCell.Offset(0, -10).Select

                End If
        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' Eyeblinks für das linke Auge filtern

    Worksheets(13).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Then

        ' Abfangen des Fehlers "Zwei Eyeblinks direkt hintereinander"
        ' durch Aufsummieren der beiden Blinks

            ActiveCell.Offset(2, 0).Select

            If ActiveCell.Value = "SBLINK" Then

                ActiveCell.EntireRow.Delete

                If ActiveCell.Value = "EBLINK" Then

                    ActiveCell.Offset(0, 3).Select
                    Blinkende = ActiveCell.Value
                    ActiveCell.EntireRow.Delete
                    ActiveCell.Offset(-1, 0).Select
                    ActiveCell.Value = Blinkende
                    ActiveCell.Offset(0, -1).Select
                    Blinkanfang = ActiveCell.Value
                    Summe = Blinkende - Blinkanfang
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Summe
                    ActiveCell.Offset(-1, -4).Select

                End If ' If ActiveCell.Value = "EBLINK" Then

            End If 'ActiveCell.Value = "SBLINK" Then

            ActiveCell.Offset(-2, 0).Select


        ActiveCell.Offset(-1, 0).Select

                If ActiveCell.Value = "SSACC" Then
```

```
                    ActiveCell.Offset(0, 2).Select
                    sakkade_anfang = ActiveCell.Value
                    ActiveCell.EntireRow.Delete
                    Eyeblink_anfang = ActiveCell.Value
                    Dauer_SSACC_SBLINK = Eyeblink_anfang - sakkade_anfang
                    ActiveCell.Offset(1, 1).Select
                    eyeblink_ende = ActiveCell.Value

                    ActiveCell.Offset(1, -3).Select
                    If ActiveCell.Value = "ESACC" Then

                        ActiveCell.Offset(0, 3).Select
                        sakkade_Ende = ActiveCell.Value
                        Dauer_EBLINK_ESACC = sakkade_Ende - eyeblink_ende
                        ActiveCell.Offset(0, 1).Select
                        Eyeblink_dauer = ActiveCell.Value
                        ActiveCell.EntireRow.Delete
                    End If

                    ActiveCell.Offset(-1, 2).Select
                    ActiveCell.Value = Dauer_SSACC_SBLINK
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Dauer_EBLINK_ESACC
                    Dauer_EBLINK_ESACC = sakkade_Ende - eyeblink_ende
                    ActiveCell.Offset(0, 2).Select
                    ActiveCell.Value = Eyeblink_dauer
                    ActiveCell.Offset(0, -10).Select

                End If
            End If

            ActiveCell.Offset(1, 0).Select

        Loop

' Alle Sakkaden für das rechte Auge in eine eigene Datei schreiben

        Worksheets(14).Activate
        Range("a1").Select
        Leer = False
        Do Until Leer = True

            If ActiveCell.Value = "" Then Leer = True Else Leer = False
            If ActiveCell.Value = "SSACC" Or ActiveCell.Value = "ESACC" Then
                ActiveCell.EntireRow.Select
                ActiveCell.EntireRow.Copy
                Worksheets(12).Activate
                ActiveCell.EntireRow.Insert
                ActiveCell.Offset(1, 0).Select
                Worksheets(14).Activate


            End If

            ActiveCell.Offset(1, 0).Select

        Loop

' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

        Worksheets(12).Activate
        Range("a1").Select
```

```
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop



' Alles MSG Zeilen aus dem Arbeitsblatt "Rechtes Auge" ins Arbeitsblatt
"Sakkaden rechtes Auge" kopieren

    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(12).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select

    Loop


' Alle Sakkaden für das linke Auge in eine eigene Datei schreiben

    Worksheets(13).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SSACC" Or ActiveCell.Value = "ESACC" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(9).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(13).Activate


        End If
```

```
        ActiveCell.Offset(1, 0).Select

    Loop


' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

    Worksheets(9).Activate
    Range("a1").Select

    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop


' Alles MSG Zeilen aus dem Arbeitsblatt "linkes Auge" ins Arbeitsblatt
"Sakkaden linkes Auge" kopieren

    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(9).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select

    Loop



' Alle Fixationen für das rechte Auge in eine eigene Datei schreiben

    Worksheets(14).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SFIX" Or ActiveCell.Value = "EFIX" Then
```

```
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(11).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(14).Activate


        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

    Worksheets(11).Activate
    Range("a1").Select

    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop


' Alles MSG Zeilen aus dem Arbeitsblatt "Rechtes Auge" ins Arbeitsblatt
"Fixationen rechtes Auge" kopieren

    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(11).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select

    Loop

' Alle Fixationen für das linke Auge in eine eigene Datei schreiben

    Worksheets(13).Activate
```

```
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SFIX" Or ActiveCell.Value = "EFIX" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(8).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(13).Activate


        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

    Worksheets(8).Activate
    Range("a1").Select

    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop


' Alles MSG Zeilen aus dem Arbeitsblatt "Linkes Auge" ins Arbeitsblatt
"Fixationen linkes Auge" kopieren

    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(8).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select
```

```
    Loop


' Alle Eyeblinks für das rechte Auge in eine eigene Datei schreiben

    Worksheets(14).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Or ActiveCell.Value = "EBLINK" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(10).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(14).Activate


        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

    Worksheets(10).Activate
    Range("a1").Select

    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop



' Alles MSG Zeilen aus dem Arbeitsblatt "Rechtes Auge" ins Arbeitsblatt
"Eyeblinks rechtes Auge" kopieren

    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
```

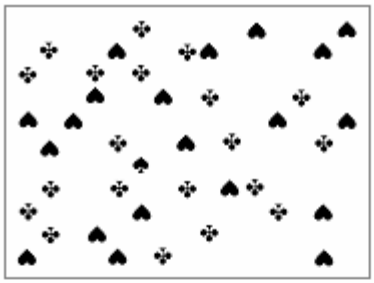
```
        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(10).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select

    Loop


' Alle Eyeblinks für das linke Auge in eine eigene Datei schreiben

    Worksheets(13).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "SBLINK" Or ActiveCell.Value = "EBLINK" Then
            ActiveCell.EntireRow.Select
            ActiveCell.EntireRow.Copy
            Worksheets(7).Activate
            ActiveCell.EntireRow.Insert
            ActiveCell.Offset(1, 0).Select
            Worksheets(13).Activate

        End If

        ActiveCell.Offset(1, 0).Select

    Loop

' ESACC_EFIX_EBLINK_formatieren (Anfangs und Endzeit vertauschen)

    Worksheets(7).Activate
    Range("a1").Select

    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False
        If ActiveCell.Value = "ESACC" Or ActiveCell.Value = "EFIX" Or
ActiveCell.Value = "EBLINK" Then
            ActiveCell.Offset(0, 2).Select
            Zeitstempel_Anfang = ActiveCell.Value
            ActiveCell.Offset(0, 1).Select
            Zeitstempel_Ende = ActiveCell.Value
            ActiveCell.Value = Zeitstempel_Anfang
            ActiveCell.Offset(0, -1).Select
            ActiveCell.Value = Zeitstempel_Ende
            ActiveCell.Offset(0, -2).Select

        End If
            ActiveCell.Offset(1, 0).Select

    Loop


' Alles MSG Zeilen aus dem Arbeitsblatt "Linkes Auge" ins Arbeitsblatt
"Eyeblinks linkes Auge" kopieren
```

```
    Worksheets(1).Activate
    Range("a1").Select
    Leer = False
    Do Until Leer = True

        If ActiveCell.Value = "" Then Leer = True Else Leer = False

        ActiveCell.EntireRow.Select
        ActiveCell.EntireRow.Copy
        Worksheets(7).Activate
        ActiveCell.EntireRow.Insert
        ActiveCell.Offset(1, 0).Select
        Worksheets(1).Activate
        ActiveCell.Offset(1, 0).Select

    Loop



' Sakkaden rechts + MSG Rechts nach Zeit sortieren

    Worksheets(12).Activate

    Columns("A:M").Select
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

' Sakkaden links + MSG Rechts nach Zeit sortieren

    Worksheets(9).Activate

    Columns("A:M").Select
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom


' Fixationen rechts + MSG Rechts nach Zeit sortieren

    Worksheets(11).Activate

    Columns("A:M").Select
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

' Fixationen links + MSG Rechts nach Zeit sortieren

    Worksheets(8).Activate

    Columns("A:M").Select
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

' Eyeblinks rechts + MSG Rechts nach Zeit sortieren

    Worksheets(10).Activate

    Columns("A:M").Select
```

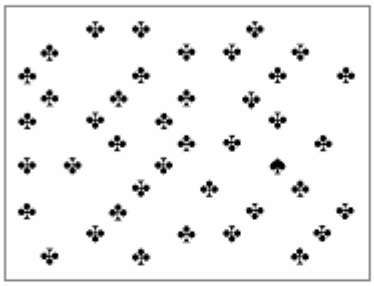
```
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

' Eyeblinks links + MSG Rechts nach Zeit sortieren

    Worksheets(7).Activate

    Columns("A:M").Select
    Selection.Sort Key1:=Range("C1"), Order1:=xlAscending, Header:=xlGuess,
_
        OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom

End Sub
```

Visual search displays

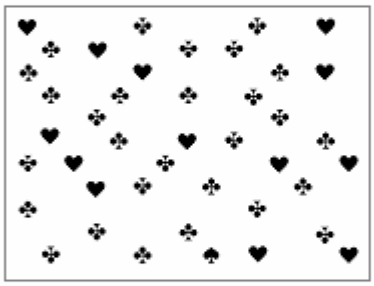
1



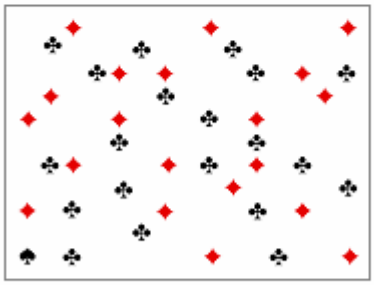
2



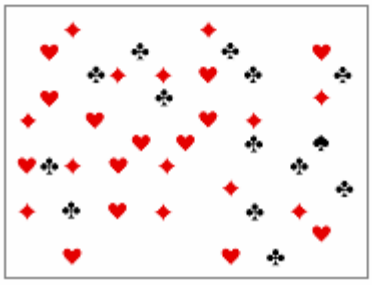
3



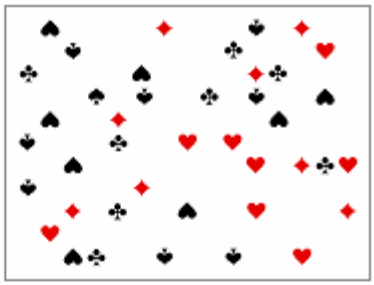
4



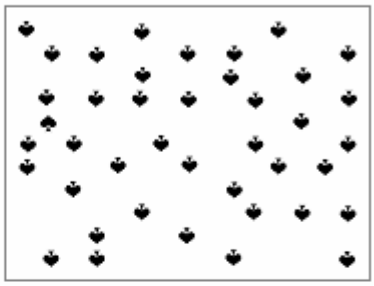
5



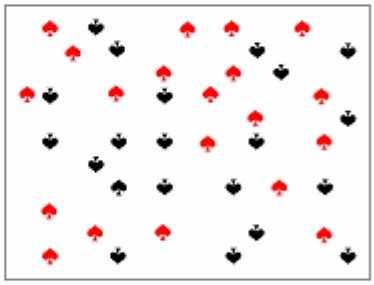
6



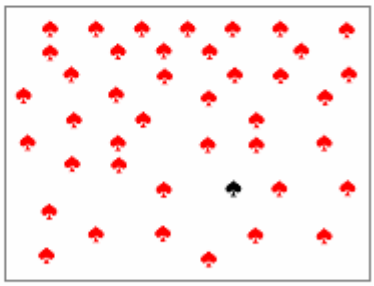
7



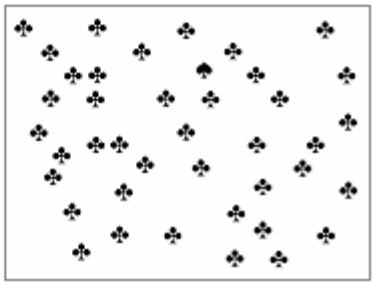
8



9



10



Appendix F