On the relation between active and passive behaviour in patients with spatial neglect
Insights from acute stroke and the course of recovery

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SUMMARY

The most characteristic impairment of patients with spatial neglect is a bias of "active" exploratory movements towards the lesion side. Previous research revealed that this ipsilesional deviation is highly specific to spatial neglect both, in light and in complete darkness, and is not observed in other stroke patients. Consequently, tasks requiring searching for targets became standard clinical tests for the diagnosis of the disorder.

In contrast, quantitative measures of the patients' spontaneous, "passive" behaviour independent of any external requirements exist neither with nor without a visual context. Indeed, some reviews and observational studies reported that neglect patients may deviate the eyes and the head towards the ipsilesional side. These reports, however, based their assumptions on clinical experience and observations and partly reached opposite conclusions on the relation to spatial neglect. Moreover, there is a widely held belief that acute unilateral stroke per se leads to a bias of the eyes towards the lesion side. Currently, it remains open, for the acute stage as well as for the course of recovery, if a spontaneous horizontal deviation of the eyes and the head towards the ipsilesional side is specific to stroke patients with spatial neglect -as it is the case for the bias of active exploratory behaviour- or if it also occurs in other patients with hemispheric stroke, i.e. independently of spatial neglect.

The present work thus investigated if there is a direct and systematic relation between a spontaneous deviation of the eyes and the head (= gaze) and spatial neglect in patients with hemispheric stroke regarding both, acute phases and the development over time. For this purpose, recording methods were implemented that allow for a precise measurement and subsequent quantitative analyses of the eye and head orientation at rest and during active exploratory search in patients with and without the disorder.

These analyses revealed that a marked spontaneous horizontal gaze deviation is not a symptom associated with any acute cerebral lesions per se, nor is a general symptom of right hemisphere lesion, but rather is a specific sign of spatial neglect. The results thus suggest modifying former assumptions that acute unilateral cerebral lesions -in general- lead to an ipsilesional bias of the patients' eye position. Further, the patients' passive neglect behaviour is not a distinct symptom that may solely co-occur with traditionally defined "active" components of the disorder, as it is e.g. the case for visual extinction, but rather seems to be directly related to it.

The data allow for conclusions on the hitherto unknown development of these symptoms in the course of recovery as well. Clinical observation suggested that a possible deviation of the eyes improves fast compared to its traditionally measured active components in patients with spatial neglect, favouring distinct rather than related phenomena that may even dissociate over time. In contrast, the present investigation observed a gradually different, but parallel recovery of gaze orientation during active and passive conditions as well as of neglect severity as measured by standardised clinical tasks. Seemingly, a passive gaze deviation will not recover faster but is still obvious in some neglect patients up to 10 months post stroke, though to a lesser degree than in active exploration tasks.

The present work thus suggests that spatial neglect is equally characterised by a deviation of the eyes and the head during "active" visual search as well as at "passive rest", arguing for related symptoms that both specify the disorder even beyond the acute stage. It further emphasises that the most characteristic impairment in these patients –i.e. the marked deviation towards the ipsilesional side- is due to a very elementary disturbance of the information process that converts multimodal sensory input into longer-lasting spatial representations and provides us with redundant information about the position and motion of our body relative to external space. While eye and head orientation in individuals without the disorder is in line with the mid-sagittal body axis, it is markedly shifted towards the ipsilesional side under both, rest and active task conditions in patients with spatial neglect. This shift may be understood as a pathological adjustment of the normal "default position" of the eyes and the head at a new origin on the ipsilesional side. In the present sample of very acute stroke patients, this default position was adjusted at about 46 degree on the right side of space.

ZUSAMMENFASSUNG

Die wohl charakteristischste Beeinträchtigung von Patienten, die nach einem Schlaganfall einen Neglect aufweisen, ist die Begrenzung ihrer "aktiven" Explorationsbewegungen auf die ipsiläsionale Seite. Dieses asymmetrische Verhalten findet sich sowohl bei Helligkeit als auch in völliger Dunkelheit. Zahlreiche Untersuchungen zeigen, dass es in hohem Maße spezifisch, und bei keiner anderen Gruppe von Schlaganfallpatienten zu beobachten ist. Dementsprechend zählen visuelle Suchaufgaben, die das Detektieren von Zielreizen erfordern zur klinischen Standarddiagnostik.

Im Gegensatz dazu liegen keine quantitativen Untersuchungen des spontanen, "passiven" Blickverhaltens vor. Zwar berichten einige Überblicksartikel und Beobachtungsstudien, dass manche Neglectpatienten eine Augen- und Kopfdeviation zur ipsiläsionalen Seite aufweisen. Diese Annahmen gründen jedoch ausschließlich auf klinischer Erfahrung und Beobachtung und führen hinsichtlich des Zusammenhangs mit der Neglectsymptomatik zu gegensätzlichen Schlussfolgerungen. Neurologische Skalen und Lehrbücher implizieren zudem, dass Schlaganfallpatienten im Akutstadium -generell- einen "Herdblick", d.h. eine Blickdeviation in Richtung der Hirnschädigung aufweisen. Bislang ist daher in der akuten Phase und im klinischen Verlauf offen, ob eine spontane Augen- und Kopfdeviation zur ipsiläsionalen Seite ebenso spezifisch für diese Patienten ist wie ihr asymmetrisches Explorationsverhalten, oder ob diese unabhängig von der Neglectsymptomatik auch bei anderen Patientengruppen mit unilateralen Hirnläsionen auftritt.

Die vorliegende Arbeit untersuchte, ob es einen direkten und systematischen Zusammenhang zwischen einer spontanen Augen- und Kopfdeviation (= Blickdeviation) und dem Phänomen des Neglects nach unilateralem Schlaganfall gibt. Hierzu wurde die individuelle Augen- und Kopforientierung von Patienten mit und ohne Neglect sowohl in Ruhe als auch während aktiver Exploration unter verschiedenen Lichtbedingungen im Akutstadium sowie im klinischen Verlauf gemessen.

Es zeigte sich, dass eine ausgeprägte, spontane Blickdeviation weder ein Zeichen einer akuten Hirnschädigung an sich, noch ein allgemeines Symptom nach rechts-hemispärischem Schlaganfall, sondern ein spezifisches Zeichen des Neglects ist. Dies spricht für eine Modifikation bisheriger Annahmen, die bei akutem Schlaganfall generell eine Augendeviation zur Seite der Hirnläsion postulieren. Zudem scheint das spontane Blickverhalten von Neglectpatienten kein unabhängiges Symptom zu sein, das lediglich

mit den traditionell diagnostizierten, "aktiven" Komponenten des Neglects nach einem Schlaganfall auftreten kann (wie beispielsweise die visuelle Extinktion), sondern ein Charakteristikum das unmittelbar mit der Neglectsymptomatik zusammenhängt.

Die Untersuchungen erlauben zudem Schlussfolgerungen über den bislang unbekannten klinischen Verlauf beider Symptome. Auf Grundlage klinischer Beobachtung wurde angenommen, dass sich eine potentielle Augendeviation im Vergleich zu traditionell diagnostiziertem Neglectverhalten schnell zurückbildet. Solch ein Verlauf ließe eher unabhängige als zusammenhängende Phänomene vermuten, die über die Zeit eine Dissoziation aufweisen können. Im Gegensatz dazu zeigt diese Arbeit eine graduell unterschiedliche, aber parallele Entwicklung der hier untersuchten aktiven und passiven Komponenten des Neglectverhaltens sowie des klinisch diagnostizierten Schweregrades. Eine Blickdeviation infolge eines unilateralen Schlaganfalls, gemessen in Ruhe, bildet sich offensichtlich nicht schneller zurück, sondern ist bei einigen Neglectpatienten noch nach 10 Monaten zu beobachten, wenn auch in geringerer Ausprägung als die Blickposition während aktiver Exploration.

Die vorliegende Arbeit legt daher nahe, dass die Neglectsymptomatik gleichermaßen durch eine Blickdeviation während der "aktiven" Suche als auch in einer "passiven" Ruheposition gekennzeichnet ist. Dies lässt auf zusammenhängende Symptome schließen, die das Neglectphänomen über das akute Stadium hinaus spezifizieren. Die charakteristische Beeinträchtigung von Neglectpatienten, d.h. die ausgeprägte Deviation zur ipsiläsionalen Seite legt darüber hinaus eine grundlegende Störung des Transformationsprozesses nahe, der multimodale, sensorische Eingangssignale in (bewegungs)stabile Raumrepräsentationen umwandelt und redundante Informationen über die Position und Bewegung unseres Körpers in Bezug zum Außenraum zur Verfügung stellt. Während die Orientierung der Augen und des Kopfes bei Personen ohne räumlichen Neglect in Referenz zur Körpermittelebene erfolgt, ist sie bei Neglectpatienten ausgehend von dieser "Grund- bzw. Ruheposition" deutlich zur ipsiläsionalen Seite rotiert und das sowohl in Ruhe als auch während aktiver Exploration. Diese Rotation um die Körpermittelebene kann als pathologische Ausrichtung der normalen Ruheposition in Richtung der Hirnschädigung verstanden werden, die in einer neuen Grundposition resultiert. In der hier untersuchten Stichprobe akuter Neglectpatienten war diese neue Ruheposition im Durchschnitt um 46 Grad zur ipsiläsionalen Seite rotiert.

ABBREVATIONS

CON	Whole group of control patients without spatial neglect (RBD and NBD)
CT	Computed tomography
DSL	Days since lesion
EOG	Electrooculography
Exam	Examination
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
LBD	Left hemisphere stroke patients without spatial neglect
LED	Light emitting diodes
M	Mean
MRI	Magnetic resonance imaging
NBD	Healthy control subjects without brain lesions and without spatial neglect
NEG	Right hemisphere stroke patients with spatial neglect
RBD	Right hemisphere stroke patients without spatial neglect
SD	Standard deviation
SSA	Subjective straight ahead
STG	Superior temporal gyrus
TPO	Temporo-parietal-occipital junction

SUMMARY

ZUSAMMENFASSUNG

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1 INTRODUCTION

"I have finished. I've searched the whole site and cannot find any more lines". The same or similar answers are given by a specific group of stroke patients after finishing a clinical search task, when they were finally asked whether they have cancelled all lines distributed on a standard A4 sheet of paper. However, already at first sight, the observation of their cancellation performance reveals a remarkable number of omissions on the side contralateral to the brain lesion. Such discrepancies between the patients' self-assessment and the objective score achieved in a standardised cancellation task (see Figure 1) most likely agree with the diagnosis of spatial neglect.

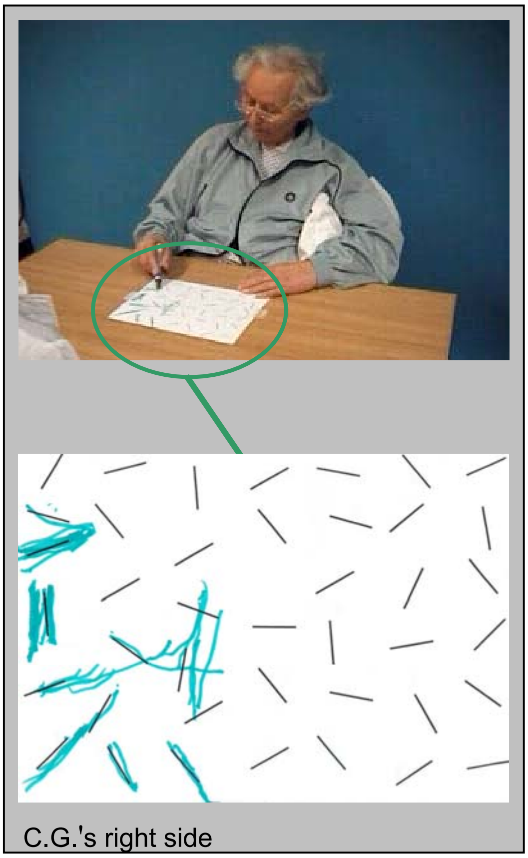

Figure 1.

Standardised diagnosis of spatial neglect. Patient C.G. has had acute symptoms of spatial neglect due to a right hemisphere stroke. While performing a standardised clinical task to diagnose the disorder, his search was exclusively confined to the right side of the paper.

Result of C.G.'s performance. In this task, patients are asked to cancel all lines distributed on the entire sheet of paper (Albert, 1973). There are no time constraints. After the patients have finished, they are asked whether they have searched everywhere and have found each single line on the whole sheet of paper.

Compared to other patients, those with spatial neglect usually attract the clinicians' attention by their most characteristic impairment, namely the deviation of exploratory movements towards the ipsilesional side of space as illustrated in Figure 1. This bias of active behaviour is specific to spatial neglect and is not observed in other stroke patients. It is particularly apparent in tasks requiring skills like searching and cancelling targets, copying complex scenes, and reading. Consequently, such tests are used to detect, to diagnose, and to quantify the disorder in a clinical context.

Various theories seek to explain this striking symptom, but no consensus about its underlying mechanisms has been reached so far. Some experimental approaches like studying the patients' eye movement behaviour seem to be targeting to examine the different predictions and to gain insight into this characteristic disturbance of spatial information processing caused by cerebral stroke. To date, such studies had solely addressed the patients' active behaviour, for example during exploring or reading.

In contrast, the assumption that patients with spatial neglect may also spontaneously orient their eyes and head towards the ipsilesional side is based on clinical experience and on few observational studies. The later had determined the discrete presence or absence of eye and/or head deviation solely with the naked eye by clinical inspection but had neither measured its degree nor had systematically investigated its relation to spatial neglect, for example by comparisons to patients without the disorder. Although a deviation of the eyes and the head is a striking symptom of hemispheric stroke and may -with respect to clinical experience- co-occur with spatial neglect, the relation between both symptoms remains open so far.

The present work was motivated by the lack of clarity on this relation. It asked whether a spontaneous ipsilesional deviation of the eyes and of the head following unilateral cerebral stroke is *specific* to spatial neglect –like it is the active search behaviour of patient C.G.- or if it also occurs in stroke patients without the disorder. Using quantitative recording methods to define the degree of eye and head positions in different patient groups, the resting and active exploratory behaviour was measured under varying lightning conditions as well as at various times in the acute stages and in the chronic phase of the disorder.

Uncovering the relation and development of both symptoms may have clinical implications for the observational value of the patients' gaze in the daily clinical context as well as for the diagnosis of spatial neglect. Moreover, the present approach seeks to gain further insight into the main characteristics of one of the most striking neuropsychological disorders and to contribute to the lively ongoing debate on the underlying mechanisms of spatial neglect.

2 THEORETICAL BACKGROUND

2.1 Clinical Aspects of Spatial Neglect

Spatial neglect is a common and disabling syndrome following unilateral, usually right-sided stroke, which defines a characteristic failure to report, respond, or orient to novel or meaningful stimuli presented to the side contralateral of the brain lesion that cannot be accounted for elementary sensory or motor dysfunction (Heilman, Valenstein, & Watson, 1984). Many terms are used synonymously to describe the disorder, including unilateral neglect, hemi-inattention, visual neglect, and (hemi-)spatial neglect. Neglect patients typically show a combination of deficits that may affect one or more modalities, but their tendency to ignore visual information on the contralesional (usually left) side of space -as exemplarily shown in Figure 1 by a visuo-motor exploration task- is one of the most striking clinical observations. Although most review articles on spatial neglect include illustrations of the characteristic drawing or cancellation performance of these patients, it is no less impressive for clinicians to observe it for the first time. Beyond these cardinal behavioural changes in human behaviour, the first chapter gives a thorough insight into the various clinical aspects of spatial neglect.

2.1.1 Cardinal symptoms

In the visual modality, which is the scope of the present work, the ipsilesional bias is observed by contralateral omissions during searching for targets, copying, drawing, or reading. Patients with spatial neglect typically disregard contralesional located objects when copying a scene, fail to complete the side of a clock-face opposite to the brain lesion, or omit contralateral targets in standard cancellation tasks (Johannsen & Karnath, 2004; Johnston & Diller, 1986; Karnath, Niemeier, & Dichgans, 1998). This lateralised disorder may also affect the patients' space-related behaviour in the auditory and tactile modality. As eye and head movements, tactile exploration is predominantly carried out towards the ipsilesional side (Broeren, Samuelsson, Stibrant-Sunnerhagen, Blomstrand, & Rydmark, 2007; Karnath & Perenin, 1998; Schindler, Clavagnier, Karnath, Derex, & Perenin, 2006). Further, the patients' reaction to sound or speech stimuli located on the contralesional side can be reduced or absent (Pavani, Ladavas, & Driver, 2002; Zimmer, Lewald, & Karnath, 2003). Beyond, representational failures may occur. During the recall of a familiar scene from memory, these patients may for example ignore objects from the contralesional side (Bisiach & Luzatti, 1978; Denis, Beschin, Logie, & Della Sala, 2002).

Although the individual pattern of symptoms varies between patients with spatial neglect, the following clinical signs may additionally characterise the disorder. Typically, they behave as if half or more-or-less half of their spatial world contralateral to the lesion side is lost. They may shave or clean their face, eat food, or comb their hair only on the ipsilesional side. When addressed from the front or from the contralateral side, patients with spatial neglect usually orient towards the lesion side and ignore contralesionally located people or objects. Importantly, these striking changes in the patients' behaviour are not the result of elementary sensory, motor, cognitive or psychiatric disorders, such as for example hemianopia, hemiparesis, or depression.

Spatial neglect was repeatedly considered as a syndrome consisting of a number of component deficits (Bisiach & Vallar, 2000; Driver & Husain, 2002; Mattingley, Husain, Rorden, Kennard, & Driver, 1998; Mesulam, 1999; Rafal, 1994). In addition to the spatially lateralised behaviour, some authors suggested that the neglect syndrome also consists of so-called "non-spatially lateralised" dysfunctions that involve both sides of space. Non-lateralised components include impairments of sustained attention (I. H. Robertson et al., 1997) or of spatial working memory (Husain, Mannan, Hodgson, Wojciulik, Driver, & Kennard, 2001; Mannan, Mort, Hodgson, Driver, Kennard, & Husain, 2005), a prolonged time course of visual processing (Duncan, Bundesen, Olson, Humphreys, Chavda, & Shibuya, 1999; Husain; Shapiro, Martin, & Kennard, 1997), or a bias towards local features in the visual scene (L. C. Robertson, Lamb, & Knight, 1988). These deficits just recently have been reassumed to contribute to the neglect syndrome, such that they may exacerbate its severity and influence the course of recovery. Although these components alone might not cause spatial neglect, their varying combinations are thought to lead to intraindividual differences between neglect patients (see Husain & Rorden, 2003).

Importantly, these so-called "non-lateralised" deficits are non-specific to spatial neglect since they may also occur in patients without the disorder (Kessels, Postma, Wijnalda, & De Haan, 2000; Shapiro, Hillstrom, & Husain, 2002). Previous work revealed that a non-lateralised impairment of spatial updating across saccades is rather anatomically than neglect-specific (Duhamel, Goldberg, Fitzgibbon, Sirigu, & Grafman, 1992; Heide, Blankenburg, Zimmermann, & Kömpf, 1995). Perseverative search behaviour is not specific to spatial neglect as well (Nys, Van Zandvoort, Van der Worp, Kappelle, & De Haan, 2006). In fact, repeated responses of stroke patients without the disorder in a cancellation task relate to their task performance in executive functioning. Beyond, perseverative responses also occur in patients with general inattention and in healthy control subjects (Nys et al., 2006).

The same accounts for symptoms like "anosognosia", describing the phenomenon of a denial of for example the own limb paresis (Baier & Karnath, 2005) as well as for "extinction", i.e. the disregard of the contralateral stimulus during simultaneous visual, tactile, or auditory stimulation (Driver & Vuilleumier, 2001). Such deficits may co-occur, but are not specific to and can even dissociate from spatial neglect as well (Bisiach, Vallar, Perani, Papagno, & Berti, 1986; Milner, 1997; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994). Accordingly, the present work focuses not on additional components, but on the neglect patients' characteristic attentional bias, i.e. on their "lateralised" behaviour that is apparent for example during active visual search.

2.1.2 Incidence and course of recovery

Spatial neglect most frequently occurs with right hemisphere infarction (Bowen, McKenna, & Tallis, 1999; Mesulam 2002; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997). Its incidence ranges between 13 and 82 percent following right hemisphere lesions and between 0 and 76 percent after left hemisphere stroke. This variation is likely because of differences in sample selection, definitions of neglect as well as nature and timing of assessment (cf. a systematic review of 17 studies by Bowen et al., 1999). The Copenhagen stroke study on a huge sample of 602 acute stroke patients found an incidence of 42 percent in patients with right hemisphere lesions, and of 8 percent in patients with left hemisphere stroke (Pedersen et al., 1997).

The presence of spatial neglect is associated with severity of stroke and patients' age (Appelros, Karlsson, Seiger, & Nydevik, 2002; Pedersen et al., 1997) but not with prior stroke, comorbidity (e.g. heart failure, respiratory insufficiency, parkinsonism), gender or handedness (Pedersen et al., 1997), or strength of contralateral limb paresis (Kalra, Perez, Gupta, & Wittink, 1997). Compared to patients without the disorder, those with neglect show reduced sensory-motor and cognitive abilities, lower performance in activities of daily living (Katz, Hartman-Maeir, Ring, & Soroker, 1999), longer duration of therapy and hospital stay (Kalra et al., 1997) as well as lower levels on measures of functional ability at discharge (Kinsella & Ford, 1985). While Katz et al. (1999) rated spatial neglect as major predictor of rehabilitation outcome, Petersen and co-workers (1997) demonstrated that its presence has neither independent influence on the functional outcome at admission or discharge nor on the length of rehabilitation, mortality or the rate of discharge to independent living.

The recovery of spatial neglect as well as its determining factors have been discussed controversially (Appelros, Nydevik, Karlsson, Thorwalls, & Seiger, 2004; Black, Ebert, Leibovitch, Szalai, & Blair, 1995; Campbell & Oxbury, 1976; Cassidy, Bruce, Lewis, & Gray, 1999; Cassidy, Lewis, & Gray, 1998; Cherney & Halper, 2001; Colombo, De Renzi, & Gentilini, 1982; Farnè et al., 2004; Hier, Mondlock, & Caplan, 1983b; Jehkonen et al., 2000; Nys et al., 2005; Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997; Stone, Patel, Greenwood, & Halligan, 1992; Weiller et al., 1993). Lesion size, premorbid cerebral atrophy (Levine, Warach, Benowitz, & Calvanio, 1986), and the patients' age (Hier et al., 1983b) seem to influence the neglect severity as well as the course of recovery. Stone et al. (1992) found the initial severity of spatial neglect and the presence of anosognosia to be predictive for the degree of neglect recovery. Recovery rates vary between 12.5 percent (Farnè et al., 2004) and approximately 83 percent (Nys et al., 2005). Such marked differences presumably are due to differences in the initial severity of spatial neglect and the tests used to diagnose the disorder as well as to the various delays between symptom onset and subsequent investigation.

Many authors assumed that neglect recovery is fast, such that the most evident and conspicuous symptoms vanish within the first couple of months (for review see Ferro, Mariano, & Madureira, 1999). Accordingly, Stone and co-workers (1992) observed that recovery was most pronounced within 10 days post stroke and reached a plateau in the following 3 months. At this time, up to 30 percent of their neglect sample still showed considerable deficits. A follow-up study carried out 7 months after stroke found 83 percent of patients with acute neglect symptoms completely recovered (Nys et al., 2005). In marked contrast, other studies observed recovery rates below 15 percent when patients with acute neglect symptoms were re-evaluated more than three months post stroke (Farnè et al., 2004) or 6 respectively 12 months after symptom onset (Appelros et al., 2004).

A further controversy concerns the prognosis of spatial neglect following subcortical lesions. The syndrome is known to occur not only with cortical injury but likewise after right-sided subcortical stroke restricted to either the basal ganglia or to the thalamus (e.g. Caplan et al., 1990; Healton, Navarro., Bressman, & Brust, 1982; Karnath, Himmelbach, & Rorden, 2002; Kumral, Kocaer, Ertubey, & Kumral, 1995; Watson, Valenstein, & Heilman, 1981). Subcortical neglect is traditionally seen as a mild and transient phenomenon and thus has a favourable long-term prognosis. However, compared to cortical lesions, this assumption is based on rather few studies carried out on single cases or rather small patient samples. Samuelsson et al. (1997) concluded that lesions confined to the basal ganglia and adjoining white matter produce mild to moderate neglect that completely recovers after the early phase of stroke. Persisting symptoms of spatial neglect were observed in only 18 percent of a sample with circumscribed lesions of the right thalamus while the remaining portion of acute neglect patients had recovered completely three months post stroke (Motomura, Yamadori, Mori, Ogura, Sakai, & Sawada, 1986). Weiller et al. (1993) investigated both the recoveries of aphasia and of neglect following basal ganglia lesions. One year post stroke, the prognosis was excellent for patients with initial neglect after right-sided lesions and was slightly reduced for patients with initial aphasia due to left hemisphere stroke. While neglect had recovered completely in all patients with acute symptoms, language disturbances persisted in 20 percent of the patients with initial aphasia (Weiller et al., 1993).

However, also contrasting observations were reported. Three months post stroke, chronic neglect symptoms persisted in three out of 5 patients (i.e. 60 %) with subcortical lesions (Ferro, Kertesz, & Black, 1987). Recently, we re-examined the prognosis and severity of spatial neglect in stroke patients with right-sided subcortical lesions restricted either to the basal ganglia or to the thalamus (Fruhmann Berger, Johannsen, & Karnath, submitted). After a first investigation in the acute phase, the follow-up was carried out on average 1.15 years post stroke. Even after this long period, chronic symptoms were observed in 40 percent of those patients who initially showed spatial neglect. The severity of neglect symptoms was reduced to about one third compared to the acute phase of the stroke.

2.1.3 Diagnostic procedures

Spatial neglect obviously can persist in a considerable number of patients with cortical and subcortical lesions. Thus, its early identification and quantification is as essential as it is for other neurological disorders like limb pareses or visual field defects. The diagnosis of spatial neglect helps clinicians and therapists to evaluate the patients' status and to keep track of the individual progress. To provide comprehensive care and assistance, also an early information of carers, of their relatives, and of the patients themselves is important. Already during acute care, detailed knowledge about the patients' limited abilities is needed to select appropriate therapies and to identify those patients who will need intensive neuropsychological, occupational, and physiological treatment. In individuals with little or no improvement of the disorder within the acute stage, follow-up information may facilitate their referral to rehabilitation units or to specialised ambulatory care.

For the assessment of spatial neglect, different simple screening tests (Albert, 1973; Gauthier, Dehaut, & Joanette, 1989; Weintraub & Mesulam, 1985) as well as large batteries have been developed (Azouvi et al., 1996; Black, Vu, Martin, & Szalai, 1990; Wilson et al., 1987), particularly because no single test will be able to detect the disorder in all patients (Azouvi et al., 1996; Binder, Marshall, Lazar, Benjamin, & Mohr, 1992). Although the use of a test battery is recommenced by several studies (Agrell, Dehlin, & Dahlgren, 1997; Halligan, Marshall, & Wade, 1989; Ogden, 1985a; Schenkenberg, Bradford, & Ajax, 1980; Stone et al., 1991), brief and convenient bedside tests are needed for most clinical purposes. Such screening tasks have been confirmed to provide sensitive tools to diagnose spatial neglect within the acute and subacute stage of the disorder (Azouvi et al., 2002; Cassidy et al., 1998; Ferber & Karnath, 2001a; Halligan et al., 1989, Halligan, Wilson, & Cockburn, 1990).

One of the most useful types of these bedside tests are the so-called "cancellation tasks" of which several different versions are available. These tools require active visual search skills and co-ordinated exploratory eye and hand movements in all directions in order to find and to cancel (i.e. to mark with a pen) all targets distributed on an A4 landscape paper that is directly placed in line with the patient's mid-sagittal body axis. A higher number of contralesional target omissions compared to the ipsilesional side is typically considered as a basic component of spatial neglect, whereas each test provides different cut-off criteria. The patients' performance in cancellation tasks may vary from just a few omissions on the contralateral side to detecting only the very ipsilesional located targets (cf. Figure 1). These tasks have in common that they highly depend on vision or visuo-motor control but they differ for example with respect to the kind, amount, and size of targets or distractors as well as to their difficulty and time input.

Some of these tasks like the "Albert's test" (Albert, 1973, cf. Figure 1) in which 41 lines are arranged in seven rows or the "Line cancellation" from the Behavioural inattention test (BIT; Wilson, Cockburn, & Halligan, 1987) include only target items. They are particularly convenient for severely impaired patients or those with language disorders, since they are economical of time and can be explained even with gestures, i.e. by exemplarily conducting the test in front of the patient. However, most cancellation tasks have target items embedded within various types of distractors (cf. Figure 2A to C).

Weintraub and Mesulam (1985) intended to assess spatial neglect with a tool that is more compatible with the natural, complex environment. Consequently, patients were asked not to simply detect (as in the Albert's test) but rather to select items within a dense array of distractors. The authors argued that -compared to line crossing- their task, which requires searching for an 'A' within randomly distributed letters is more sensitive to subtle or recovered neglect (cf. Figure 2A). Further, more targets should be neglected when the items are randomly rather than structured arranged. Both, the "Star cancellation" (Wilson et al., 1987; Figure 2C) and the "Bells test" (Gauthier et al., 1989; Figure 2B) followed this idea by either presenting small stars (targets) evenly distributed among large stars and capital letters, or by displaying bells within an array of distractors such as keys, horses, and other objects of equal size.

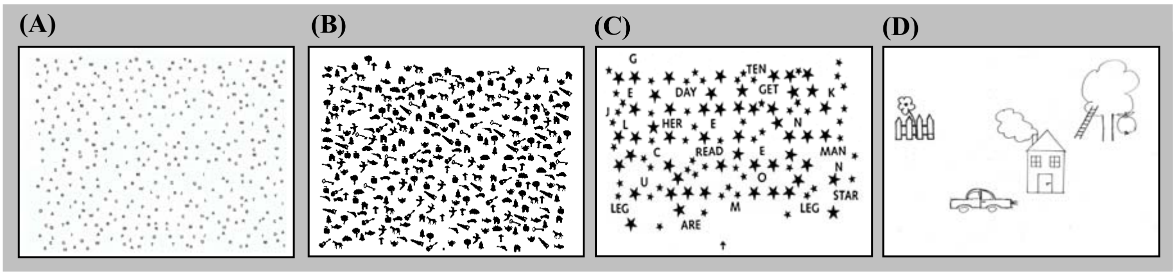

Figure 2. *Examples of traditional clinical tests to diagnose spatial neglect. (A) Letter cancellation task, (B) Bells test, (C) Star cancellation, and (D) a copying task.*

Besides, single object copying or drawing tasks are traditionally used to diagnose spatial neglect. These tests usually consist of simple line drawings that have to be copied (e.g. a daisy, a clock, a star, a cross, or a cube) or to be completed by the patients (e.g. clock faces), but also of more complex drawings like the Rey-Osterrieth figure (Osterrieth, 1944; Rey, 1941). However, these tasks are not sensitive on their own. Some of them (including clock drawing) have been criticised for their low sensitivity and high subjectivity in scoring (Bailey, Riddoch, & Crome, 2000; Ishiai, Sugishita, Ichikawa, Gono, & Watabiki, 1993). Moreover, single copy tasks were rated to be less feasible to diagnose neglect in the course of recovery (Campbell & Oxbury, 1976). Further, it has to be noted that patients with visuo-constructive disorders also perform poorly on such tasks and may show errors on both sides of space (Gainotti, D'Erme, & Diodato, 1985; Griffiths, Cook, & Newcombe, 1988; Laeng, 2006).

In contrast, copy performance in a multi-object task is a good predictor of spatial neglect (Gainotti, Messerli, & Tissot 1972; Johannsen & Karnath, 2004; Seki & Ishiai, 1996). Johannsen and Karnath (2004; cf. Figure 2D) showed that a multi-object scene presenting a fence, a car, a house, and a tree (two in each half of an A4 landscape format) is a sensitive tool to detect spatial neglect in the acute as well as in the chronic stage (more than 1 year post stroke). Moreover, the scoring scheme of this task (cf. Chapter 4.1.4) was explicitly designed to uncover the characteristic bias of exploratory behaviour and has been previously confirmed to be highly sensitive in detecting spatial neglect (Ferber & Karnath, 2001a).

Another simple paper-and-pencil tool that is often used, is the so-called "line bisection" task (Heilman & Valenstein, 1979). It usually consists of a horizontal line of varying length that is presented on an A4 landscape paper in front of the patients, who are asked to mark the midpoint of the line with a pen. Usually, a displacement of the bisection mark towards the lesion side is interpreted as a symptom of spatial neglect. However, this tool is not as specific to spatial neglect as it is the case for simple cancellation tasks (Ferber & Karnath, 2001a). It does not or only poorly correlate with letter, bells, and star cancellation (Binder et. al., 1992; Ferber & Karnath, 2001a) and may even reveal a double dissociation in stroke patients (Halligan & Marshall, 1992; Marshall & Halligan, 1995). A factor analysis with various neglect tests separated line bisection as a single factor, but not as part of the factor loading on letter or symbol cancellation (McGlinchey-Berroth, Bullis, Milberg, Verfaellie, Alexander, & D'Esposito, 1996). Moreover, previous research revealed that patients with hemianopia but without spatial neglect displace the bisection mark contralateral to the side of the brain lesion (Barton & Black, 1998; Kerkhoff, 1993). Thus, a patient with a right-sided hemianopia exhibits the same bisection error as a patient with left-sided neglect. Consequently it was argued that line bisection and cancellation rely on different skills and cognitive processes, of which one -namely cancellation- is basically associated with spatial neglect while the other may only correlate with it (Ferber & Karnath, 2001a). This conclusion is supported by the fact that bisecting a line demands correct size perception of a single stimulus, while cancellation requires visual exploration within a search array. Moreover, a recent study using transcranial magnetic stimulation (TMS) revealed a clear dissociation in healthy subjects between visual exploration and the "landmark task" (Bisiach, Ricci, Lualdi, & Colombo, 1998; Milner, Brechmann, & Pagliarini, 1992; Milner, Harvey, Roberts, & Forster, 1993), which is closely related to manual line bisection (Ellison, Schindler, Pattison, & Milner, 2004).

While line bisection errors may arise from a variety of factors other than spatial neglect, search tasks directly address the lateralised behaviour of such patients. In line with the widely accepted definition of spatial neglect - saying that patients with spatial neglect show a failure "to report, or to respond or orient to, novel or meaningful stimuli presented to the side opposite a brain lesion" (Heilman et al., 1984; p. 209) - visual exploration as implemented in diagnostic tasks or in experimental designs therefore is most suitable to uncover the basic pathology that leads to this characteristic orientational bias. As previously mentioned, no other group of stroke patients shows a comparable lateralised, direction-specific behaviour. Thus, it is highly specific to spatial neglect. Even in a clinical setting, this characteristic deficit can be easily detected by a combination of cancellation and multi-object copying tasks.

2.1.4 Anatomical findings

Despite decades of research, the anatomical correlates of spatial neglect in humans are still an object of intense debate. Thanks to modern imaging techniques, many studies performed within the last decade provide new insights into the neural correlates of spatial neglect that subsequently will help to integrate the findings on the neural mechanisms involved in the origin of the disorder. Beyond dispute, spatial neglect predominantly occurs with right hemisphere lesions (Bowen et al. 1999; Mesulam 2002; Pedersen et al. 1997), indicating an asymmetrically lateralised mechanism that leads to these striking behavioural symptoms. In fact, spatial neglect occurs as asymmetrical after right hemisphere stroke as aphasia is observed after left hemisphere lesion.

Traditionally, injury to the right inferior parietal lobule (IPL) and right temporo-parietal-occipital (TPO) junction was considered the best predictor for spatial neglect. These conclusions were mainly based on early studies using computer tomography (CT). The CT analysis of 10 patients with spatial neglect found the most injured brain regions in exactly these regions (Heilman, Watson, Valenstein, & Damasio, 1983b). Three years later, Vallar and Perani (1986) showed an overlap involving peri-sylvian regions in 16 neglect patients. The lesions of 6 patients centred on the parieto-occipital junction while those of further 8 patients mainly highlighted the supramarginal gyrus, which is part of the IPL (Vallar & Perani, 1986). Ongoing research had largely confirmed these early findings but also recommended additional areas to be crucial for spatial neglect. The CT scan analysis of Samuelsson and colleagues (1997) detected in 12 out of 18 patients with spatial neglect a lesion in the posterior part of the middle temporal gyrus and/or the temporo-parietal paraventricular white matter. Leibovitch, Black, Caldwell, McIntosh, Ehrlich, and Szalai (1998) reported on a lesion overlap in the right parietal cortex, the anterior, central and, posterior white matter as well as in the primary sensory and motor cortices. By an additional analysis with single photon emission computed tomography (SPECT) they found the right TPO junction and the anterior cingulate cortex to be mainly involved in patients with spatial neglect.

Expanding the findings of the early CT scan analyses, the next generation of anatomical studies included new lesion delineation techniques as well as statistical methods to improve the precision of their results (for review see Rorden & Karnath, 2004). In doing so, Karnath and colleagues (Karnath, Ferber, & Himmelbach, 2001; Karnath, Fruhmann Berger, Küker, & Rorden, 2004a; Karnath, Fruhmann Berger, Zopf, & Küker, 2004b) observed the core region of structurally injured brain tissue in the right superior temporal gyrus (STG) as well as in the right insula. A study on 140 unselected patients with acute right hemisphere stroke used voxelwise statistical analysis to compare each injured voxel of patients with and without spatial neglect. We found the centre of overlap in the STG, the planum temporale, the insula, the pre- and postcentral gyri as well as subcortically in the putamen and in the caudate nucleus of the right hemisphere (cf. Figure 3; Karnath et al., 2004a). In contrast, a recent study that also used modern delineation techniques in 14 patients with neglect due to middle cerebral artery stroke suggested the angular gyrus on the lateral surface of the IPL to be most crucial for the disorder (Mort et al., 2003).

Beyond, spatial neglect is observed rarely following strokes of the right inferior frontal lobe (IFG; Husain & Kennard, 1997; Karnath et al., 2001; Samuelsson et al., 1997; Vallar & Perani, 1986) as well as with injury to subcortical structures like the thalamus (Cambier, Masson, Graveleau, & Elghozi, 1980) and the basal ganglia (Damasio, Damasio, & Chui, 1980; Karnath et al., 2002). In case of a subcortical lesion, accompanied hypoperfusion of overlying cortical areas seem to determine whether neglect will occur or not (Hillis et al., 2002; Karnath, Zopf, Johannsen, Fruhmann Berger, Nägele, & Klose, 2005). Using perfusion weighted imaging (PWI) technique, neglect following circumscribed stroke of the right basal ganglia was observed to induce perfusion deficits in those cortical areas that have previously been described to cause the disorder, namely in the STG, the IPL, and the IFG (Karnath et al., 2005). This implies that spatial neglect following a right basal ganglia lesion typically is provoked by the dysfunction of (part of) these cortical areas.

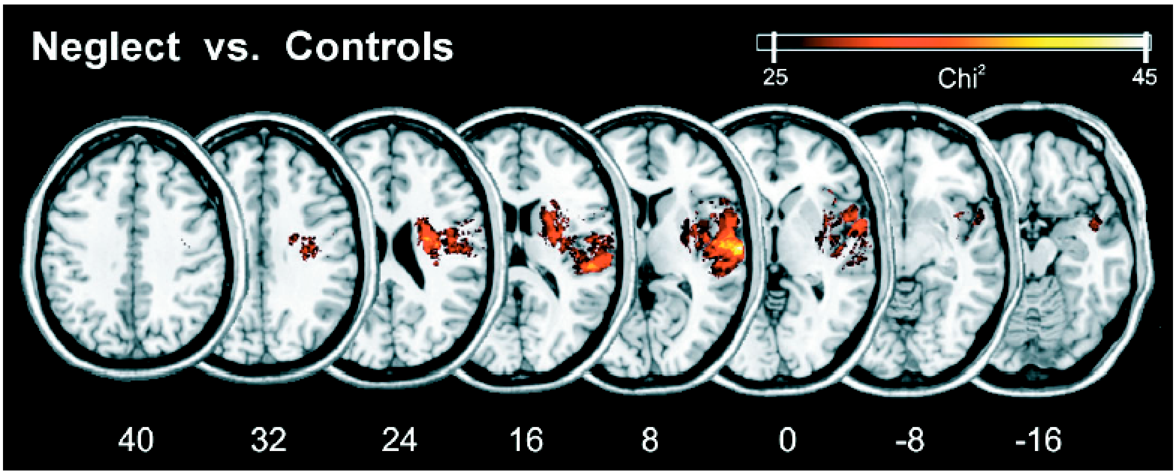

Figure 3. *Anatomical correlates of spatial neglect. Voxelwise statistical analysis, comparing 78 stroke patients with spatial neglect to 62 stroke patients without the disorder (controls). Presented are all voxels that were significantly more often injured in neglect patients than in controls after using a Bonferroni corrected alpha level of p < 0.05. The black-white colour gradient corresponds with the chi-square value. No voxel was found that was significantly more likely to be damaged in control patients than in those with spatial neglect. Talairach z-coordinates (Talairach & Tournoux, 1988) of each transverse section are given. (From Karnath et al., 2004a.)*

Interestingly, our findings on cortical level -that rather confirm an important role of the right STG than of right parietal areas for spatial orientation and exploration and thus in case of a damage to this region for the occurrence of spatial neglect- (for review see Rorden, Fruhmann Berger, & Karnath, 2006), are supported by transcranial magnetic stimulation and functional imaging results in healthy subjects as well as by intraoperative electrical stimulation in awake neurosurgery patients.

A recent experiment using functional magnetic resonance imaging (fMRI) in healthy individuals investigated visual exploration of a stimulus array similar to the letter 'A' search task of Weintraub and Mesulam (1985) and comparable to the one used in the present work. Importantly, all of these tasks require a serial search strategy. The authors contrasted brain activity during visual exploration with the execution of stepwise saccades. Beyond the temporo-parietal junction and the IFG, significant differences in activation were located at the middle part of the superior temporal cortex (Himmelbach, Erb, & Karnath, 2006).

Ellison et al. (2004) applied repetitive transcranial magnetic stimulation (rTMS) over the superior temporal cortex to study visual search behaviour in 5 healthy subjects. The authors recorded reaction times and accuracy in three different visual search paradigms while stimulating either the right STG or the right posterior parietal cortex (PPC). The analysis of mean reaction times revealed a specific impairment of serial feature search induced by rTMS over the right STG but no effect on accuracy, uncovering the hitherto unknown role of the superior temporal cortex in serial visual search. Importantly, exactly this kind of active search behaviour is tested by the more complex cancellation tasks constructed to diagnose spatial neglect (cf. Chapter 2.1.3).

Their findings were supplemented by a study carried out to prevent visual search performance in a patient with a brain tumour that needed neurosurgical resection (Gharabaghi, Fruhmann Berger, Tatagiba, & Karnath, 2006). We showed that intraoperative monitoring is not only a useful tool to protect language processes (Ojemann & Whitaker, 1978; Penfield & Roberts, 1959; Van Buren, Fedio, & Frederick, 1978) but also to preserve other cognitive functions, such as the patient's ability to successfully explore the environment in order to find visual targets. Adopting the feature search task of Ellison and co-workers (2004; cf. Figure 4, left panel), we found that transient inactivation of the STG leads to impaired serial exploratory search in our patient, namely to a reduced detection rate to chance level. Based on these results the neurosurgeons carried out the microsurgical resection by approaching the tumour distant to the areas where electrical stimulation elicited transient exploratory visual search (cf. Figure 4, right panel, position 3) or language deficits (position 4) and preserved these functions successfully. The data supplement the findings by Ellison et al. (2004) who observed a crucial role of the right STG by means of reaction times. Further, this study supports the view that part of the STG is critically involved in visuo-spatial processing and is also integral to active exploratory behaviour. It thus was concluded that part of the right STG plays an essential role in processes of spatial representation that underlie exploratory visual search in humans (Gharabaghi et al., 2006).

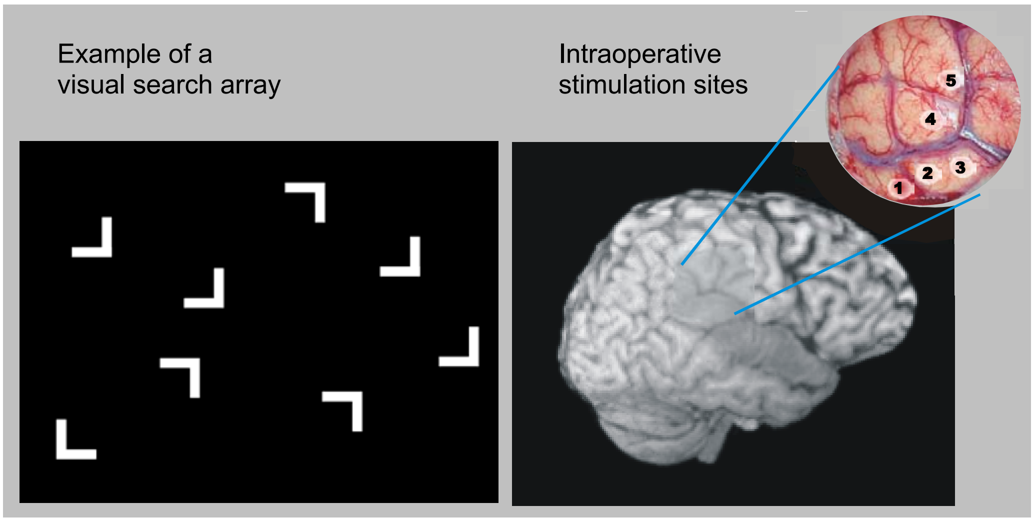

Figure 4. *The role of the right superior temporal gyrus (STG) in visual search as revealed by intraoperative electrical stimulation.* ***Left panel:*** *Example stimulus. Stimuli were adopted from the "hard feature search task" of Ellison et al. (2004), in which one single L-shaped target was presented amongst 180° and 270° rotated L-shaped distractors.* ***Right panel****: Lateral surface view (left) of patient R.K.'s brain in relation to the intraoperative situation before tumour resection (right). The superficial median cerebral vein (sylvian fissure), the superior anastomotica vein (Trolard), and the inferior anastomotica vein (Labbe) are visible. Electrical stimulation was applied to five different positions (1 to 5). Three of the stimulation sites were located on the convexity of the STG beginning at its caudal portion (position 1) and extending rostrally (positions 2 and 3). Application sites 4 and 5 were located on the convexity of the supramarginal gyrus in the inferior parietal cortex. Intraoperative electrical stimulation of the middle portion of the STG (position 3) elicits a transient disturbance of the patient's visual search behaviour.*

2.2 Possible Mechanisms Contributing to Spatial Neglect

Countless empirical data of brain-injured patients who had agreed to participate in the studies of the past decades offered an invaluable insight into the underlying mechanisms of spatial orientation and representation. These results have mainly been interpreted in the context of "attentional", "representational", or "transformational" models. Beyond, early models of spatial neglect emphasised the impact of low-level sensory deficits as well as of generalised impairments of cognitive and intellectual function (Battersby, Bender, Pollack, & Kahn, 1956; Bender, 1952; Denny-Brown, Meyer, & Horenstein, 1952). However, since spatial neglect is known to occur without elementary sensorimotor or cognitive deficits (cf. Chapter 2.1.1), such disorders may have aggravating effects but cannot sufficiently explain the possible mechanism leading to the lateralised behaviour of these patients.

2.2.1 Attentional models

The "orientation bias model of unilateral neglect" by Kinsbourne (1970, 1977, 1987, 1993) proposed that both hemispheres generate a kind of orienting vector that directs attention towards the contralateral side, each inhibiting the opposite hemisphere. Brain lesions are supposed to affect the function of these putative vectors, leading to an activation imbalance between the left and the right hemisphere, which biases the vector of attentional orienting towards the right and elicits ipsilesional shifts of attention and gaze. In order to account for hemispheric asymmetries, particularly for the higher incidence of neglect following right-sided lesions, Kinsbourne (1987) postulated a stronger orienting bias of the left hemisphere compared to the right, which is supposed to produce only a weak vector. After a right hemisphere stroke, the unopposed left hemisphere vector of attention is assumed to provoke a strong orientation bias to the right side of space. Consequently, attention is biased towards the ipsilesional side in these patients resulting in a peak on its extreme outer positions. Following Kinsbourne's idea, the performance of patients with spatial neglect is expected to successively improve from the very left to the extreme right side. The probability of detecting stimuli thus is predicted to follow a contralesionally skewed (usually left-to-right) gradient, with only a few omissions on the very right side of a given array and increasing omissions towards the contralesional parts of the display (cf. Figure 5). These lateral orienting tendencies are proposed to account for visual exploration of external space and overt gaze deviation as well as for internal space representations (Kinsbourne, 1993).

Like Kinsbourne, Heilman and Van den Abell (1980) proposed a right hemisphere dominance for spatial attention and arousal. The authors suggested that the right hemisphere is able to direct attention towards both, the left and the right hemispace, while the left hemisphere only provides attention for the contralateral, right space. In case of a right-sided lesion, the left hemisphere thus is supposed to be poorly equipped to direct attention contralesionally, leading to neglect of the left side of space. Consequently, neglect following a left-sided stroke should not occur with the same severity as predicted for the right hemisphere that provides attention for both sides of space.

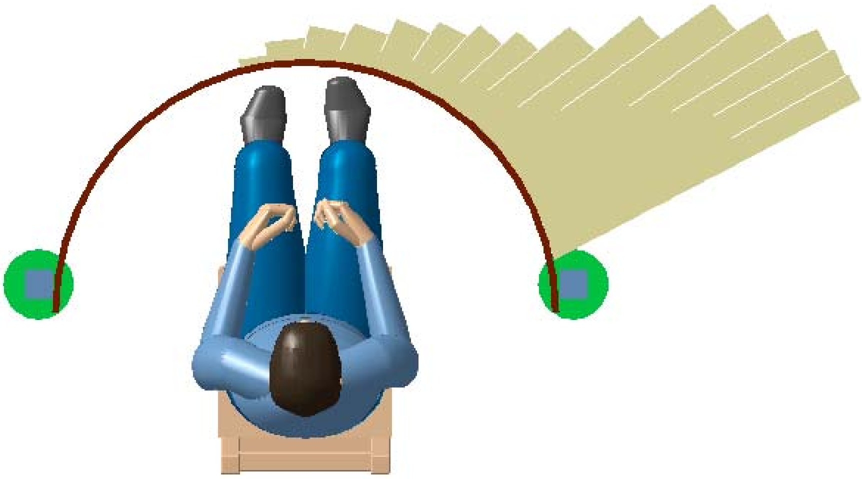

Figure 5. *Gradient model of unilateral neglect. Expected distribution of horizontal exploratory gaze movements of right hemisphere stroke patients with spatial neglect as predicted by the left-right gradient model (Kinsbourne, 1993; Rizzolatti & Berti, 1990). The authors propose a continuous increase of visual exploration behaviour along the horizontal axis from a minimum on the outer contralesional side to a maximum on the extreme ipsilesional positions.*

In contrast to Kinsbourne's assumption of an orienting bias towards the ipsilesional side, Posner and co-workers (Posner, Walker, Friedrich, & Rafal, 1987; Posner & Petersen, 1990) argued for an impairment in disengaging and shifting attention towards the contralateral side in patients with spatial neglect. According to Posner's theory, a covert shift of attention follows a three-stage process of disengaging, shifting, and finally of re-engaging attention at the new position in space. The author developed a cueing task in which subjects are required to maintain fixation at the centre of a display while a cue (e.g. an arrow) directs them to attend to a given location in the left or right visual periphery (Posner, 1980). Compared to uninformative (neutral) or incorrect (invalid) cues, "location-cueing" towards the target position accelerates the subjects' reaction time. Consequently, invalid cueing towards another location results in costs of reaction time or accuracy, presumably because of the need to "disengage" and shift attention away from the incorrect to the correct location. Investigating patients with parietal lesions, Posner and Petersen

(1990) found reduced manual reaction times in those trials that required a shift of attention towards contralesional targets. This finding led to the assumption that such patients are impaired in disengaging attention from the current focus of attention. Within the "spotlight-of-attention" theory, Posner and Driver (1992) described the impairment in disengaging attention from a current focus on the ipsilesional side towards a contralesional located target as the core deficit in spatial neglect.

2.2.2 Representational models

As Kinsbourne (1993), also Rizzolatti and co-workers (Rizzolatti, Gentilucci, & Matelli, 1985; Rizzolatti & Berti 1990) proposed an increasing gradient of severity from the ipsilesional towards the extreme contralesional side. According to their "premotor theory of attention", spatial neglect is interpreted as an imbalance of spatial representation caused by a disturbance in cortical and subcortical perceptual-motor "maps" that normally -i.e. when simultaneously activated- control motor programs. Each map has different mechanisms that are responsible for arm, leg, and head movements and its own representation of neural space (Berti & Rizzolatti, 1994). Brain lesions, affecting one or more of these maps are assumed to result in neglect of the corresponding aspects of space representation. Moreover, these lesions are supposed to release competitive actions from its normal inhibition function (Rizzolatti & Berti, 1990), leading to additional imbalance in favour of the ipsilesional side.

An admirable study by Bisiach and Luzzatti (1978) led to the assumption that an aspect of spatial neglect is due to a failure in computing a full and distinct internal mental representation of the side contralateral to the brain lesion, thus affecting both imagination and memory. The authors reported on two patients with left neglect, who were asked to imagine and describe a familiar surrounding with its buildings and other features in their native city from memory, namely the "Piazza del Duomo" in Milan. Crucially, the patients were asked to imagine the square from two perspectives, once when standing on the steps of the cathedral located at one end of the Piazza, and then from the opposite end, facing the cathedral. Bisiach and Luzzatti (1978) found that under both "mental imagery conditions", the patients mentioned fewer details on the left compared to the respective right side of the square, i.e. regardless of the "mental" perspective from which they "viewed" the square. Obviously, these patients had stored topographical information on features of both sides, but depending on their internal perspective, they were impaired in accessing features on the left from imagery. Bisiach and colleagues (Bisiach, Capitani, Luzzatti, & Perani, 1981;

Bisiach and Luzatti, 1978) concluded that although sensation remains intact in such patients, the stored information (e.g. in the form of topographical memory) is not integrated into a higher order representation of the contralesional, usually left side of space. Consequently, there is a lack of mental representations of stimuli to be responded to on the side of space opposite to the brain lesion (Bisiach et al., 1981). Since then, representational neglect has been repeatedly investigated using other locations and stimuli, ranging from irregular shapes to maps of France (e.g. Bartolomeo, D'Erme, & Gainotti, 1994; Bisiach et al., 1981; Meador, Loring, Bowers, & Heilman, 1987; Ogden, 1985b; Rode, Rossetti, Li, & Boisson, 1998; Rode, Rossetti, Perenin, & Boisson, 2004).

Beyond these findings on a loss of mental representation, more physiological approaches suggest that spatial neglect may result from a distortion of horizontal space representation in the perceptual domain. These authors assume either a compression or extension of space (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Bisiach, Rusconi, Peretti, & Vallar, 1994; Gainotti & Tiacci, 1971; Halligan & Marshall, 1991; Milner, 1987), while establishing their results mainly on the investigation or interpretation of the patients' line bisection performance (cf. Chapter 2.1.3). Both, Milner (1987) and Bisiach et al. (1996) suggested an anisometric compression of horizontal space representation that increases towards more left-sided located parts. Bisiach et al. (1996) instructed patients with neglect to mark the left and the right endpoint of an imagined horizontal line based on a given midpoint. In doing so, the patients misplaced the endpoints in a manner that is known from line bisection performance of patients with either left neglect or right visual field defects, i.e. the longer segment lay on the left side of the midpoint. The authors interpreted the results in the scope of a horizontal anisometry that progressively relaxes from the right to the left side, with compression on the ipsilesional and extension on the contralesional side (Bisiach et al., 1996). Halligan and Marshall (1991) investigated one patient who suffered from both, spatial neglect and hemianopia. In contrast to Milner (1987) and Bisiach et al. (1994), they argued that the patient's subjective perception was influenced by a reduced spatial scale, namely by a uniform compression of space towards the lesion side.

In this context, studies on size perception were interpreted to support a distortion of space representation in spatial neglect. Gainotti and Tiacci (1971) asked their patients to compare two geometrical figures one of each located on either the left or the right side of a sheet of paper. Compared to contralateral presented figures, neglect patients tended to overestimate the size of those on the ipsilesional side. The authors assumed that this behaviour was due to an asymmetric exploration of space in favour of ipsilesional located objects. More recent results on a comparable paradigm by Milner and Harvey (1995) have been attributed to a "shrinkage" in the perception of object size in the left hemisphere. Except of vertical rectangles, neglect patients consistently overestimated right-sided shapes. The authors assumed that a misperception of horizontal size in left parts of space might explain the rightward error in line bisection tasks.

The previous findings have been challenged by investigations showing an unaltered perception of horizontal space (Karnath & Ferber, 1999) and a lack of specificity of object size estimates for spatial neglect (Doricchi & Angelelli, 1999; Ferber & Karnath, 2001b). When patients with mere neglect symptoms had to position 10 LEDs equidistantly along the horizontal axis in complete darkness, Karnath and Ferber (1999) found no evidence for an anisometric, compressed or expanded perception of subjective space, which would account to the characteristic ipsilesional bias in orienting and exploring. The same authors investigated size perception in four different groups each of them including right hemisphere patients with one of the conceivable crucial symptoms, i.e. mere neglect or mere hemianopia as well as patients showing both or neither of these impairments (Ferber & Karnath, 2001b). According to Milner and Harvey's paradigm (1995) patients had to compare the size of either two horizontal or two vertical rectangles. Although object size perception was altered in patients with pure neglect, patients with pure hemianopia were even more impaired in this task. Thus, as reported for other associated deficits (cf. Chapter 2.1.1 & 2.1.3), an altered size perception is not specific to spatial neglect but can also occur in other groups without the disorder (see also Doricchi & Angelelli, 1999). Beyond, theories on anisometric space representation cannot explain why neglect patients omit left-sided targets during visual exploration tasks.

2.2.3 Transformational models

Transformational approaches assume a disturbance of processes that convert the co-ordinates from sensory input of for example the eyes, the head, and the neck into an egocentric, body-related reference system. While some authors based their assumptions on animal models in order to relate it to human behaviour (Pouget & Driver, 2000; Ventre & Faugier-Grimaud, 1986; Ventre, Flandrin, & Jeannerod, 1984), others focussed mainly on reference systems of human spatial representation (Karnath, 1994a, 1997; Vallar, 1997).

In their thorough review, Pouget and Driver (2000) discussed the relation between findings on the physiology of parietal neurons in monkeys and observations on patients with spatial neglect due to *parietal* lesions. Under this "neural" perspective, the patients' deficits were related to cellular properties, allowing for example coding of space or multimodal integration. In monkeys, Gottlieb, Kusunoki, & Goldberg (1998) showed that the response of neurons in the lateral intraparietal area (LIP) specifically concern the most salient or most attended stimulus, thus providing a highly selective representation of the current visual scene. If unattended, pre-existing stimuli that suddenly enter a receptive field of the monkey following saccadic eye movements thus elicit little or no neuronal response. However, if the stimulus was not already present before, its sudden appearance produces a strong response in the corresponding receptive field (cf. also Humphreys & Riddoch, 1995). Adapting these findings to human behaviour, Pouget and Driver (2000) concluded, that the ipsilesional bias in neglect patients may reflect a dysfunction or partial loss of such similar cell populations in human parietal cortex, representing particular positions in space by means of combined spatial sensory input and/or motor plans. A loss in one hemisphere is assumed to produce a pathological gradient that is not only determined by the number of cells representing different positions in space, but also by their "salience" or "attentional weight". Moreover, the authors assumed that a spatial bias could arise in many different brain areas after a diffuse lesion, and thus may reflect different pathological gradients within several neuronal subsystems. However, human and monkey parietal cortex is not functionally homologous and several brain regions differ for example with respect to their cerebral lateralisation (for review see e.g. Karnath, 2001). The neural model of monkeys thus cannot explain the consistent findings on a right hemisphere dominance in patients within spatial neglect (cf. Chapter 2.1.2), which is specific to humans but not observed in monkeys.

Karnath (1994a, 1997, Karnath, Schenkel, & Fischer, 1991) has argued that an important aspect leading to neglect of the contralesional side may be a disturbance of the central information process that converts multimodal sensory, i.e. vestibular, auditory, neck proprioceptive, visual, olfactory input into longer-lasting spatial representations. In case of a brain lesion that provokes spatial neglect, the author assumed that this co-ordinate transformation is working with a systematic error, resulting in a rotation of the reference frames towards the ipsilesional side. In marked contrast to the left-right gradient models (cf. 2.2.1 & 2.2.2), he predicts a shift of the entire search distribution towards the ipsilesional side, i.e. with decreasing frequencies at the extreme left and right positions of the distribution as it is observed in healthy subjects and patients without the disorder (cf. Figure 6). Karnath (1997, 2001) underlined his idea of an altered body-centred space representation by evidence from neurophysiological findings in monkeys as well as functional imaging results in humans (Andersen, Snyder, Bradley, & Xing, 1997; Andersen, Snyder, Li, & Stricanne, 1993; Bottini et al., 2001; Boussaoud & Bremmer, 1999; Brotchie, Andersen, Snyder, & Goodman, 1995; Galletti, Battaglini, & Fattori, 1993; Snyder, Grieve, Brotchie, & Andersen, 1998; for review cf. Thier & Karnath, 1997). These results support the assumption that the brain uses neural representations of space, which are organised in non-retinal, body- and/or world-centred co-ordinates.

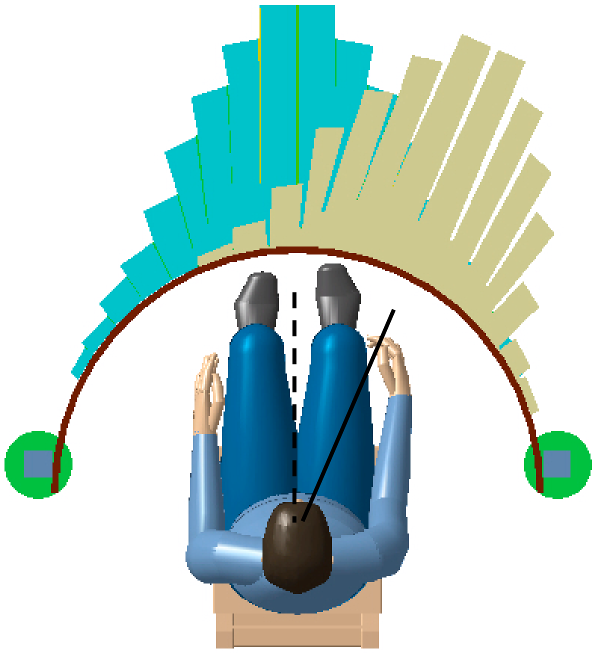

***Figure 6**. Deviation model of unilateral neglect. Expected distribution of horizontal exploratory gaze movements with respect to the egocentric reference system in right hemisphere stroke patients with spatial neglect (solid line, light grey bars) compared to healthy subjects or stroke patients without spatial neglect (dashed line, dark grey bars). For patients with spatial neglect, this model proposes a rotation of the egocentric space representation around the earth-vertical (yaw) body axis leading to a shift of the whole field of exploration toward the ipsilesional side. In contrast to the gradient model (cf. Figure 5), the author assumes decreasing frequencies towards left and right positions like in subjects without the disorder, but no lateral gradient with a peak on the extreme ipsilesional side of space. (Modified from Karnath, 1997.)*

Based on anatomical findings, Karnath (2001) suggested that the superior temporal cortex, the insula, and the temporo-parietal junction in the right hemisphere are crucial regions for the neural integration of multimodal sensory input into these higher order spatial reference systems. The multimodal cell populations of these areas are assumed to have an essential role in spatial encoding of the surrounding space with reference to the individuals' body position. The process of multimodal integration from different sensory input channels is thought to constitute a unitary representation of egocentric, i.e. body-centred space, which works erroneously in patients with spatial neglect.

Vallar (1997) also proposed that the transformation process is working with a constant error and produces the ipsilesional bias in spatial neglect. In contrast to Karnath (1997), the author suggested a translation of the subjective representation of body-centred space in relation to the patients' trunk, while Karnath postulated a rotation around the patients' mid-sagittal body axis (see Figure 7).

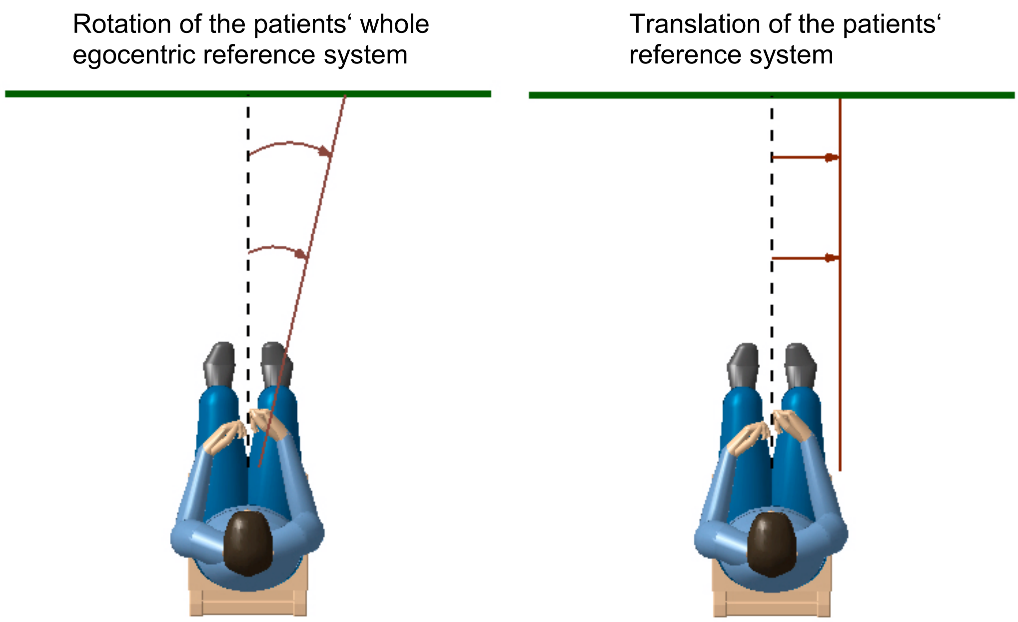

***Figure** 7. Different predictions of altered space representation in spatial neglect. In neglect patients, these models suggest either a rotation (left side) of the whole egocentric reference frame around the yaw axis or a translation (right) towards the ipsilesional side with respect to the objective earth-vertical body axis (dashed lines). The solid lines illustrate the different hypotheses of the two transformational models on the patients' subjective perception of their mid-sagittal body axis. (Modified from Karnath, 1997.)*

In order to distinguish between these predictions, patients were asked to verbally direct an LED located at different distances towards that position, which they subjectively perceived as being "straight ahead" of their mid-sagittal body axis. Compared to controls, neglect patients subjective straight ahead perception was markedly shifted to the right side.

Crucially, the ipsilesional displacement increased linearly with the distance of the adjusted LED position. Karnath (1997) concluded that this finding indicates a rotation around the patients' body axis rather than a translation of the subjective, body-centred reference system.

To summarise, a huge number of different theoretical approaches seek to explain the striking symptoms of spatial neglect, but no consensus about its underlying mechanisms has been reached so far (for review see e.g. Halligan, Fink, Marshall, & Vallar, 2003; Karnath & Dieterich, 2006). Congruently, all models share the view that spatial neglect is due to a higher-order spatial impairment and not caused by low-level sensory integration deficits. Some models are difficult to differentiate and it may seem as if different ideas may refer to different aspects of the syndrome rather than being incompatible (cf. e.g. Vallar, 1998). However, some experimental approaches such as studying the patients' exploratory behaviour in space (cf. Chapter 2.3.2) have been proposed to be targeting to examine the different predictions and to discriminate between them (Karnath, 1997).

2.3 Active Visual Exploration and Spatial Neglect

Scanning the visual world for new or well-known, meaningful or irrelevant information in our environment is a highly characteristic activity for human beings. Independently of luminance, we are engaged in this process for most of our waking hours while largely being unaware of the gaze movements executed to select items of interest or to safely navigate ourselves through a complex visual environment. For individuals who do not suffer from any disorders affecting visual perception, it must remain rather inconceivable what patients with spatial neglect may experience when exploring their visual surroundings. In clear contrast to each other group of stroke patients without the disorder and normal subjects, patients with spatial neglect show a specific inability to attend to the side contralateral to the lesion. This attentional bias towards the ipsilesional side decisively alters their perception of the environment and thus their behavioural outcome. As shown previously (see Chapter 2.1.3), this phenomenon could be easily observed in clinical tasks used to diagnose the disorder. However, studies on the specificity of visual search pattern by means of eye movement recordings allow for a more detailed analysis of the patients' behaviour and of the possible underlying mechanisms of spatial neglect (see Chapter 2.2).

2.3.1 Methods of eye and head recording

Measuring eye and head movements offers an invaluable insight into the processes and characteristics of visuo-spatial behaviour in patients with spatial neglect. Studies using eye-recording methods, however, are rare compared to behavioural observations of visuo-motor exploration in cancellation tasks, since they usually require more time and effort from the patients. Particularly in the acute stage of the disorder, such insightful approaches mainly depend on the patients' general constitution, alertness, concentration, and the need of medical attendance. Consequently, most previous eye movement studies include rather small sample sizes or single cases and were mostly confined to patients in the subacute or chronic stages of the disorder.

Studies on oculomotor behaviour in stroke patients usually apply eye-tracking methods that necessitate recording of eye movements with respect to the system. If the device is head mounted, eye-in-head positions are detected (e.g. Electrooculography, see below). If the system is table mounted, gaze angles are measured (e.g. video-based or scleral coil systems). In most devices, the head is fixed by a chin rest or a bite bar so that eye and gaze position (i.e. where the patient is looking at) are the same. In some systems, the head is free to move and is measured with a further magnetic coil or with video based head trackers. As far as information about head movements is provided, eye-in-head respectively gaze positions could then be calculated. In head-mounted systems, head and eye-in-head positions are added to determine gaze direction, while in search coil systems the patients' head position is subtracted from gaze to obtain eye-in-head angles. A main advantage of approaches allowing for unrestricted eye and head movements is the opportunity to record free exploration of a natural environment or of broad scenes without interference or restriction of the subjects' natural active or passive behaviour as realised in the present work.

The different types of eye (and head) recording devices can generally be divided into three main categories. Two types are used in the present experiments and are further described in the corresponding methods chapters (Chapters 4.2.2 & 4.3.2), while main characteristics of each category are given in the following.

The principle of the <u>*scleral search coil technique*</u> is based on the magnetic induction of a small coil (Robinson, 1963) that allows for simultaneous measure of horizontal and vertical eye position. The so-called "magnetic search coils" are embedded in a contact lens, which adhere to the sclera by suction (Collewijn, Van der Mark, & Jansen, 1975). This technique allows applying a further coil to measure head position within the same reference frame. Subjects are seated in an oscillating magnetic field that induces an alternating current in the coils. The voltage is transferred by a thin flexible copper wire (diameter ~0.1 mm) from the lens to an amplifier. After the signal passed the amplifier, two analogue voltages are provided to analyse horizontal and vertical eye position. Constraints are the limit of about 30 minutes for wearing a scleral coil and possible discomfort, since this technique is invasive and requires the use of a topical anaesthetic before insertion of the contact lens. Crucially, people with glasses could be investigated. In studies with healthy subjects, the scleral search coil system is widely used because of its high accuracy and bandwidth. Its mean accuracy for horizontal eye movements is reported about 0.45° (Imai et al., 2005). Importantly, it allows for an investigation of unrestricted eye and head movements within the entire magnetic field. This is comparable to head mounted systems despite that trunk movements are not permitted.

Electrooculography (EOG) makes use of the steady electrical potential field, which arises across the eyes. The mechanism is based on polarity and could be described as a fixed dipole that is positive at the retina and negative at the cornea. The magnitude of this corneo-retinal potential is attributed to the higher metabolic rate of the retina (see e.g. Büttner-Ennever, 1989). The potential difference and the movement of the eyes are the basis for the signal, which is usually measured with pairs of electrodes placed near the outer canti of the eyes. Limitations of this method concern the fact that the corneo-retinal potential may vary with light changes, fatigue as well as may be influenced by muscle artefacts and the basic non-linearity of the method (Carpenter, 1988). To obtain accurate measures, frequent calibration and re-calibration of EOG systems is thus required. Usually, accuracy about ± 2° and maximum rotation about ± 70° is assumed, while linearity becomes progressively worse for angles beyond 30° (Young & Sheena, 1988). However, EOG drift can be considered linear over short recording periods up to 2 minutes (Schackel, 1967). Compared to other methods, this technique could be applied with minimal discomfort as well as minimal interference of the patients' activities. Thus, EOG is routinely used in clinical settings to investigate the oculomotor system.

At present, the most widely applied devices are so called *"video-based" eye trackers* that uses the video images from one or from both eyes provided by a camera. More detailed, they typically process the reflection from the outer surface of the cornea (the first Purkinje image) and the centre of the pupil as main features to track the eye over time. A more sensitive type uses two reflections (Cornsweet & Crane, 1973), one from the front of the cornea (first Purkinje image) and one from the inner (posterior) surface of the lens (fourth Purkinje image). The eye is tracked by measuring the scattered light emitted by an infrared light and reflected by the subjects' iris. The signal is then analysed to detect eye movements by changes in these reflections. Compared to the scleral search coil technique, video-based methods are favoured for being non-invasive. However, head movements cannot be compensated by these systems. Thus, the patients' head needs to be fixed for example by a chin rest and sometimes additionally by a bite bar. Otherwise, small head movements would lead to large measurement errors. Accuracy mainly depends on the system and the calibration procedure used. Newer technologies provide head mounted systems. However, such devices are less comfortable and practicable in acute patients who suffered a brain injury (e.g. because of cerebral spinal fluid shunts, discomfort, etc). Moreover, they may interfere with wearing eye classes.

The kind of system decides whether a study is carried out by restricted visual displays (usually presented on a monitor screen) or if natural, exploratory movements of the eyes and the head could be investigated. Thus, oculomotor exploration studies could mainly be differentiated by the (horizontal and vertical) extent of the search area used and by the variables measured, i.e. whether they provide information solely on eye-in-head/gaze or on the patients' gaze, eye-in-head, *and* head-on-trunk positions. Most studies in the following chapter investigated the patients' oculomotor behaviour using a restricted exploration field while the head was fixed.

2.3.2 Eye movement recording studies

Studies focussing on horizontal eye movements in patients with spatial neglect usually report on differences between the left and right side of the display or of the stimuli used. Such discrepancies concern fewer fixations and shorter total fixation times on the contralateral side as well as rare or even no returns towards the midline or the neglected side of space. Beyond recording techniques (cf. Chapter 2.3.1), these observations on scanning behaviour mainly differ in stimulus characters used, including measures while the patients' were looking at various simple line or object drawings (Ishiai, Furukawa, & Tsukagoshi, 1987; Rizzo & Hurtig, 1992), during line bisecting (Barton, Behrmann, & Black, 1998; Kim, Anderson, & Heilman, 1997; for review see Ishiai, 2006), verbal descriptions of simple drawings (Karnath, 1994b), and text or word reading (Behrmann, Black, McKeeff, & Barton, 2002; Karnath & Huber, 1992), but also during visual search under normal room light conditions (see below). Congruently, all these observations were based on the patients' performance during presentation of visual stimuli, i.e. the eye/gaze orientation was directly elicited by its features.

The present focus is on studies that measured the characteristic spatial bias during active visual search by means of horizontal eye movement recordings, using complex stimuli arrays comparable with those used in clinical neglect tests (cf. Chapter 2.1.3). Apart from one research group, all authors recorded eye movements within a restricted search array while the head was fixed and patients' were not permitted to move it (Behrmann, Watt, Black, & Barton, 1997; Chédru, Leblanc, & Lhermitte, 1973; Hornak, 1992; Sprenger, Kömpf, & Heide, 2002). All of these studies were carried out in subacute or chronic patients.

An initial study by Chédru and his group (1973) noted that the characteristic deficit as observed in clinical tasks (cf. Chapter 2.1.3), impairs the patients' ability to search the space contralateral to the lesion side, and thus constitutes a sensitive indicator for spatial neglect. At first, the authors were interested in the effects of unilateral cerebral lesions on the efficiency and strategy of visual search behaviour and its comparison to subjects without brain injury. For this purpose, patients were divided into several groups by the presence and absence of visual field defects as well as by the affected hemisphere. Thirty-seven percent of the entire group had suffered a stroke, the remaining portion was subsumed under "other lesions" (e.g. tumours); about 39 percent of all patients had "old" brain injuries, defined as ischaemic vascular accident or removed space occupying processes older than 3 months. The authors found that although normal subjects did not show identical scanpaths, they spend comparable time to search the left and right hemispace for target items. In contrast, patients with right hemisphere lesions confined their eye movements to the ipsilesional hemi-field and even limited them to the very right side. Additional data collected on coexisting spatial neglect allowed for an instructive subsequent analysis, which revealed that this asymmetric behaviour was due to the presence of visual neglect but not of visual field defects. Chédru and co-workers (1973) concluded that "the degree of asymmetry in this exploration is [...] a direct measure of unilateral inattention (p. 106). Unfortunately, the authors did not report the degree of mean rightward deviation in this group.

Subsequent studies addressed this observation in detail, providing important implications of the distribution of the patients' ipsilesional orientated eye movement pattern on the mechanisms leading to spatial neglect. More than a decade, the horizontal distribution of exploratory eye movements is being discussed in the framework of either a left-right gradient as proposed by attentional and representational models (cf. Figure 5 & Chapters 2.2.1, 2.2.2) or regarding the idea of a whole shift of the egocentric, body-related reference frames (cf. Figure 6 & Chapter 2.2.3). A crucial prediction of the former models is a disturbance of each hemispace that follows a lateral gradient of neglect severity ranging from its extreme maximum at the very contralesional side to a minimum on the outer ipsilesional end (Heilman & Van den Abell, 1980; Kinsbourne, 1987; Rizzolatti & Berti 1990). In contrast, the transformational model proposes a rotation of the whole field of exploration toward the ipsilesional side with symmetrically distributed saccades towards the left and right side. Consequently, as in healthy subjects, no lateral gradient should underlie exploration of space (Karnath, 1997).

Hornak (1992) discussed these models based on his results in a task that required searching in complete darkness within a range of approximately 70° (± 30 to 35° on each side). On average 3 months post stroke, 5 patients with neglect and hemianopia were compared to 5 control patients with visual field defects but no neglect. Subsequent to a calibration procedure carried out with red LEDs at different positions and ended by a central fixation light, which was finally turned off, patients were ask if the room now appeared completely dark. Those patients who agreed after inspecting only one side were asked "whether they had checked 'everywhere' " (p. 549). While the patients with hemianopia searched equally towards both sides, those with spatial neglect executed horizontal eye movements within an area of minus 10° to plus 30°. Importantly, there was no peak at the furthermost right margin of the entire recording field (i.e. at plus 35°), but a maximum of mean percentage of fixations around plus 15° degree of visual angle, i.e. far away from the very right side. Based on the assumptions of previous "stimulus driven" findings using single objects or line drawings (for references see first part of this section), Hornak (1992) attributed the absence of a rightmost peak to the leftward eye movements that had occurred after his task-specific verbal encouragement to search the whole sphere.

In contrast, Behrmann and co-workers (1997) recorded eye movement pattern during visual search for target letters distributed among several distractors within a horizontal array of ± 22.5° under normal room light conditions. They compared a group of 9 neglect patients with additional hemianopia who were investigated in the chronic stage (12.7 months post stroke) to a group of 4 patients who suffered from visual field defects but no neglect. The authors reported on a steep gradient of eye movements from the left to the right visual display with a right-sided maximum around 18°. The continuous increase of fixation frequency as well as of total exploration time along the horizontal axis was interpreted in favour of Kinsbourne's idea, who assumed a left-right gradient with a minimum of exploratory movements on the extreme contralesional side and a maximum on the outer right margin of a given array (cf. Figure 5). However, neither Hornak (1992) nor Behrmann et al. (1997) found distributions in line with the gradient model but single peaks between 15° to 18° on the ipsilesional, right side. Moreover, both studies revealed a notable decrease of exploratory movements towards the contralesional side as well as at least a comparable trend of decline within the maximum parts on the extreme ipsilateral side that could be detected within the given limits of the display used.

Based on these findings on restricted exploratory search, Karnath (1997) argued that the horizontal range of previous studies was too narrow to detect how the distribution would continue further to the ipsilesional, right side of space. Additionally, he assumed that spontaneous visual search behaviour should be investigated by tasks in which no external visual stimuli can attract attention and thus would influence the spatial distribution of natural eye and head movements. According to the procedure introduced by Hornak (1992), he suggested to study free exploratory search in complete darkness since "it can be assumed that the part of outer space subjects spontaneously explore under this condition is a direct function of the subject's representation of egocentric space" (Karnath, 1997, p. 1413). The "whole room" thus can be regarded as an analogue of the neural representation of individually attended space.

These conclusions were based on eye movement studies in complete darkness carried out within an array that covers an entire horizontal range of 100° (± 50°; Karnath & Fetter, 1995; Karnath, Fetter, & Dichgans, 1996; cf. also Karnath, 1997). These studies included 5 respectively 3 neglect patients with normal visual fields predominately due to right hemisphere stroke (3 of them due to a tumour) and 5 respectively 10 healthy neurological control patients. The investigations were carried out in the subacute stage (48 respectively 25 days). In clear contrast to former reports, both studies revealed a symmetrical bell-shaped distribution with a maximum around 15° on the right side of the mid-sagittal body axis in patients with spatial neglect, but no continuously increasing gradient of saccadic eye movements from the left to the right side of space. Contrary to previous predictions, neglect patients showed a quasi "normal" distribution of exploratory search towards both sides of the array in relation to their rightward rotated egocentric mid-sagittal body axis.

In order to strengthen this conclusion as well as to test for the impact of display size, the same group conducted the first study on visual exploration in its natural course, i.e. their patients were allowed to freely move the eyes *and* the head (cf. Chapter 2.3.1). Under normal room light conditions, patients had to search for a (non-existing) target letter within a large array covering 280° of visual angle in the horizontal and 100° in the vertical plane (Karnath et al., 1998). The patient groups consisted of 4 patients with mere spatial neglect due to right-sided lesions (mean time since lesion: 2.4 months) as well as 10 control subjects without the disorder, including 4 patients with right hemisphere stroke and no neglect. In clear contrast to previous results on restricted search performance in light (Behrmann et al., 1997), neglect patients showed mean horizontal gaze positions located far away from the rightmost end of the display, namely around 41° as well as a bell-shaped distribution of visual exploratory movements. Compared to controls, the variability of gaze movements was only reduced in the horizontal but not in the vertical dimension. Obviously, patients with spatial neglect directed the eyes and the head symmetrically around a deviated centre of exploration, however within a smaller horizontal range than control patients without the disorder had done. More generally it was assumed, that the co-ordination of eye and head movements in patients with spatial neglect resembles the pattern reported for healthy subjects, namely hypometric head movements accompanied by additional shifts of eye-in-head position when orienting towards eccentric visual targets is required (cf. e.g. Uemura, Arai, & Shimazaki, 1980). The results were interpreted in favour of the deviation model (cf. Figure 6), suggesting an ipsilesional rotation of the whole exploratory field as well as a reduced variability around the deviated centre of visual exploration. In line with these assumptions, a further study revealed that patients with spatial neglect -like brain injured and healthy subjects without the disorder- direct voluntary saccades equally towards the right and the left side during unrestricted, free exploratory search (Niemeier & Karnath, 2000; cf. also Sprenger et al., 2002).

More recently, Sprenger and colleagues (2002) recorded eye movements within an array of 30° of horizontal extent, i.e. comparable to the study of Behrmann et al. (1997) and Hornak (1992). Beyond healthy controls and recovered patients, the study included 5 patients with chronic neglect due to right hemispheric lesions. Detailed information about time since stroke was not given, but symptom onset in the whole group (including recovered patients) ranged between 10 days and 2 years. These patients had to detect one, six, or eight targets of different colour or shape among three different displays consisting of 40, 60, or 80 items. Even though the slope of the distribution of eye movements showed a gradient from left to right, it reached its maximum already at about 13° on the ipsilesional, right side, i.e. again far away from the rightmost end of the stimulus display. Moreover, after reaching this level, eye movements showed a steep decrease towards the most eccentric ipsilesional positions independently of item density (cf. their Figure 3C). According to Sprenger et al. (2002), the horizontal distribution thus seems to mimic a left-right gradient only if the central 20° of eccentricity are investigated. In contrast, measures of gaze using arrays that cover the whole field of exploration are thought to result in the bell-shaped distribution as proposed by Karnath and colleagues (see above).

Beyond the focus on the "centre of exploration", other studies had mainly concentrated on saccadic impairments, i.e. reduced latencies or amplitudes towards contralateral space (Girotti, Casazza, Musicco, & Avanzini, 1983; Heide & Kömpf, 1998). In patients with spatial neglect, reflexive saccades towards suddenly appearing targets on the contralesional, usually left side, show direction-specific deficits. Girotti and co-workers (1983) reported on hypometric contralesional saccades with increased reaction times when neglect patients were confronted with unpredicted stimuli at randomised positions on the left or right side. Moreover, saccadic responses towards 25 percent of targets presented on the side contralateral to the lesion were missed. In contrast, voluntary eye movements measured during free exploration in an unrestricted array (see above) showed reduced amplitudes in *all* directions but no specific impairment towards contralesional space, neither in light nor in complete darkness (Karnath et al., 1996; Niemeier & Karnath, 2000). Like subjects without the disorder, patients with spatial neglect direct their voluntary gaze movements equally towards the right and the left side. Moreover, neither the duration of fixation nor the number of contralateral saccades is altered compared to subjects without spatial neglect (Niemeier & Karnath, 2000; see also Husain et al., 2001).

Further, some authors focussed on recursive search behaviour in light (Behrmann et al., 1997; Husain et al., 2001; Mannan et al., 2005; Zihl & Hebel, 1997) or additionally when patients were blindfolded (Olk & Harvey, 2006). Zihl and Hebel (1997) attributed this phenomenon, which is determined by multiple re-fixations, to deficits in working memory for target locations across saccades. Accordingly, present findings were mainly interpreted as failure to update the representation of space, exacerbating spatial neglect and being associated with but not causative for the disorder (see also Chapter 2.1.3). In addition, unsystematic eye movement pattern have been repeatedly reported to constitute an important component of active visual search behaviour in patients with spatial neglect (Chédru et al., 1973; Sprenger et al, 2002).

2.3.3 *Task-specific effects in visual search*

As already introduced in the previous chapter, studies on exploratory search may differ for example with respect to display size, stimulus character, and lightning condition (Chapter 2.3.2). These "task-specific" effects are thus just addressed briefly in this section.

In line with other reports, Husain and Kennard (1997) showed that increasing the discriminability of targets and distractors facilitates visual search performance in patients with spatial neglect by means of speed and efficiency of target detection (see also De Renzi, Gentilini, Faglioni, & Barbieri, 1989; Kaplan, Verfaellie, Meadows, Caplan, Pessin, & De Witt, 1991; Kartsounis & Findley, 1994; Mark, Kooistra, & Heilman, 1988; Rapcsak, Verfaellie, Fleet, & Heilman, 1989). When patients were asked to search a dense clustered array, the degree of contralesional neglect is often enhanced compared to a non-clustered scene. Further, the bias in exploratory visual search was found to be more pronounced in light compared to complete darkness (cf. e.g. Hornak, 1992 versus Karnath et al., 1998). However, this conclusion is based on different task requirements, recording techniques and -most important- on different patient groups. To date, there is no direct comparison on the performances in light compared to darkness within the same patient group, even though it has been shown that the degree of spatial neglect varies between patients as well as within the same individual depending on task and stimuli characteristics (e.g. Mannan et al., 2005).

Karnath and Niemeier (2002) analysed task-dependent effects on the spontaneous visual exploratory behaviour in patients with spatial neglect. When these patients were asked to allocate their attention to the entire space (i.e. within an area of ±140°), all of them completely neglected the contralesional side and spontaneously explored only the ipsilesional hemispace. However, in a subsequent condition using a post-hoc selected segment on the right periphery, in which no left-right asymmetry was detected in the first condition, the same patients ignored the contralesional side when the task was to concentrate the attention only on this specific section. These results demonstrated that –corresponding to changing task demands- the brain continuously organises and reorganises its representation of the same physical stimulus, favouring instead of a static model a more dynamic view of the subjects' representation of the multimodal egocentric reference frames (Karnath & Niemeier, 2002).

2.3.4 Considerations on the time course of active visual search behaviour

Numerous studies on recovery rates as defined by omission rates in standardised clinical tasks have been conducted in patients with spatial neglect (cf. Chapter 2.1.2). In contrast, eye-recording studies have not addressed the course of recovery by means of e.g. follow-up measures of the patients' exploratory visual search behaviour so far. Information about persisting, subtle, or recovered eye movement pattern in spatial neglect thus is confined to previous one-time examinations on visual search, carried out in subacute or chronic patients. Correspondingly, some of the studies cited in Chapter 2.3.3 that were predominantly carried out in patients beyond the acute phase, implicitly provide information on the degree of rightward deviation, and thus on the centre of exploration in later stages of the stroke.

Sprenger and colleagues (2002) recorded eye movements once in 5 chronic as well as 5 recovered patients within a horizontal range of 30° (cf. Chapter 2.3.2 for details on the tasks used). While the mean bias of exploratory eye movements amount to plus 13° in the group with chronic symptoms, patients with recovered neglect showed a flat distribution of search pattern, which was comparable to the performance of healthy control subjects without the disorder. A study by Pflugshaupt et al. (2004), carried out 11 months post stroke in 8 recovered neglect patients, even revealed a small bias of eye movements towards the contralateral, left side during time constraint, exploratory search of everyday scenes. In chronic patients, Behrmann et al. (1997) found a deviation of about 18° to the ipsilesional, right side on average 12.7 months post stroke. These studies clearly point to differences in the exploratory search behaviour of chronic and recovered patients. However, information about acute search performance and thus about the intraindividual development of this kind of symptoms in patients with spatial neglect is missed. Further, such findings may argue for a relation between the performance in clinical neglect tasks and a bias of active exploratory search.

Beyond, some single case studies on active search patterns in patients with either recovered or both, chronic and recovered neglect focussed on residual aberrant search pattern, such as starting positions on the ipsilesional side, direction of the first saccade, or repetitive visual search behaviour, but not on a bias of horizontal gaze positions (Harvey, Olk, Muir, & Gilchrist, 2002; Olk & Harvey, 2006; Olk, Harvey, & Gilchrist, 2002). Olk and colleagues (2002) studied saccadic eye movements 13 weeks post stroke in a single case with residual, clinically defined neglect symptoms. The authors concluded that eye movement patterns are far more susceptible to subtle spatial impairments than standardised neglect assessment, and thus can provide a sensitive instrument to uncover the extent of neglect recovery.

2.4 Clinical Aspects of "Passive" Eye and Head Orientation in Stroke

Despite the investigation of neglect symptoms apparent in neglect patients' "active" skills, for example during visual exploration (cf. Chapter 2.3.2), observations on their "passive" behaviour have been made. Some review articles reported that patients with spatial neglect may spontaneously deviate their eyes and the head towards the ipsilesional side (Bisiach & Vallar, 1988; Fink & Heide, 2004; Friedland & Weinstein, 1977; Heilman et al., 1984; Parton, Malhotra, & Husain, 2004). In particular, this behaviour seems to be obvious in the acute stage of the stroke and might be observed in the daily clinical context on the ward when the patients just rest in the bed or (wheel) chair. Importantly, this assumption is based on clinical experience and upon few observational studies, i.e. to date no study directly measured the individual degree of passive eye and head deviation in patients with and without spatial neglect, thus preventing useful quantitative comparisons (see Chapter 2.4.3).

Importantly, a *passive* deviation of the eye and the head has to be differentiated from the so-called "magnetic gaze attraction", which was previously described by Cohn (1972) in patients with hemianopia during visual field assessment and which was considered as "an oculomotor analog of [visual] extinction" (Friedland & Weinstein, 1977, p. 6). This behaviour is defined as "the occurrence of spontaneous, automatic shifts of the patients' eyes toward the side ipsilateral to the lesion, as soon as the arms of the examiner were outstretched and before the administration of the stimuli" (Gainotti, D'Erme, & Bartolomeo, 1991, p. 1084). Thus, the phenomenon of "magnetic gaze attraction" is not comparable to a conjugate bias of the eyes (and the head) in patients' at rest. Crucially, the use of standard neurological confrontation technique or the presentation of bilateral stimuli to test for visual extinction, i.e. the presence of the left respectively the right hand in the visual fields even if the assessment has not been started by actually moving the fingers, directly interferes with the patients' passive behaviour that could only be observed at rest. This spontaneous resting situation, namely when patients' "do nothing", is a primary scope of the present work.

2.4.1 *Impact of eye and head position on the diagnosis of stroke*

Since a spontaneous horizontal deviation of the eyes at rest is a striking symptom in acute stroke, its evaluation is part of different clinical stroke scales, including e.g. the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989; Goldstein, Bertels, & Davis, 1989), the European Stroke Scale (Hantson et al., 1994), the Orgogozo Stroke Scale (Orgogozo et al., 1983), or the Scandinavian Stroke Scale (Multicenter trial, 1985, 1987).

Such scales seek to quantify different aspects of function within the framework of the World Health Organization hierarchy of impairment, disability, and handicap (World Health Organization, 1980). Principally, these scales provide a scoring system for specific manifestations of cerebrovascular disease, such as consciousness, hemiparesis, reflex abnormalities, gaze, etc. Scoring is simple and offers a multiple choice based assessment. In the acute phase of the stroke, an assessment of various neurological impairments is relevant for both diagnosis and prognosis (Allen, 1984; Oxbury, Greenhall, & Grainger, 1975), while in the chronic phase it is considered to be less important or even to underestimate the impact of impairments on functional outcome (De Haan, Horn, Limburg, Van der Meulen, & Bossuyt, 1993; Van Gijn, 1992). One potential weakness of these scales is their greater emphasis on deficits associated with left hemisphere lesions than on those related to right-sided stroke (Brott et al., 1989; Fink et al,. 2002; Krieger, Demchuk, Kasner, Jauss, & Hantson, 1999; Woo et al., 1999).

In scales addressing the patients "eye/gaze deviation", the terminology is rather vaguely used and is seldom accompanied by an observation of the patients' head position (like in observational studies as well, see Chapter 2.4.3). Moreover, there are marked differences in the criteria provided to assess the symptom. The NIHSS subdivide its item "Best Gaze" into (i) normal, (ii) partial gaze palsy, i.e. gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present, and (iii) forced deviation, or total gaze paresis that cannot be overcome by the oculocephalic manoeuvre[1]. If a conjugate eye deviation is observed that can be overcome by voluntary or reflexive activity, the diagnosis of "partial gaze palsy" is recommended (Brott et al., 1989). In contrast, the Orgogozo Stroke Scale (Orgogozo et al., 1983) includes the item "Eyes and head shift" consisting of (i) forced, (ii)

[1] Oculocephalic manoeuvre: This technique is valuable for assessing vestibular function. If the vestibulo-ocular system is functioning, a passive rotation of the patient's head while instructing him/her to look straight ahead should result in a slow eye movement towards the opposite direction of the passively provoked head movement.

gaze failure, and (iii) none shift, while the Canadian Neurological Scale contains neither an item on eye nor on head orientation (Cote, Battista, Wolfson, Boucher, Adam, & Hachinski, 1986; Cote, Hachinski, Shurvell, Norris, & Wolfson, 1989).

It is particularly important to note that stroke scales do not observe the patients' eye position to detect signs of spatial neglect. While the patients' "gaze" is determined separately, some scales additionally address "spatial neglect" by means of line bisection and anosognosia (Hemispheric Stroke Scale; Adams, Meador, Sethi, Grotta, & Thomson, 1987) or in terms of extinction and personal inattention (NIHSS; Brott et al., 1989). Crucially, these symptoms may co-occur or may be associated with spatial neglect but they are not specific to the disorder (see Chapter 2.1.3; also Hier, Mondlock, & Caplan, 1983a; Karnath, Himmelbach, & Küker, 2003a; Milner, 1997; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992). Even a double dissociation has been reported for spatial neglect and anosognosia (Bisiach et al., 1986) respectively line bisection (Halligan & Marshall, 1992; Marshall & Halligan, 1995). To summarise, while the so-called "neglect" items in stroke scales are no valid parameters to measure the characteristic symptoms of spatial neglect, the patients' "gaze" positions do not play a role in the diagnosis of the disorder within these clinical scoring systems to date.

2.4.2 Aetiology, definition, incidence, and hemispheric dominance

Following hemispheric stroke, a deviation of the eyes is found almost exclusively towards the *ipsilesional* side. In these cases, it is often accompanied by a deviation of the head towards the same hemispace (Goodwin & Kansu, 1986; Tijssen, 1988). Consequently, there are only rare cases of contralateral eye deviation following stroke (Messe & Cucchiara, 2003; Pessin, Adelman, Prager, Lathi, & Lange, 1981; Tijssen, 1994). Tijssen (1994) for example, reported an incidence of about 3.8 percent in a study of 133 patients with acute cerebral lesions. All of these patients had intracerebral haemorrhages and showed a shift of midline structures on CT scans as well as clinical signs of rostral brain stem dysfunction. The author concluded that the phenomenon of the so-called "wrong-way eyes" is always associated with haemorrhagic stroke, mostly in the thalamus. Beyond supratentorial lesions, a lateralised orientation of the eyes has also been observed for example following epileptic seizures (cf. e.g. Thurston, Leigh, & Osorio, 1985; Tusa, Kaplan, Hain, & Naidu, 1990), brainstem (e.g. Bogousslavsky, 1989; Solomon, Galetta, & Liu, 1995), or cerebellar lesion (e.g. Mossman & Halmagyi, 1997). Pontine lesions, for example, may lead to horizontal oculomotoric paresis, mesencephalic injury causes vertical paresis of the oculomotoric system, while a "Blickrichtungsnystagmus" indicates brain stem or cerebellum dysfunction.

The scope of the present work is confined to unilateral cerebral brain lesions due to first ever stroke, leading to a conjugate eye/head deviation towards the ipsilesional side. In this context, it has to be noted that patients with spatial neglect mainly suffer from infarction of the middle cerebral artery (MCA) or from subcortical lesions e.g. due to basal ganglia or thalamic stroke (cf. Chapter 2.1.4). Regarding unilateral cerebral lesions, Jean Louis Prévost reported already in 1865 that "in all cases [of acute hemiplegia following unilateral stroke] I have observed, the two ocular axes were always deviated to the side opposite the paralysis, thus the two eyes looked towards the damaged hemisphere" (Prévost 1865, p. 649). Since then, only a few studies investigated this symptom in patients with unilateral cerebral stroke. Some of them were predominantly carried out to study the deviation of the eyes following cerebral stroke (De Renzi, Colombo, Faglioni, & Gibertoni, 1982; Kömpf & Gmeiner 1989; Mohr, Rubinstein, Kase, Price, Wolf, Nichols, & Tatemich, 1984; Okinaka, Toyokura, Nakamura, Kuroiwa, & Tsubaki, 1952; Prévost 1868; Ringman, Saver, Woolson, & Adams, 2005; Simon, Morgan, Pexman, Hill, & Buchan, 2003; Steiner & Melamed 1984; Tijssen, 1988), while others mainly focussed on specific subgroups and/or clinical aspects (Aring & Meritt, 1935; Chung et al., 2000; Horowitz & Tuhrim, 1997; Kelley & Kovacs, 1986; Lawrence et al., 2001; Walshe, Davis, & Fisher, 1977).

These studies differ in terms of terminology (gaze paresis, gaze or eye deviation, gaze palsy) and observational techniques used to define the presence or absence of eye (and partial of head) deviation, preventing a direct comparison of results on this topic. Comparable to the procedures suggested in stroke scales (cf. Chapter 2.4.1), some authors focussed solely on the patients' eye-in-head positions (Mohr et al., 1984; Okinaka et al., 1952; Ringman et al., 2005; Simon et al., 2003; Steiner & Melamed, 1984), while others regarded the orientation of the eyes and/or the head (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Prévost, 1868; Tijssen, 1988). Moreover, some studies used a response to external requirements such as eye movements to verbal and sensory contralateral stimuli (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Ringman et al., 2005; Tijssen, 1988) to diagnose the presence and the severity of the symptom, while others did not report the procedure used (Mohr et al., 1984; Okinaka et al., 1952; Steiner & Melamed, 1984). Apart from Simon et al. (2003) who determined eye deviation directly on CT scans (but did not account for spatial neglect), it thus remains open how many studies just observed the *spontaneous* orientation of the eyes (and/or head) without external interference by the examiners as it is intended by the present work.

Neurological textbooks often include statements saying that stroke patients usually steer the eyes towards the side of the brain lesion (e.g. Poeck, 1987, p. 70: "Der Kranke blickt seinen Herd an"). According to this theorem, it appears as if this sign occurs after both, right-sided as well as left-sided stroke. In the upper mentioned observational studies, the prevalence rate ranges between 13.9 percent (*n* = 330 patients; Ringman et al., 2005) and 50 percent (*n* = 48, Kömpf & Gmeiner, 1989) independent from the side of the lesion. However, like spatial neglect (cf. Chapter 2.1.2) also a deviation of the eyes (and the head) seems to show a right hemisphere dominance. De Renzi and co-workers (1982) reported that "gaze paresis" was more frequent in patients with right compared to left cerebral lesions (ratio 60/40). Yet, these findings were solely based on clinical data and the majority of cases had no imaging based verification of lesion locations. Subsequently, the right hemisphere dominance for an ipsilesional eye deviation was confirmed by a number of observational studies that validated the patients' brain injury by CT or MRT scans (Kömpf & Gmeiner, 1989; Ringman et al., 2005; Tijssen, 1988). Summarising the results of these three studies, the mean ratio between right and left hemisphere patients is 65 to 35. A hemispheric asymmetry was also reported for severity (De Renzi et al., 1982; Simon et al., 2003) and persistence (De Renzi et al., 1982; Tijssen, 1988; cf. Chapter 2.4.4) of symptoms in patients with right cerebral lesions.

An insightful study by Meador and co-workers (1989) investigated the dominance of the right hemisphere for gaze orientation in 90 patients with epilepsy using the intracarotid sodium amobarbital procedure (ISAP), known as "Wada test" (Wada & Rasmussen, 1960). Gaze deviation was more frequent after right-sided intracarotid injection and persisted for several minutes in some cases. After left-sided injection, 32 percent of the patients showed an ipsilesional deviation, while 60 percent had a gaze deviation after application on the right side. The authors interpreted the results within the scope of a functional asymmetry in gaze mechanisms between the two hemispheres. They argued that although gaze is primarily a motor phenomenon and expresses mainly intentional mechanisms, attentional and intentional mechanisms appear to function interactively.

2.4.3 Ambiguous findings on its relation to spatial neglect

From the few studies on unilateral cerebral stroke patients (see Chapter 2.4.2), four have particularly addressed the relationship between a deviation of the eyes/head and spatial neglect (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Ringman et al., 2005; Tijssen, 1988). Searching for clinically observable changes of spontaneous eye (and partly head) position, some authors argued for a close relation between spatial neglect and an ipsilesional deviation of the eyes/head (De Renzi et al., 1982; Ringman et al., 2005; Tijssen, 1988), while others rejected it (Kömpf & Gmeiner, 1989). However, none of these studies had directly measured the individual degree of eye and/or head deviation, even though it has been shown that observational determinations of eye positions have a poor interobserver agreement (Edwards, Chen, & Diringer, 1995).

A relation between spatial neglect and a horizontal deviation of the eyes (and the head) was not noted until 1982 when De Renzi and co-workers investigated both symptoms in a subsample of patients with initially "gaze paresis" (n = 44/120). In a minority of the 120 patients, lesions were validated by structural CT and could be controlled for the presence of brain stem lesions, former strokes, tumours, etc. Based on clinical data and partly on CT scans, 10 of these patients were diagnosed to suffer from a left hemisphere lesion and 34 from a right-sided stroke. With a delay of 14 to 18 days after stroke, neglect symptoms as diagnosed by coping, cancellation, reading, or pointing were found in 3 patients with left-sided lesions and 23 patients with right hemisphere stroke. The authors concluded that the asymmetric occurrence of eye and head deviation has implications for the interpretation of spatial neglect, namely that an imbalance in oculomotor orientation underlies hemi-inattention (cf. Chapter 2.2.1; Kinsbourne, 1993). However, at the time of diagnosis, which took place on average more than 2 weeks post stroke, spatial neglect was also observed in patients who had already recovered from gaze deviation (n = 15). In this group, the relation between an eye and head deviation and neglect remained open. Importantly, since De Renzi et al. (1982) had not investigated patients without eye and head deviation for spatial neglect, the authors could not answer the question if neglect may also occur in patients who had never shown a gaze deviation.

In contrast to De Renzi et al. (1982) a study by Tijssen (1988) claimed to examine eye deviation and spatial neglect at the first day after admission. The sample consisted of 74 patients with ipsilesional eye/head deviation mainly due to hemispheric lesions, including patients with tumours, encephalitis, brainstem, or cerebellar lesions. Like Ringman et al. 's study (2005, see below), this examination comprised none of the tests that have been reported to be appropriate to diagnose spatial neglect (cf. Chapter 2.1.3). Actually, Tijssen (1988) investigated visual and tactile extinction, asomatognosia, and anosognosia. These symptoms were reported in 98 percent of the right hemisphere group (n = 42/43) and in 3 patients with left hemisphere lesions (entire sample size not given, < 27). The author concluded that spatial neglect seems to play an important role for the occurrence of an ipsilesional shift of the eyes and the head. As De Renzi et al. (1982), also Tijssen (1988) did not systematically investigate patients *without* eye/head deviation for spatial neglect. Moreover, since Tijssen (1988) and Ringman et al. (2005) did not examine the syndrome but accompanied disorders (cf. Chapter 2.4.1), both studies obtained no information on the patients' neglect behaviour in the very acute stage of the stroke.

Kömpf and Gmeiner (1989) investigated a sample of 24 patients with an ipsilesional eye and/or head deviation and 24 patients without these symptoms following left or right hemisphere lesions as defined by CT scans. Spatial neglect was diagnosed by six different tasks, including for example cancellation, copying, reading, and line bisection. Due to the severity of language impairment, none of these tests could be performed in the left hemisphere group (*n* = 20), which thus was excluded from further analysis. From the remaining patients with right hemisphere stroke, 22 patients were investigated for spatial neglect "when neurological status allowed this" (Kömpf & Gmeiner, 1989, p. 50). In 9 patients both, spatial neglect and gaze deviation were present. Three patients demonstrated spatial neglect but no deviation of the eyes or the head and one single patient showed a discrete gaze shift without neglect symptoms. A further 9 patients had no symptoms at all. The authors rejected previous assumptions that neglect is due to oculomotor imbalance (De Renzi et al., 1982) or may be represented by a gaze deviation, as it has been mentioned in a number of review articles (cf. Chapter 2.4). In contrast, Kömpf and Gmeiner (1989) argued for intertwined but separate underlying mechanisms as well as for a dissociation of both symptoms. The later was based on their observation of spatial neglect in patients without an ipsilesional gaze shift as well as of one single case showing the reverse, i.e. no neglect but a discrete deviation of gaze orientation.

Recently, Ringman et al. (2005) conducted a post-hoc analysis on data from a previous multicentre study (cf. Ringman, Saver, Woolson, Clarke, & Adams, 2004). As Tijssen (1988), they included none of the traditional tests to diagnose spatial neglect. According to the NIH Stroke Scale definition (cf. Chapter 2.4.1), the authors determined eye deviation as well as tactile extinction and the performance in a *verbal* description of a complex picture scene (Cooky Theft Picture, Goodglass & Kaplan, 1983). Within the entire sample of 1161 patients from their first study, 4.6 percent (*n* = 53) showed both "complete neglect at presentation [and] some GD" (Ringman et al., 2005; p. 1662). Regarding the subset of patients with "neglect" (*n* = 88), 60.2 percent of those patients with tactile extinction and erroneous verbal description showed a deviation of the eyes towards the lesion side. Crucially, the authors determined the frequency of eye deviation only in patients with "neglect" but did not report how many patients without deficits in the applied tasks showed the same behaviour. Ringman et al. (2005) thus did not uncover the relation between a horizontal eye deviation and spatial neglect as introduced by their article title, but confirmed that a horizontal eye deviation predominantly occurs after right hemisphere lesions (see Chapter 2.4.2 for details).

2.4.4 Clinical findings on the course of recovery

A review by Fink and Heide (2004) stated that patients with spatial neglect may additionally exhibit a conjugate gaze deviation towards the lesion side, which usually recovers fast compared to the neglect syndrome. This conclusion, however, is just based on clinical experience. Although some previous mentioned studies followed the patients' spontaneous eye position by clinical inspection in the acute and subacute stage (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Steiner & Melamed, 1984; Tijssen, 1988), the progress of eye orientation was not related to the co-occurrence of spatial neglect so far.

Such reports that solely give the average duration of eye deviation regardless of spatial neglect, vary markedly from a few minutes (Okinaka et al., 1952) or hours (Okinaka et al., 1952; Steiner & Melamed, 1984) to 12.5 days (De Renzi et al., 1982) and 18.5 days (Kömpf & Gmeiner, 1989). Steiner and Melamed (1984) concluded that a deviation of the eyes following unilateral cerebral stroke is of brief duration and lasts in most cases (90 %) no longer than 5 days. Already 57 percent of their sample had recovered within 48 hours. Usually, these studies found a longer mean duration following right compared to left hemispheric lesions. After left-sided stroke the presence of clinically observed eye deviation ranges from 4.5 (Tijssen, 1988) to 8.6 days (De Renzi et al., 1982), in right hemisphere stroke between 14.9 (De Renzi et al., 1982) and 17.6 days (Tijssen, 1988). Three months post stroke, Ringman et al. (2005) found a spontaneous deviation of the eyes neither in left nor in right hemisphere patients. However, the authors did not report on the recovery of spatial neglect in these groups. The study of De Renzi et al. (1982) investigated the co-occurrence of spatial neglect once between day 14 and 18. At this time, all patients with a clinically defined eye or head deviation showed neglect symptoms. However, the disorder was also found in some of those patients whose initial eye/head deviation had already recovered, but who were not previously investigated for spatial neglect. If spatial neglect in the latter group was already present at stroke onset, these data suggest that a deviation of the eyes or the head may recover even if other clinical neglect symptoms, as for example measured by clinical tasks, persist.

To summarise, two observational studies (De Renzi et al., 1982; Kömpf & Gmeiner, 1989) actually investigated spatial neglect and its relation to the patients' eye position, while others mainly addressed extinction. These two observations came to opposite conclusions, favouring respectively rejecting a direct relationship between neglect and a biased eye/head orientation. Further, none of these studies investigated the course of recovery of both symptoms. In contrast to the characteristic search bias towards the ipsilesional side (cf. Chapter 2.1.1 and 2.3.2), it thus remains open whether the spontaneous deviation of the eyes and the head is a definite sign of spatial neglect as well. The lack of studies on the relation between spatial neglect and a passive deviation of the eyes and the head might explain why systematic changes of the patients' spontaneous spatial orientation does not play a mandatory role in the today's diagnosis of spatial neglect (see Chapter 2.4.1).

3 SCOPE AND RESEARCH QUESTIONS

The main objective of the present work is to investigate whether there is a direct and systematic relation between a spontaneous eye and head deviation and spatial neglect in patients with unilateral cerebral lesions regarding acute phases as well as the course of recovery.

Previous research revealed that the most characteristic impairment of patients with spatial neglect is a bias of "active" exploratory movements towards the side of the brain lesion. This ipsilesional deviation in search performance is highly specific to spatial neglect both, in light as well as in complete darkness and is not observed in other stroke patients (cf. Chapters 2.1.1 and 2.3.2 ff). In contrast, quantitative measures of the patients' spontaneous, "passive" resting behaviour, i.e. independently of any external requirements, have been conducted neither with nor without a visual context. To date, no study exists that could sufficiently answer the question whether a spontaneous ipsilesional deviation of the eyes and the head is *specific* to patients with spatial neglect or whether it may also occur in other stroke patients with unilateral cerebral lesions (cf. Chapter 2.4.3). Moreover, it is a widely held belief that acute stroke patients with hemispheric lesions -in general- direct their eyes towards the lesion side (cf. Chapter 2.4.1 and Chapter 2.4.2).

Current knowledge about a potential relation of spatial neglect and a passive eye and head deviation is based on clinical observations on the presence or absence of the latter but not on quantitative investigations that would allow for an appropriate statistical analysis and comparison to other groups without the disorder. Beyond, there are further methodological constraints such as sample selection, tests used to diagnose spatial neglect, and time of assessment that do not allow for convincing conclusions. To date, a direct relation between the patient's passive eye and head (= gaze) orientation and spatial neglect thus remains open for both, the acute phase as well as for the development over time (cf. Chapter 2.4.3 & 2.4.4). Moreover, regarding the course of recovery as mentioned by review articles and by clinical observations, it is assumed that a putative passive eye and head deviation at rest recovers fast in neglect patients (cf. Chapter 2.4.4). This view may favour distinct symptoms as well as a dissociation rather than an association between both phenomena.

The present work thus seeks to gain insight into the specificity and relation of a passive gaze orientation to spatial neglect in acute stages as well in the course of recovery. For this purpose, eye-recording methods were implemented that allow for a precise measurement of the patients' eye and head orientation as well as for subsequent quantitative analyses between patients with and without the disorder in three sequential studies that will be presented and discussed in the following chapter.

The *first study* aimed to clarify if spatial neglect is predominantly linked with active behaviour or if it is in fact obvious without any explicit requirements, namely in the patients' spontaneous resting position as suggested by clinical observations. Thus, we implemented a "resting condition" without any active requirements and recorded the mean gaze, eye-in-head, and head-on-trunk positions of right hemisphere stroke patients with spatial neglect in order to compare them to right hemisphere stroke patients without any signs of the disorder. Using the scleral search coil, an investigation of eye and head orientation was feasible both, in light and without any visual context, thus allowing to gain insight into the resting behaviour of stroke patients in complete darkness.

Based on the findings of Study 1 the *second study* allowed for investigating an unselected sample of very acute patients directly at the bedside. We asked whether a spontaneous deviation of the eyes and the head is a specific sign of spatial neglect and/or right hemisphere lesion, or whether it also occurs regularly after left hemisphere stroke. We measured the passive behaviour of patients with very acute left and right hemisphere stroke as soon as possible after admission to our stroke unit by recording eye and head position with a mobile and easy to apply EOG system under normal room light conditions.

The *third study* finally investigated the development of spontaneous orienting at rest and active exploration in patients with spatial neglect over a period of 10 months. We sought to uncover if a deviation of eye and head during "active" search and at "passive" rest develops in parallel or if these are independent, distinct symptoms, that may even show a dissociation over time. The follow-up study thus asked whether the orientational bias of eyes and head at rest and during visual exploration are related or if these variables show an independent development in the course of recovery. As in the first study, we used the magnetic search coil system allowing for investigating the patients' behaviour under normal room light conditions as well as in complete darkness.

4 EXPERIMENTAL STUDIES

This chapter gives an overview of the common neurological characteristics of the stroke patients investigated in the present studies as well as the neurological examination and neuropsychological test procedures applied. Subsequently, it describes the methods and results of each of the three studies in detail and discusses the findings on the relationship between spatial neglect and a spontaneous deviation of the eyes and the head. Additional information on each study is given in its corresponding chapter.

4.1 Clinical Test and Patient Characteristics

4.1.1 Inclusion criteria

Strict inclusion criteria were applied. Since patients with spatial neglect show unique symptoms that could not be observed in any other group of stroke patients (cf. Chapter 2.1.1), however even small sample sizes ($n \geq 5$) are feasible to uncover potential differences to patients without the disorder. All patients with brain lesions had to have a circumscribed unilateral ischaemic first-ever stroke or haemorrhage, verified by magnetic resonance imaging (MRI), i.e. diffusion-weighted imaging (DWI) and T2-weighted fluid-attenuated inversion recovery (FLAIR), and/or by computed tomography (CT). Patients with diffuse or bilateral brain lesions, or with lesions in the brainstem or the cerebellum were excluded. The same accounted to patients with previous brain lesions, cerebral atrophy, tumours, or other confounding neurological diseases (such as parkinsonism, dementia, etc.) and to those in whom imaging revealed no brain injury. None of the stroke patients had a history of vestibular or oculomotor abnormalities.

4.1.2 Patient groups

Stroke patients were separated by standardised clinical neglect tests described below into (i) stroke patients with spatial neglect (NEG) and (ii) stroke patients who also suffered from acute hemispheric lesions but did not show any symptoms of spatial neglect (RBD, right hemisphere control patients; LBD, left hemisphere control patients). In addition, each study included (iii) neurological patients without brain lesions (NBD), who had no history of cerebrovascular or psychiatric diseases but suffered from peripheral neurological disorders such as herniated vertebral discs, etc. All patients gave their written informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki (see e.g. World Medical Association, 2002; for different issues please see www.wma.net).

4.1.3 Neurological investigation

Visual field defects (i.e. hemianopia, quadrantanopia, scotoma) were tested by the common confrontation testing. Somatosensory loss and severity of paresis were assessed by standard neurological examination. The latter was scored with the usual clinical ordinal scale, where '0' represents no trace of movement and '5' normal movement. Further testing included ocular motility (smooth pursuit, saccadic eye movements), pupil reactivity to light, oculocephalic manoeuvre, and head motility. The oculocephalic manoeuvre was carried out by passively rotating the patients' head towards the anatomically defined limits on the left and right side, while instructing the patients to look straight ahead at the examiner. It was considered normal if the passive rotation resulted in a slow eye movement towards the opposite direction of the head movement. In all acute stroke patients that participated in Study 2, the level of consciousness was determined by the Glasgow Coma Scale (Jennett & Teasdale, 1977). Further study-specific information is provided in the corresponding chapters.

4.1.4 Diagnosis of spatial neglect

Each stroke patient was investigated for spatial neglect with the following clinical neglect tests (cf. Figure 2): the "Letter cancellation" task (Weintraub & Mesulam, 1985), the "Bells test" (Gauthier et al., 1989), and a copying task (Johannsen & Karnath, 2004). In the second study, we additionally applied the "Albert's test" (Albert, 1973). Spatial neglect was diagnosed when the patient fulfilled the criterion in at least two of these tests.

Patients sat comfortable in a chair, a sick bed, or a wheelchair in front of a table across the examiner. Successively, each test sheet (DIN A4 landscape format) was taped to the desk such that it was in line with the patients' mid-sagittal body axis. Moving the test sheet was not permitted. Patients were told that there were no time constraints and that they should announce when they were satisfied with their performance. Before starting, the patients were provided with the task-specific instructions given below. When the patients stopped performing, they were asked three times if they had searched the whole sheet respectively had copied all objects. When the patients approved this three times, the test sheet was removed and replaced by the next task. Whenever patients became tired, testing was terminated and finished later. Usually, the following tests were performed within one session.

Letter Cancellation Task (Weintraub & Mesulam, 1985). Sixty target letters 'A' are distributed amid distractors on a horizontally oriented 21 x 29.7 cm sheet of paper; 30 targets on the right half of the page and 30 on the left. Patients were asked to cancel all of the target letters 'A' on the entire sheet. They were classified as suffering from spatial neglect when more than 4 contralateral located targets were omitted.

Bells Test (Gauthier et al., 1989). The task consists of seven columns each containing 5 targets (bells) as well as 40 distractors evenly distributed over the sheet. Three of the seven columns (= 15 targets) are on the left side of a horizontally oriented 21 x 29.7 cm sheet of paper, one in its middle, and three on its right side (= 15 targets). Again, patients were asked to cancel all of the targets by searching the entire sheet. More than 5 contralateral located target omissions were taken to indicate spatial neglect.

Copying Task (Johannsen & Karnath, 2004). Patients were asked to copy a complex multi-object scene consisting of four figures (a fence, a car, a house, and a tree), two in each half of a horizontally oriented 21 x 29.7 cm sheet of paper. Omission of at least one of the contralateral features of each figure was scored as one; omission of each whole figure was scored as two. One additional point was given when contralateral figures were drawn on the ipsilesional side of the paper sheet. The maximum score was eight. A score higher than one (i.e. more than 12.5 % omissions) was taken to indicate spatial neglect.

Albert's Test (Albert, 1973). The test consists of seven columns of black lines. Three of the seven columns (= 18 targets) are on the left side of a horizontally orientated 21 x 29.7 cm sheet of paper, one column containing 5 targets in its middle, and three columns (= 18 targets) on its right side. Patients again were asked to cancel all targets on the entire test sheet. More than one contralateral located target omission was taken to indicate spatial neglect.

4.1.5 Neglect severity

Percentage omission scores were calculated separately for each patient and for each standardised clinical neglect test (cf. Ferber & Karnath, 2001a). For cancellation tasks, the total number of omissions was divided by the maximum number of targets. For the copying task, the achieved score was divided by the maximum score. Each quotient was multiplied by 100, yielding a percent omission score. Individual severity scores were calculated by averaging all omission scores of each single patient. A high percentage omission score reflects a high number of omissions; a low score indicates fewer omissions.

4.2 Spontaneous Eye and Head Position and its Relation to Spatial Neglect

4.2.1 Introduction

This study investigated if spatial neglect is predominantly linked with active behaviour as it is for example measured by clinical neglect tests or if it is also obvious without any explicit requirements, namely in the patients' spontaneous resting position. Indeed the view that patients with spatial neglect may deviate their eyes and head towards the lesion side was held by some review articles (Bisiach & Vallar, 1988; Friedland & Weinstein, 1977; Heilman et al., 1984; Parton et al., 2004). However, none of the few observational studies carried out on this topic sufficiently answered the question whether a spontaneous ipsilesional deviation of the eyes and the head is *specific* to spatial neglect. Some authors argued for a close relationship between a deviation of eyes and head towards the ipsilesional side and spatial neglect (De Renzi et al., 1982, Tijssen, 1988) while others rejected this assumption (Kömpf & Gmeiner, 1989). Crucially, none of these studies had measured the patients' eye and head positions but all had determined the discrete presence or absence of eye deviation with the naked eye by clinical inspection (cf. Chapter 2.4.3).

We thus invented a resting condition without any active requirements and recorded the mean gaze and head-on-trunk positions under normal room light conditions in neglect patients with right hemispheric first-ever stroke. The results were compared to a control group without any signs of the disorder. Additionally, we were interested in the patients' resting position in the absence of any visual context and its subsequent comparison to their performance in light. For this purpose, we used a set-up that allowed investigating eye and head movements in complete darkness. Finally, this experiment was conducted to find out if the patients' resting position might correspond to their subjective straight ahead position.

Patients without the disorder were expected to show eye and head positions around their mid-sagittal body axis, while in patients with spatial neglect a deviation towards the right side was hypothesised (cf. Chapter 2.2.3, Figure 6). This deviation was assumed to be more pronounced in light compared to a condition without any visual context, i.e. to complete darkness (cf. Chapter 2.3.3). As in healthy subjects, we expected a straight ahead orientation in line with the patients' resting position (cf. Chapter 2.2.3, Figure 6).

4.2.2 Methods

Subjects

We tested 12 consecutively admitted patients with spatial neglect due to right hemispheric first-ever stroke (NEG) verified by MRI and/or CT. They were compared to (i) 6 stroke patients who also suffered from acute right hemispheric lesions but did not show any symptoms of spatial neglect (RBD) as well as to (ii) 6 patients without brain injury (NBD). In the study period, no patient with a left hemispheric stroke and spatial neglect was admitted. Patients had to fulfil the criterion for spatial neglect in at least two of the following clinical tests: the "Letter cancellation" task (Weintraub & Mesulam, 1985), the "Bells test" (Gauthier et al., 1989), and a copying task (Johannsen & Karnath, 2004). RBD patients showed normal behaviour in each clinical neglect tests. None of the patients had a history of vestibular or oculomotor abnormalities. Further, standardised neurological examination of all patients revealed no acute vestibular or oculomotor signs or deficits (e.g. nystagmus), and no visual field defects. Demographic and clinical data as well as lesion locations are given in Table 1. For full details about test procedures and inclusion criteria, please see Chapter 4.1.4.

Apparatus

Using the magnetic field-search technique (Robinson, 1963), gaze and head-on-trunk positions were measured under two experimental conditions, (i) in a spontaneous resting position and (ii) when patients were asked "to look exactly straight ahead". This technique is used for physiological research on the oculomotor system in man and animals (Judge, Richmond, & Chu, 1980). Its high accuracy and bandwidth allows for precise recording of eye and head movements (cf. Chapter 2.3.1). Three orthogonal alternating magnetic fields were generated by three pairs of Helmholtz coils mounted on the outer surface of a cubic frame (diameter 105 cm). Patients sat upright in a wooden chair or wheelchair within the cubic frame such that the head was positioned centrally (see Figure 8). The head could be freely moved while the trunk was immobilised on the chair by a belt and shoulder straps. On the inner surface of the frame, a unitary array of black letters (each 1.8° high) on a white ground was presented to avoid a potential attraction to visual objects in the examination room (left or right wall, items on the wall, borders of the cubic frame, etc). The letters covered a rectangular area of ± 120° left and right of the body's mid-sagittal plane, and of ± 40° above and below the patient's eye level. The room was normally lightened or completely darkened, depending on the experimental condition (see below).

There was no fixation target or any other hint indicating the objective straight ahead position (0°/0°), neither in light nor in darkness. Patients' gaze positions were measured by a 2D scleral search coil lens (Skalar Medical, Delft, The Netherlands) that was adhered on the sclera of the left eye by suction. Head-on-trunk positions were recorded with a further solenoid attached to the patients' foreheads. The sampling rate was 100 Hz. Data were stored on hard disk for off-line analysis. Eye-in-head positions represent the difference between the corresponding gaze and head-on-trunk positions and were determined by multiplying the rotation matrices of gaze positions with the inverse rotation matrices of head-on-trunk positions. Gaze positions represent combined eye-in-head and head-on-trunk positions. Head-on-trunk and gaze co-ordinates 0°/0° were aligned with the patient's mid-sagittal body axis in the horizontal plane and the individual eye level in the sagittal plane. Eye-in-head co-ordinates were head-centred with co-ordinates 0°/0° aligned with the head's mid-sagittal axis at eye level. Positive values thus indicate locations right of these centres, negative values those on the left.

<u>Procedure</u>

<u>Rest condition</u>. The main objective of the present study was to measure the patients' spontaneous orientation of gaze, eye-in-head, and head-on-trunk while "doing nothing", i.e. in a spontaneous resting situation. Before starting, we informed the patients about the search coil technique and "that they will have to perform normal, every-day eye movements to certain places, which will be specified during the experiment". Once the patients were seated in the chair and the coils were attached, they were informed that "it is still necessary to wait for a while until the preparations of the apparatus are finished and the experiment can start". The initial calibration was possible in all patients and was carried out before they patients had been told that they should just sit and wait in a comfortable position "while the clinicians carry out their preparations for the experiment". "To test the technical set-up, it will be necessary to switch on and off the room light in the next minutes. Don't care about the prearrangements. Just relax, do nothing, until being informed that the experiment is ready to start". No further communication took place between the experimenters and the patients while data were recorded for 30 seconds right afterwards in complete darkness, followed by 30 seconds recording in light. The cycle of data acquisition was repeated three times, such that the total recording period in light and in darkness was 90 seconds each. After ending data recording, the patients were told that "now all technical arrangements have been completed and the experiment is ready to start".

Table 1.
Demographic and clinical data of the 12 patients with spatial neglect (NEG) and the 12 control patients without the disorder (RBD and NBD).

			Neglect	No neglect (Controls)	
				RBD	NBD
Number of patients			12	6	6
Sex			3f, 9m	2f, 4m	2f, 4m
Age (years)		*Mean (SD)*	62.9 (14.4)	51.8 (13.5)	59.8 (8.3)
Aetiology		Infarct	11	4	
		Haemorrhage	1	2	
Time since lesion (days)		*Mean (SD)*	13.3 (6.4)	12.0 (7.4)	
Lesion location			NEG1: Bg	RBD1: P	
			NEG2: F, P, T, I	RBD2: Bg, I	
			NEG3: Bg	RBD3: Bg	
			NEG4: F, P, T, I, Bg	RBD4: T, I, P	
			NEG5: Bg	RBD5: F, P	
			NEG6: F, I, Bg	RBD6: P, O, Th	
			NEG7: F, P, T, I, O, Bg		
			NEG8: F, T, P, Bg		
			NEG9: F, T, I, Bg, Th		
			NEG10: F, T, I, Bg		
			NEG11: F, P, T, I, Bg		
			NEG12: F, P, T, I, Bg		
Contralateral paresis		% present	100	100	
Visual field defect		% present	0	0	
Neglect		% present	100	0	
Letter cancellation (hits)	Left	*Mean (SD)*	4.2 (5.9)	29.7 (0.8)	
	Right	*Mean (SD)*	18.9 (10.7)	29.3 (0.5)	
Bells test (hits)	Left	*Mean (SD)*	1.3 (2.6)	14.2 (0.8)	
	Right	*Mean (SD)*	8.5 (5.0)	15.0 (0.0)	
Copying (% omitted)		*Mean (SD)*	58.0 (31.3)	0.0 (0.0)	

Note. NEG, right hemisphere stroke patients with spatial neglect; *RBD*, right hemisphere stroke patients without spatial neglect; *NBD*, healthy subjects without brain lesions; *f*, female; *m*, male; *SD*, Standard deviation; *F*, frontal; *P*, parietal; *T*, temporal; *O*, occipital; *I*, insula; *Th*, thalamus; *Bg*, basal ganglia.

<u>*Straight ahead condition*</u>. The straight ahead condition started right after data acquisition in the resting condition. The patients were informed that the preparations have been finished and that "the experiment" now will start. They were instructed to close the eyes until being asked to open them and to "look exactly straight ahead". The straight ahead orientation should be maintained until the examiners will announce the completion of data acquisition, i.e. throughout the following 10 seconds. During this first recording period room lights were on. Instructions were repeated and data were recorded again for 10 seconds, this time in complete darkness. This cycle was carried out three times, such that the total recording period in light and in darkness was 30 seconds each.

Figure 8. *Magnetic search coil system to measure gaze and head-on-trunk positions. Three orthogonal alternating magnetic fields were generated by three pairs of Helmholtz coils mounted on the outer surface of a cubic frame (diameter 105 cm). Patients sit centrally and can move the head freely while the trunk is immobilised by a belt and shoulder straps. On the inner surface of the frame, a unitary array of black letters on a white ground is presented that covers a rectangular area of ± 120° left and right of the mid-sagittal plane, and of ± 40° above and below the eye level. The room can be normally lightened or completely darkened, depending on the experimental condition (cf. Procedure).*

4.2.3 Results

Since no significant differences were found between the control patients with and without brain lesions, i.e. between the 6 NBD and the 6 RBD patients, statistical analyses were carried out on the data of the whole control group (CON, n = 12). Three-way repeated-measures analyses of variance (ANOVA) were conducted for each of the three parameters (gaze, eye-in-head, and head-on-trunk position) with two within-subject factors (Resting vs. Looking straight ahead; Light vs. Darkness) and the between subject factor 'Group' (NEG vs. CON). Significant three-way interactions were found for gaze and for head-on-trunk orientation; significant two-way interactions for each of the three analyses. We thus calculated repeated-measures ANOVAs separately for the 'Rest' condition and for the 'Straight ahead' condition with 'Group' as between-subject factor and 'Light vs. Darkness' as within-subject factor. Degrees of freedom were corrected with the Greenhouse-Geisser epsilon. Post-hoc tests were corrected for multiple comparisons using a Bonferroni adjusted significance level. In case of unequal variances as determined by Levene's statistics, we used the Welch's test.

Rest condition ("Doing nothing")

Figure 9 gives an exemplary illustration of the combined spontaneous eye-in-head and head-on-trunk positions (= gaze) in three patients with spatial neglect while "doing nothing", i.e. just sitting and waiting. Figure 10 provides the mean horizontal gaze, eye-in-head, and head-on-trunk positions for the groups of neglect and control patients. The statistical analyses of the three variables revealed significant main effects of factors 'Group' and 'Light vs. Darkness' as well as significant two-way interactions. Analyses of the simple main effects revealed a significant rightward deviation in neglect patients compared to controls regarding gaze, eye-in-head, and head-on-trunk orientation when room lights were on (gaze: $t_{13} = 8.01$, eye-in-head: $t_{22} = 5.48$, head-on-trunk: $t_{15} = 4.25$, $p < .001$ each). We found a huge difference between the average gaze position in neglect patients (29.4°) compared to control patients (-1.4°). In darkness, the same comparison revealed a significant rightward deviation in neglect patients for gaze ($t_{14} = 3.96$, $p = .001$) and for head-on-trunk orientation ($t_{22} = 2.54$, $p = .019$), while the difference for eye-in-head position just missed significance ($t_{22} = 2.04$, $p = .054$). Positive correlation coefficients (Pearson product-moment correlation) were observed between the percentage of omissions in the neglect tests and the horizontal position of gaze (light: $r = .74$, darkness: $r = .64$), eye-in-head (light: $r = .52$, darkness: $r = .35$), and head-on-trunk (light: $r = .67$, darkness: $r = .50$).

The rightward deviation of the neglect patients' spontaneous gaze, eye-in-head, and head-on-trunk orientation when "doing nothing" was significantly more pronounced in light compared to darkness (gaze: $t_{11} = 7.10$, eye-in-head: $t_{11} = 6.26$, head-on-trunk: $t_{11}= 4.84$, $p < .001$ each).

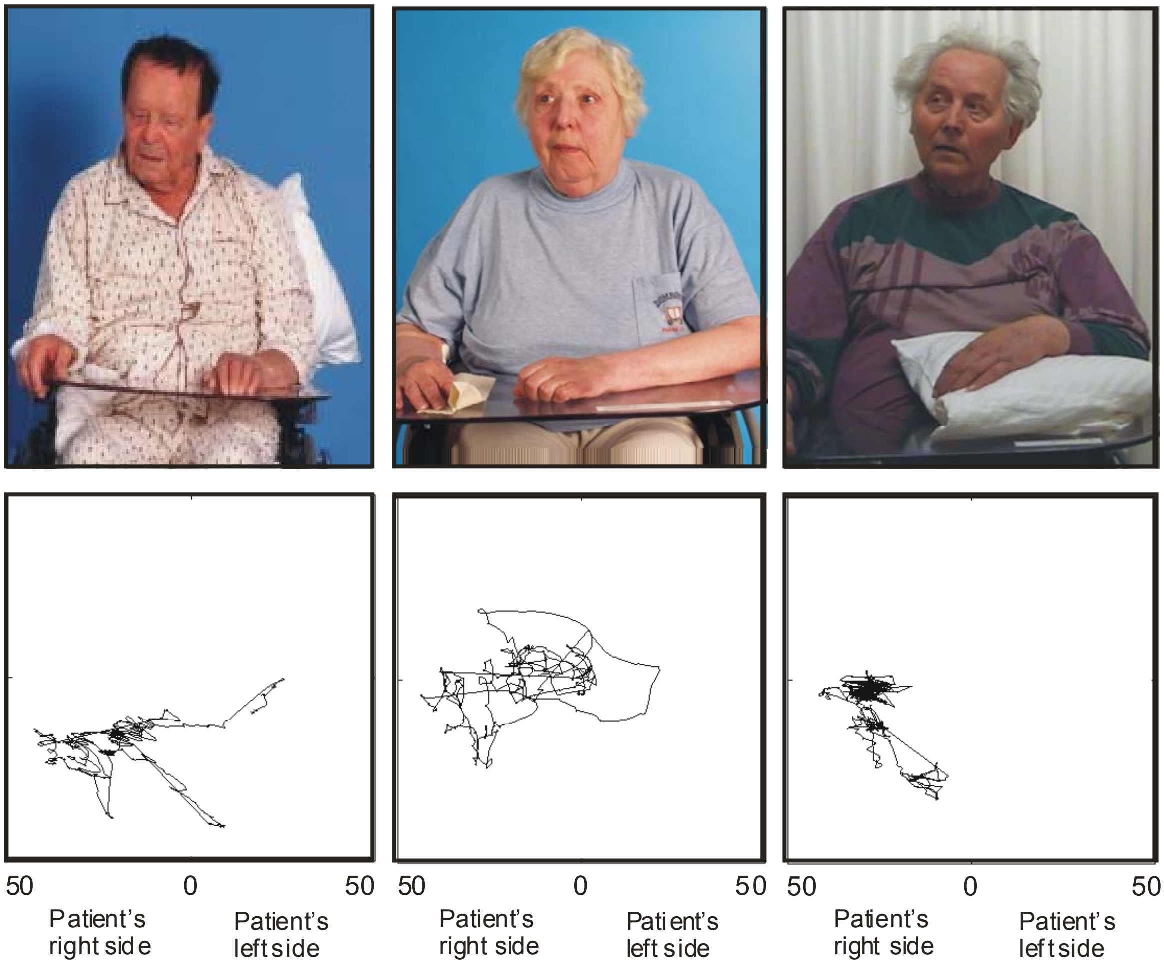

Figure 9. *Eye and head deviation in patients with spatial neglect. Examples of the spontaneous eye and head (= gaze) orientation in patients with spatial neglect following a right hemispheric stroke while "doing nothing", i.e. just sitting and waiting.* ***Upper panel:*** *The patients typically orient the eyes and the head towards the ipsilesional, right side. One could have the impression that they were fixating a certain target on the right side. However, the room was empty with only the photographer standing right in front of them.* ***Lower panel:*** *Spontaneous gaze (combined eye and head) position recorded during a period of 90 seconds when room lights were on (in degrees of visual angle). Note that the data are illustrated from the patients' perspective, i.e. their rightward gaze deviation is plotted on the left side.*

Comparison between the 'Rest' and the 'Straight ahead' condition

In control patients, the eye-in-head position (t_{11} = -3.04, p = .011) showed a more leftward orientation in the 'Rest' than in the 'Straight ahead' condition when the experiment was carried out in darkness. Beyond, no significant differences between the two conditions were found (gaze: t_{11} = -1.90, p = .084; head-on-trunk: t_{11} = 0.64, p = .535). Likewise, the degree of rightward deviation showed by neglect patients while "doing nothing" was comparable to the position measured when they were asked to "look exactly straight ahead". In darkness, the comparison between the two conditions revealed neither significant differences for gaze (t_{11} = -0.74, p = .474) or for eye-in-head (t_{11} = 0.23, p = .821), nor for head-on-trunk (t_{11} = -1.85, p = .091) positions. In light, gaze (t_{11} = 2.05, p = .065) and head-on-trunk (t_{11} = 0.66, p = .522) orientation were statistically comparable; only the neglect patients' eye-in-head orientation (t_{11} = 4.81, p = .001) showed a more rightward orientation in the 'Rest' compared to the 'Straight ahead' condition.

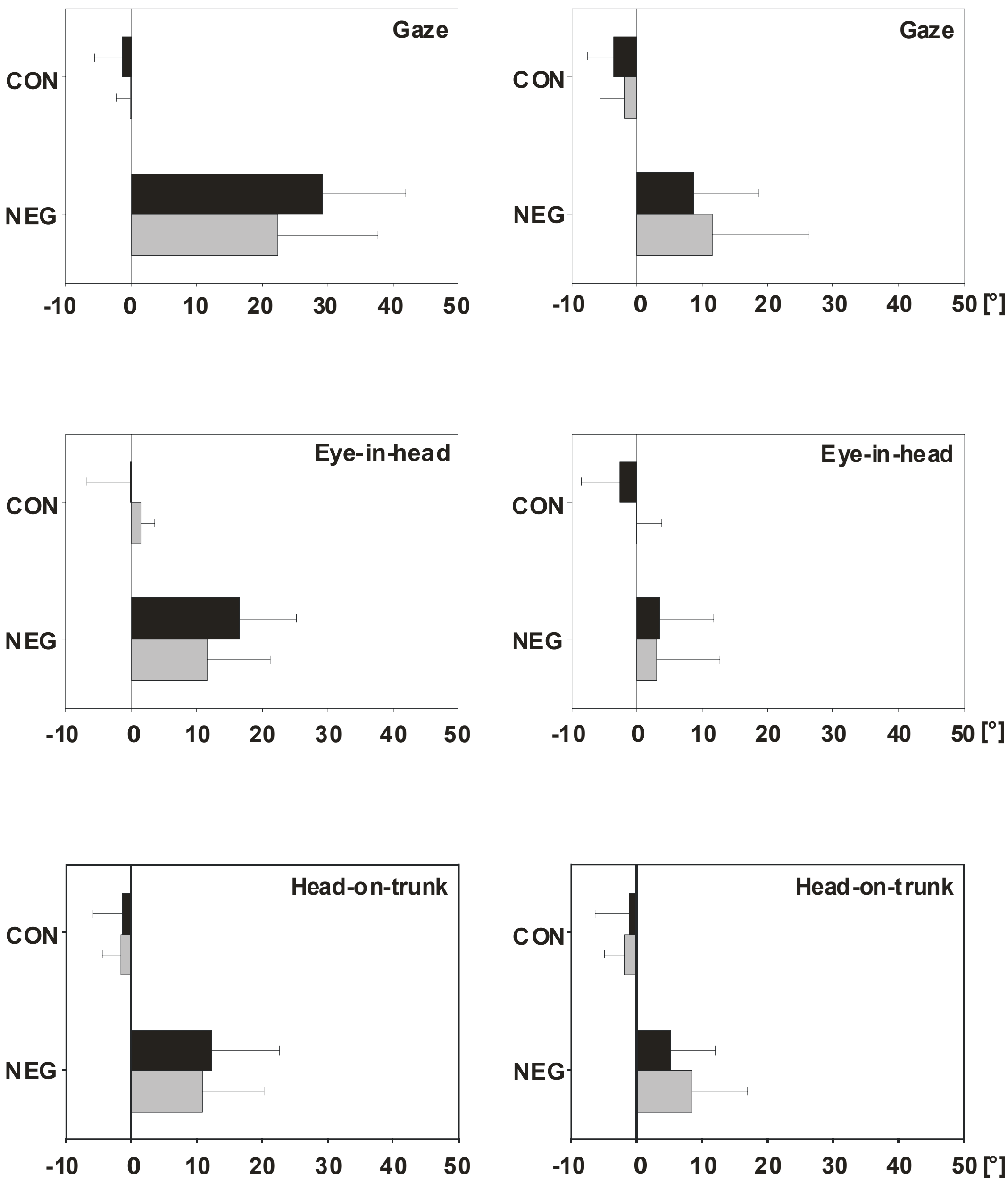

Figure 10. *Spontaneous resting position and subjective straight ahead orientation in patients with and without spatial neglect. Mean horizontal position (and standard deviation) in degrees of visual angle for gaze, eye-in-head, and head-on-trunk when neglect (NEG) and control (CON) patients were waiting, "doing nothing" (black bars) or were instructed to "look straight ahead" (grey bars). The left panel shows the positions recorded in light, the right panel those measured in complete darkness.*

4.2.4 Discussion

The present study addressed the casual clinical observation that patients with spatial neglect may deviate their eyes and head towards the ipsilesional side (e.g. Bisiach & Vallar, 1988; De Renzi et al., 1982; Friedland & Weinstein, 1977; Heilman et al., 1984; Parton et al., 2004). We asked whether such changes of spontaneous eye and head position regularly occur with spatial neglect due to right hemispheric stroke, i.e. with the well-established spatial bias obvious in the patients' active behaviour, for example during target cancellation in a clinical neglect task on command. To address this issue, we used an experimental setting without any explicit requirements. We measured the patients' spontaneous orientation of gaze, eye-in-head, and head-on-trunk while "doing nothing", i.e. in a resting situation. Our main finding was that the eyes and the head in patients with spatial neglect were markedly oriented to the right. Their average gaze position showed a rightward deviation of about 30° in light. The extent of this spontaneous deviation in the resting condition corresponded well with the position measured when the patients were instructed to "look straight ahead" as it was also the case in healthy subjects without the disorder.

In darkness, the rightward deviation of the spontaneous eye-in-head and head-on-trunk as well as of the subjective straight ahead position was smaller but still obvious and significantly different from control patients. The decrease of rightward eye and head orientation when no visible context was present corresponds with previous observations (cf. Chapter 2.3.3). Using either cancellation, exploration, or reaction time tasks, it has been demonstrated that the degree of spatial neglect is reduced by decreasing the number of stimuli (targets or distractors) in a search array, by increasing the contrast between targets and distractors (De Renzi et al., 1989; Husain & Kennard, 1997; Kaplan et al., 1991; Kartsounis et al., 1994; Mark et al., 1988; Rapcsak et al., 1989), or when searching was carried out in complete darkness (Hornak, 1992; Karnath et al., 1996). It appears as if the presence of any visual context on the right further enhances the patients' orientation bias towards the right.

The present study demonstrates that spatial neglect is apparent beyond active behaviour. A bias towards the right is not only present when neglect patients are asked to for example draw or to explore something but also without any explicit requirements, namely in their spontaneous eye and head orientation. The findings strengthen the view that one component of the patients' behaviour is due to a very elementary disturbance of spatial information processing. The disorder may be understood as a pathological adjustment of the subject's normal resting position to a more rightward located position. While the resting position of eyes and head in subjects without the disorder is in line with the trunk orientation, the "default position" of eye and head is shifted to a new origin in stroke patients suffering from spatial neglect.

To our knowledge, the present study is the first that measured "*looking* straight ahead" in patients with spatial neglect, i.e. by their individual gaze position. So far, the subjective straight ahead (SSA) was determined by instructing the patients to point straight ahead either with the index finger or with a stick (Chokron & Bartolomeo, 1997), to direct a visual target verbally towards this position (Ferber & Karnath, 1999; Karnath, 1994c), or to determine verbally whether a visual target is located straight ahead or not. Ferber and Karnath (1999) argued that these previous attempts provided no specific measure for the deviation of egocentric space representation in patients with spatial neglect and more valid procedures would thus be required. Consequently, we measured the SSA deviation in its natural course without specific motor or verbal requirements by identifying gaze positions that are not susceptible to directional hypokinesia or verbal respectively acoustic needs (see e.g. Heilman, Bowers, Coslett, Whelan, & Watson, 1985).

Like most previous studies, neglect patients showed a bias of their SSA position towards the ipsilesional side, while it was in line with the mid-sagittal body axis in healthy subjects and stroke patients without spatial neglect (see e.g. Chokron & Bartolomeo, 2000; Chokron & Imbert, 1995; Farnè, Ponti, & Ladavas, 1998; Ferber & Karnath, 1999; Heilman, Bowers, & Watson, 1983a; Karnath, 1994c, 1997; Mark & Heilman, 1990; Pisella, Rode, Farne, Boisson, & Rossetti, 2002; Richard, Honore, & Rousseaux, 2000; Richard, Rousseaux, & Honore, 2001; Rossetti et al., 1998). Only a few authors reported on neglect patients with either a normal SSA position or with SSA shifts that were not correlated with scores of traditionally neglect tests (Bartolomeo & Chokron, 1999; Chokron & Bartolomeo, 1997, 1998; Hasselbach & Butter, 1997). In this context, it is important to note that a marked shift of the SSA is not exclusively reported in patients with spatial neglect but also for those with hemianopia (e.g. Ferber & Karnath, 1999) or optic ataxia (Perenin, 1997). Moreover, since our aim was to investigate if there is a basal deviation of the "normal" resting position in patients with spatial neglect, we did not determine any other SSA measure reported in the literature. Thus, the present data do not allow for conclusions between our "looking straight ahead" paradigm and previous data.

Nevertheless, such relationship definitely is an interesting aspect that may be addressed in future studies investigating the SSA in patients with spatial neglect.

Most important in the present context is the observation that the spontaneous resting position corresponded well with the "looking straight ahead" in patients with spatial neglect, regardless of the lightning condition. The analogy between doing nothing and looking straight ahead is in line with the behaviour shown by healthy subjects and right hemisphere stroke patients without spatial neglect. However, the crucial difference is that patients without the disorder had mean eye and head positions in line with the mid-sagittal body axis, while patients with spatial neglect showed a marked deviation towards the ipsilesional side in both conditions (cf. Figure 10). Our observation thus points to a close relationship between the underlying mechanisms of these functions and their basal role for spatial information processing.

Finally, the present findings bear potential clinical impact. A deviation of spontaneous eye and head orientation observed for example during a routine clinical examination might serve as a supplementary criterion for the diagnosis of spatial neglect. All of our 12 consecutively investigated patients with spatial neglect but none of the control patients showed a marked deviation of eyes and head towards the ipsilesional, right side at the time when they were capable to take part in the present experiment, i.e. on average 13 days post stroke. The next relevant research questions thus concern the specificity of the spontaneous eye and head deviation towards the ipsilesional side for spatial neglect in the very acute stage of the disorder as well as its development in the time course of recovery (cf. Chapters 4.3. & 4.4).

4.3 Specificity of Spontaneous Eye and Head Orientation in Very Acute Stroke

4.3.1 Introduction

Regarding acute unilateral cerebral lesions, Prévost reported already in 1865 that "in all cases [of acute hemiplegia following unilateral stroke] I have observed, the two ocular axes were always deviated to the side opposite the paralysis, thus the two eyes looked towards the damaged hemisphere" (p. 649). Accordingly, current neurological textbooks often include statements saying that stroke patients usually steer the eyes towards the side of the brain lesion (e.g. Poeck, 1987, p. 70: "Der Kranke blickt seinen Herd an"). This implicates that these signs occur with both, right-sided as well as left-sided brain lesions, particularly in the acute stage of stroke (cf. Chapters 2.4.1, 2.4.2).

In contrast to these assumptions, our first study revealed strong evidence for a relationship between spatial neglect and a spontaneous eye and head deviation towards the ipsilesional side in patients with right hemispheric lesions (cf. Chapter 4.2). Compared to previous observational studies that also partly assumed such a relation (cf. Chapter 2.4.3), we had approached this longstanding question by recording and quantifying the patients' resting behaviour with the magnetic search coil system. However, due to the requirements of this method on the patients' mobility and alertness over a period of approximately one hour, the investigation had to be carried out on average 13 days post stroke. Nevertheless, our initial findings in the subacute stage clearly opposed Prévost's original assumption.

Consequently, our first study allowed for a second investigation targeting the patients' behaviour as soon as possible after stroke onset directly at the bedside, i.e. in a situation in which examinations have to be strictly adapted to the patients' constitution (cf. e.g. Chapter 2.1.3). In order to gain further insight into the degree and specificity of this striking neurological sign in patients with very acute stroke and to test Prévost's prediction by means of quantitative data, we thus used electrooculography (EOG). This technique could be applied with minimal interference to the patients' activities and minimal discomfort directly on the stroke unit (cf. Chapter 2.3.1). We asked whether the spontaneous deviation of the eyes and the head is a sign of spatial neglect and/or right hemisphere lesion, or whether it occurs regularly in very acute left hemisphere stroke patients as well.

Based on the results of the first study, we expected eye and head positions around the mid-sagittal body axis in healthy subjects and stroke patients without spatial neglect, while gaze orientation in neglect patients was supposed to be markedly deviated towards the side of the brain lesion.

4.3.2 Methods

Subjects

The prior aim of the present study was to measure the spontaneous eye-in-head, and head-on-trunk positions as early as possible after brain injury in consecutively admitted, unselected patients with unilateral first-ever stroke verified by MR and/or CT imaging. Between symptom onset and the third day post stroke (i.e. days 0 to 3) – dependent on the patients general constitution and the need of medical attendance in this very acute stage of the stroke – we were able to investigate a sample of 33 patients. In this period, a further nine patients who had met MR/CT inclusion criteria could not be examined because of severe language deficits (n = 2/9) or severely impaired consciousness.

The sample of 33 patients was assigned to three different groups with respect to the presence or absence of spatial neglect as well as to lesion location. The resulting groups consisted of 8 right hemisphere patients with spatial neglect (NEG), 9 right hemisphere patients without spatial neglect (RBD), and 16 left hemisphere patients without spatial neglect (LBD). In addition, 15 control subjects without brain injury (NBD) were investigated. During the period of the present study, no patient with spatial neglect due to a left hemisphere stroke could be examined.

Clinical and experimental investigations were carried out in one session or, if not feasible, at least at the same day. Spatial neglect was diagnosed when patients fulfilled the criterion in not less than two of the following clinical tests: the "Letter cancellation" task (Weintraub and Mesulam, 1985), the "Bells test" (Gauthier et al., 1989), the Albert's Test (Albert, 1973), and a copying task (Johannsen & Karnath, 2004). RBD and LBD patients showed normal behaviour in each clinical neglect tests. Full details about inclusion criteria and standard clinical assessment carried out in all stroke patients are given in Chapter 4.1. In the present study, we additionally determined the level of consciousness of each patient by the Glasgow Coma Scale (Jennett & Teasdale, 1977). Further, we investigated aphasic symptoms by spontaneous speech, picture naming, and auditory comprehension of single words and whole sentences. Clinical, demographic, and anatomical data of all 48 patients with and without spatial neglect are given in Table 2.

Table 2.
Demographic and clinical data of the 33 patients with and without spatial neglect and of the 15 healthy subjects without brain lesions.

			Neglect NEG	No neglect RBD	No neglect LBD	No neglect NBD
Number of patients			8	9	16	15
Sex			4f, 4m	3f, 6m	6f, 10m	11f, 4m
Age (years)		*Mean (SD)*	57.6 (14.6)	62.3 (10.3)	64.7 (9.9)	59.9 (11.8)
Aetiology		Infarct	8	6	11	
		Haemorrhage	0	3	5	
Time since lesion (days)		*Mean (SD)*	1.4 (0.9)	1.4 (0.9)	1.7 (0.9)	
Lesion location			NEG1: Bg	RBD1: Bg	LBD1: Th	
			NEG2: F,T,I,Bg	RBD2: P,T	LBD2: T,O	
			NEG3: F,P,T,O,I	RBD3: T,I,Bg	LBD3: F,I,Bg	
			NEG4: Bg	RBD4: O	LBD4: Bg	
			NEG5: F,T,I	RBD5: Bg	LBD5: Bg	
			NEG6: P	RBD6: Bg	LBD6: F,I,Bg	
			NEG7: T	RBD7: Bg	LBD7: Th	
			NEG8: F,T,I,Bg	RBD8: Bg	LBD8: P,T,I	
				RBD9: Bg,Th	LBD9: P,T,I	
					LBD10: P	
					LBD11: O	
					LBD12: I,Bg	
					LBD13: I,Th,Bg	
					LBD14: Th	
					LBD15: T	
					LBD16: Swm	
Glasgow Coma Scale		*Mean (SD)*	14.6 (0.5)	14.9 (0.3)	14.2 (1.1)	
Contralateral paresis		% present	100	55.6	56.3	
Visual field defect		% present	12.5	22.2	12.5	
Aphasia		% present	0	0	87.5	
Neglect		% present	100	0	0	
Letter cancellation (hits)	Left	*Mean (SD)*	8.5 (10.6)	29.3 (0.7)	27.3 (2.1)	
	Right	*Mean (SD)*	20.3 (8.0)	29.6 (0.5)	27.8 (1.8)	
Bells test (hits)	Left	*Mean (SD)*	4.0 (4.1)	13.9 (1.1)	13.8 (1.4)	
	Right	*Mean (SD)*	11.2 (4.1)	14.6 (0.7)	13.3 (2.1)	
Albert's test (hits)	Left	*Mean (SD)*	8.4 (9.0)	18.0 (0)	18.0 (0)	
	Right	*Mean (SD)*	14.0 (6.4)	18.0 (0)	17.8 (0.8)	
Copying (% omitted)		*Mean (SD)*	41.7 (34.2)	1.4 (4.2)	4.5 (7.9)	

Note. NEG, right hemisphere stroke patients with spatial neglect; *RBD*, right hemisphere stroke patients without spatial neglect; *LBD*, left hemisphere stroke patients without spatial neglect; *NBD*, healthy subjects without brain lesions; *f*, female; *m*, male; *SD*, Standard deviation; *F*, frontal; *P*, parietal; *T*, temporal; *O*, occipital; *I*, insula; *Th*, thalamus; *Bg*, basal ganglia; *Swm*, subcortical white matter.

Apparatus

The spontaneous horizontal eye-in-head position was measured by electrooculography (EOG; Meyers, 1929; Schott, 1922). We applied three silver/silver chlorine (Ag/AgCl) electrodes, two at the outer canthus of each eye and one at the forehead, the latter serving as the reference electrode (cf. Figure 11). All signals passed a low-pass filter (20 to 30 Hz) before they were amplified by a conventional DC amplifier. The sample rate was 70 Hz. For calibrating the EOG, patients were asked to look at light emitting diodes (LEDs) on a black cardboard that was placed 30 cm in front of the eye level. The LEDs were presented at 0°, ± 10°, and ± 20° of visual angle with respect to their mid-sagittal head axis without modifying the spontaneously chosen head position. Horizontal head-on-trunk position was measured by a standard orthopaedic graphometer circle. This tool consists of two intersected measuring tubes. One was aligned parallel to the frontal plane defined by the left and the right acromion; the other was oriented with the line between the nasion and the inion. The resulting angle and its duration within the total recording period (see Procedure) was recorded. Since the patients were asked to rest in a comfortable position, most of them did not move their head during data recording what resulted in a single head position value. When a patient moved the head within this period the new head-on-trunk angle was determined and its duration within the total recording period was directly marked in the EOG data file. The mean head-on-trunk position was calculated based on the measured head-on-trunk angles, each weighted with reference to the relative portion of the overall acquisition time.

Horizontal head-on-trunk and gaze co-ordinate 0° was defined by the subject's mid-sagittal body axis. Eye-in-head co-ordinates were head-centred, i.e. co-ordinate 0° was aligned with the head's mid-sagittal axis. Positive values thus indicated locations right of these centres, negative values locations on the left. Horizontal gaze orientation was calculated by adding the mean angles of eye-in-head and head-on-trunk positions of each patient.

Procedure

In order to measure the patients' spontaneous orientation of eye-in-head and head-on-trunk in the very acute stage of stroke (day 0 to 3 after stroke onset), the EOG investigation took place directly on the stroke unit at the bedside. Under normal daylight conditions, patients were seated in an upright position in either the sick bed or the wheelchair. Close-drawn white curtains separating the single beds on their left, right, and frontal sides provided a constant and balanced visual environment. After calibration of the EOG, patients were asked to rest in a comfortable position with eyes open and without talking. The head was not fixed but the patients were instructed, if possible, not to move the head too much. Before data recording started, experimenters were positioned out of the patients' sight, right behind the sick bed or the wheelchair to avoid any disturbances in the visual fields that could have attracted the patients' attention. Patients were informed that data will be collected now and that they should keep their comfortable position until recording will be finished. No further communication took place during the following period of data acquisition.

EOG data were recorded for 90 seconds and were stored on hard disc for off-line analysis. During the same period, patients head position was measured. Any disturbance during data acquisition, e.g. when patients closed the eyes, started to talk, or moved the head or the trunk, was marked in the data file. These periods were excluded from data analyses. After finishing recording, the calibration procedure was repeated. Two circles of data acquisition were carried out, summing up for a total recording period of 180 seconds per patient.

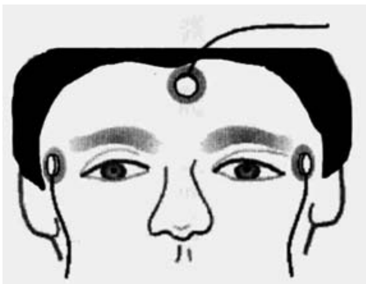

Figure 11. *Sketch of electrode application during electrooculography. Three silver/silver chlorine (Ag/AgCl) electrodes were applied, two at the outer canthus of each eye and one at the forehead (reference electrode). Eye-in-head positions were recorded directly on the stroke unit under normal daylight conditions. Patients were seated in an upright position in a sick bed or a wheelchair. The head was not fixed but the patients were asked not to move the head too much.*

4.3.3 Results

Figure 12 gives the individual horizontal gaze, eye-in-head, and head-on-trunk positions for all 48 subjects, each averaged over the 180 seconds period of data acquisition. We found a huge deviation of all three parameters in the group of neglect patients (NEG) compared to all other groups without spatial neglect (RBD, LBD, and NBD). Moreover, this deviation of gaze, eye-in-head, and head-on-trunk position was observed in every single patient with spatial neglect (NEG) and was confined exclusively (= 100 %) to the ipsilesional, right side. In contrast, the smaller deviations of gaze, eye-in-head, and head-on-trunk in the RBD, LBD, and NBD group were balanced in direction towards the left and the right side (cf. Figure 12). For statistical comparison of the four groups (NEG, RBD, LBD, NBD), we conducted separate one-way ANOVAs for gaze, eye-in-head, and head-on-trunk position, followed by post-hoc tests using a Bonferroni adjusted significance level. In case of unequal variances, we used the Welch's test.

Gaze position

We found a highly significant difference between the four groups ($F_3 = 33.12$, $p < .001$). Post-hoc comparisons revealed that this effect was due to the striking difference between the neglect patients' mean horizontal gaze position of 46.1° (*SD* = 18.0°) compared to each other group, showing comparable spontaneous gaze positions close to the mid-sagittal body axis. Right hemisphere stroke patients without spatial neglect had an average gaze position of 3.5° (*SD* = 10.5°; $t_{15} = 6.06$, $p < .001$), the left hemisphere stroke patients without neglect a mean of 1.0° (*SD* = 12.0°; $t_{22} = 7.35$, $p < .001$), and the healthy control subjects a mean of 1.9° (*SD* = 5.8°; $t_8 = 6.77$, $p < .001$).

Eye-in-head position

The one-way ANOVA conducted for eye-in-head positions revealed a significant main effect of factor "group" ($F_3 = 20.81$, $p < .001$) as well. Subsequent post-hoc comparisons showed that the neglect patients' average spontaneous eye-in-head position was markedly biased towards the right compared to each other group (RBD: $t_{15} = 6.21$, $p < .001$, LBD: $t_{22} = 7.12$, $p < .001$; NBD: $t_{21} = 7.07$, $p < .001$). The mean horizontal eye-in-head position of the neglect group was deviated by 20.5° (*SD* = 6.1°) towards the ipsilesional side, while the averaged positions of the RBD (*M* = 0.5°, *SD* = 7.1°), LBD (*M* = 0.1°, *SD* = 6.9°), and NBD (*M* = 2.8°, *SD* = 5.5°) group were close to the head midline.

Head-on-trunk position

The analysis of head-on-trunk positions also obtained a significant difference between the four groups ($F_3 = 15.53$, $p < .001$). Again, this effect was due to a marked difference between the group of neglect patients and all other groups. The neglect patients' mean horizontal head-on-trunk position showed a substantial deviation of 25.6° (*SD* = 15.8°) to the ipsilesional, right side. In contrast, the mean positions of the right hemispheric stroke patients without neglect (RBD: *M* = 3.0°, *SD* = 7.2°; $t_{15} = 3.88$, $p = .001$), of the left hemispheric stroke patients without the disorder (LBD: *M* = 0.9°, *SD* = 8.4°; $t_9 = 4.15$, $p = .002$), and of the healthy control subjects (NBD: *M* = -0.9°, *SD* = 7.5°; $t_9 = 4.49$, $p = .002$) were close to the mid-sagittal body axis.

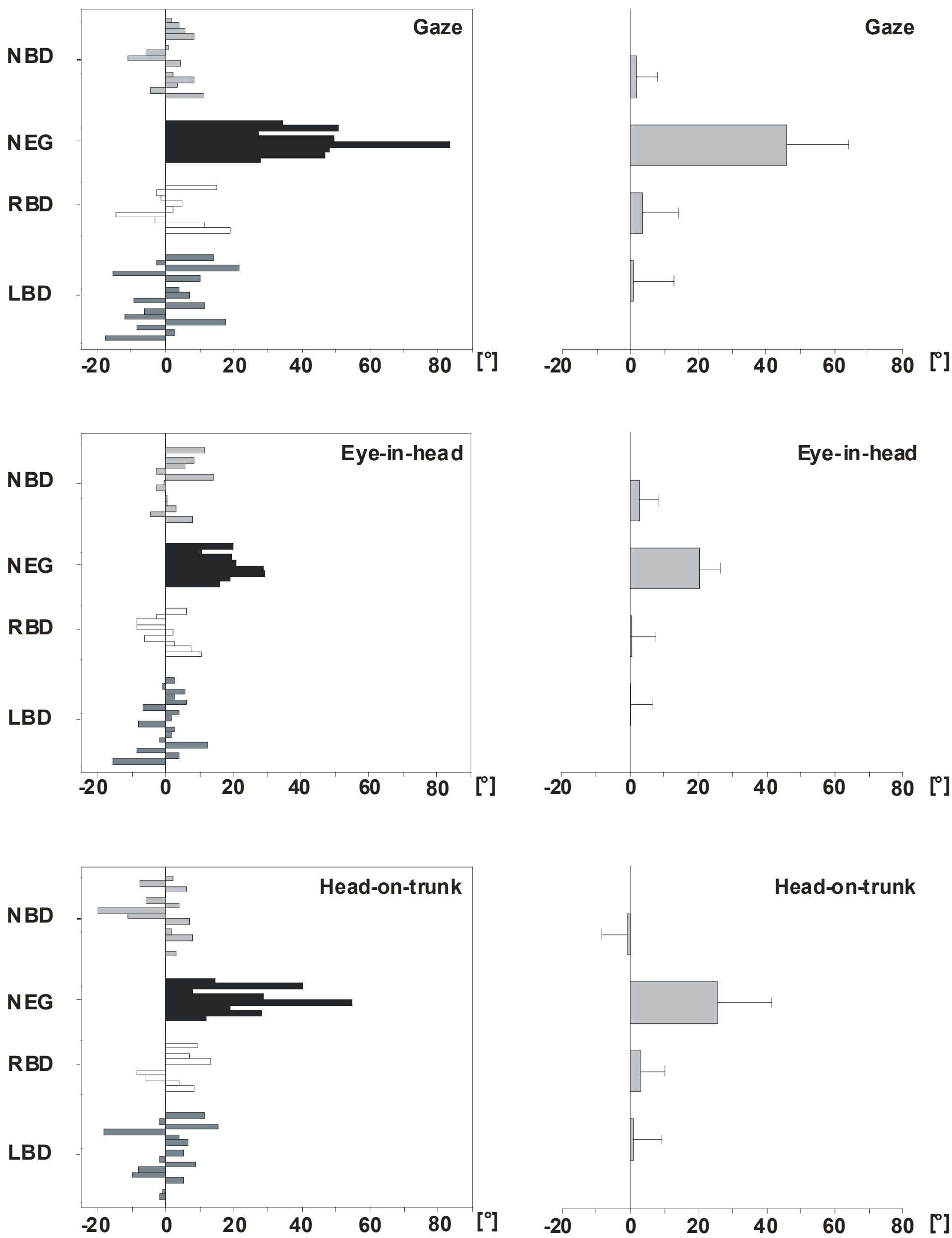

Figure 12. *Eye and head orientation in very acute stroke and its relation to spatial neglect.* ***Left panel:*** *Individual horizontal position (in degrees of visual angle) of gaze, eye-in-head, and head-on-trunk in all 48 subjects, each averaged over the 180 seconds period of data acquisition. NBD, subjects without brain lesions (light grey bars); NEG, right hemisphere stroke patients with spatial neglect (black bars); RBD, right hemisphere stroke patients without spatial neglect (white bars); LBD, left hemisphere stroke patients without spatial neglect (dark grey bars).* ***Right panel:*** *Mean horizontal position (and standard deviation) of the different groups and variables.*

4.3.4 Discussion

The present study investigated the relationship between the spontaneous horizontal eye and head deviation and spatial neglect in patients with very acute left or right hemisphere first-ever stroke. Our aim was to measure gaze, eye-in-head, and head-on-trunk positions as early as possible after stroke. We were able to investigate our patients on average 1.5 days after the onset of neurological symptoms. At this time, we observed that each single patient with spatial neglect and right hemisphere lesion showed a marked spontaneous deviation of the eyes and of the head to the ipsilesional side. The mean bias of the spontaneous horizontal gaze position in patients with spatial neglect amounted to 46° towards the right side, varying from a minimum of 27.5° to a maximum of 83.6°. Such marked deviation of the eyes and the head was neither observed in left or right hemisphere stroke patients without the disorder nor in healthy subjects. On average 1.5 days after stroke onset the spontaneous horizontal gaze, eye-in-head, and head-on-trunk positions in these latter groups varied around the sagittal trunk midline (0°), leading to a mean position very close to this axis.

The implementation of bedside EOG recording complements the findings of our first study (cf. Chapter 4.2). Actually, the present data confirm that a marked spontaneous deviation of eyes and head towards the ipsilesional side is specific to spatial neglect and do not occur with other stroke patients. However, our results do not allow to draw conclusions for the period between 0 and (on average) 1.5 days after the onset of neurological symptoms. It may indeed be possible that -within this short period after symptom onset- a marked eye and head deviation also occurs with left hemisphere injury. If this would be the case, the present results would indicate that the deviation after left hemispheric stroke has a very short convalescence and recovers within approximately 1.5 days, while the deviation of eyes and head associated with right hemispheric stroke persists.

What is the consequence of the neglect patients' huge spontaneous eye and head deviation towards the right side? We know from behavioural studies that patients with spatial neglect carry out exploratory movements predominantly on the ipsilesional side when searching for targets, reading, copying, etc. (Hornak 1992; Johnston & Diller, 1986; Karnath et al., 1998; Karnath & Perenin, 1998). It seems as if the spontaneous deviation of the eyes and the head in patients with spatial neglect provokes this asymmetric behaviour. The patients appear to carry out visual and tactile movements around their deviated centre of eye and head position, leading to neglect of information on the contralesional, left side.

Prévost (1865) pointed out that the deviation of the eyes and the head "can be an invaluable indicator for the [stroke] diagnosis" (p. 649). While Prévost assumed that a deviation of eyes and head occurs symmetrically after both left and right hemisphere lesions, the present study clearly showed that a horizontal deviation of eyes and head measured as early as possible after symptom onset is tightly connected to spatial neglect. Beyond, this also accounts for the post-acute stage (cf. Study 1, Chapter 4.2). Prévost's sign and spatial neglect thus seems to reflect the same phenomenon, namely a constantly biased orienting towards the right side. Our results thus modify Prévost's (1865) original assumption that eye and head deviation occurs symmetrically. The present data showed that this bias emerges predominantly after right-sided stroke, indicating that its underlying function is represented asymmetrically in the human hemispheres.

The present results may have implications for acute stroke diagnosis and confirm our previous assumption that a clinical examination of eyes and head might serve as supplementary diagnostic criterion for spatial neglect (see Chapter 4.2.4). As acute language disorders strongly argue for a left hemisphere stroke, our data suggest that a marked horizontal eye and head deviation observed about 1.5 days after symptom onset is a clear sign for spatial neglect (and typically a right hemisphere lesion in those patients). In addition to the traditional paper-and-pencil tests, the evaluation of stroke patients horizontal eye and head positions thus could serve as a brief and easy way to help diagnose the disorder.

Spatial neglect occurs as asymmetrically after right hemisphere stroke as for example aphasia after left hemisphere lesions (Bowen et al., 1999; Mesulam, 2002; Pedersen et al., 1997). Pedersen and co-workers (1997) found an incidence of spatial neglect of about 23 percent following unilateral stroke, of which 85 percent were patients with right hemispheric lesions. In line with this notion, we did not observe spatial neglect following a left hemisphere injury among the 33 stroke patients of the present study. However, as rare cases exist with aphasia after right hemispheric stroke, also patients with spatial neglect due to left hemispheric lesions could be expected in other samples or samples of larger size. Based on our present findings, we predict that such neglect patients will show a spontaneous horizontal eye and head deviation towards the left side, comparable to the marked rightward deviation observed in each of the neglect patients of the present study.

To summarise, the implementation of two different eye-recording methods (see Chapter 2.3.1) in two different samples including a total of 72 patients with and without spatial neglect revealed that a deviation of spontaneous eye and head position is directly related to spatial neglect. Based on these results, it seems as if the passive orientation at rest is more pronounced in the initial stage, 1.4 days after onset of neurological symptoms compared to the subacute stage 13.3 days post stroke. Consequently, it remains to be studied within the same group of right hemisphere stroke patients with spatial neglect how the extent of the ipsilateral deviation of spontaneous eye and head orientation develops in the course of recovery. Further, it remains open whether the gaze deviation at rest is related to the well-known bias of active exploratory behaviour or whether it constitutes an independent symptom of spatial neglect that even may dissociate from its active components over time.

4.4 Time Course of Eye and Head Deviation in Spatial Neglect

4.4.1 Introduction

The most prominent impairment in patients with spatial neglect is their bias of active exploratory behaviour (cf. Chapter 2.1.1). When searching for targets, copying, or reading they direct their eye and hand movements towards the ipsilesional side and neglect the contralesional side of space (Johnston & Diller, 1986; Karnath et al., 1998; Karnath & Perenin, 1998). This exploratory bias is specific to patients with spatial neglect and is not observed in other stroke patients. Consequently, tasks requiring patients to search for targets distributed among various distractors became standard screening tests for spatial neglect (cf. Chapter 2.1.3).

However, this ipsilesional bias is not only evident in tasks addressing the patients' "active" behaviour, i.e. when they are explicitly asked to explore or to draw something. It is also obvious in the spontaneous resting position of neglect patients, as shown by our eye and head movement recording studies in the acute/subacute phases of the stroke (cf. Chapter 4.2 and 4.3). The attempt of the first part of the present work was to record eye and head position while stroke patients had to "do nothing", in order to quantify this phenomenon and to compare it to other patient groups. Our subjects were just asked to sit in a comfortable position and rest for a while. In this situation, the combined eye and head position (= gaze position) in patients with spatial was constantly deviated around 30° respectively 46° towards the ipsilesional side depending on the time of investigation, while it varied around the mid-sagittal body axis (0°) in subjects without the disorder.

Based on the findings of the first part of the present work, a spontaneous gaze deviation after hemispheric stroke seems to be as specifically related to spatial neglect as a bias of exploratory movements in visuo-motor tasks. Thus, we presently conclude that spatial neglect is characterised by a deviation of eye and head during both, "active" visual search as well as "passive" rest in acute and subacute phases of stroke. However, to date we know nothing about their relationship in the course of recovery. Based on clinical observation it could be assumed that a passive deviation of the eyes recovers fast compared to the traditionally measured active components of the disorder (cf. Chapter 2.4.4). This may favour distinct symptoms as well as a dissociation between both phenomena rather than a common development over time.

Thus, we finally are interested in the relationship between these striking changes in active and passive neglect behaviour in the course of recovery. Our follow-up measures aim to investigate whether both phenomena show a common development over time or whether they may dissociate, for example such that a passive gaze deviation recovers faster than the gaze orientation in active exploratory search tasks. We ask whether the orientational bias of eyes and head (i) at rest and (ii) during active search is related or if these symptoms show an independent, dissociative development over time. As in the first study, we used the magnetic search coil system allowing for investigating the patients' behaviour under normal room light conditions as well as in complete darkness. Based on the clinical findings on the course of active search behaviour in patients with spatial neglect (cf. Chapter 2.1.2) and our previous studies, we predict a common decrease rather than a dissociation of neglect patients' active and passive behaviour over time.

4.4.2 Methods

Subjects

Twelve patients with spatial neglect (NEG) due to an acute right hemisphere stroke consecutively admitted to our department were investigated. During the follow-up period, two of these patients suffered a second stroke, two patients denied to be examined a second time, one patient was admitted to another hospital, and one patient had moved far beyond the catchment area. Thus, 6 neglect patients could be followed during recovery. They were compared with (i) 6 stroke patients who also suffered from acute right hemispheric lesions but did not show any signs of spatial neglect (RBD) and (ii) 6 patients without brain lesions (NBD) who were admitted with peripheral neurological disorders. These patients had also participated in the first study. All stroke patients (NEG, RBD) had acute circumscribed right hemispheric brain lesions due to an ischaemic or haemorrhagic first-ever stroke.

Spatial neglect was diagnosed when patients fulfilled the criterion in at least two of the following clinical tests: the "Letter cancellation" task (Weintraub & Mesulam, 1985), the "Bells test" (Gauthier et al., 1989), and a copying task (Johannsen & Karnath, 2004). RBD patients showed normal behaviour in each clinical neglect tests. None of the patients had a history of vestibular or oculomotor abnormalities. Further, standardised neurological examination of all patients revealed no acute vestibular or oculomotor signs or deficits (e.g. nystagmus), and no visual field defects. Full details about test procedures and inclusion criteria are given in Chapter 4.1.

All patients with spatial neglect were investigated three times in a 10-months period. The initial examination (Exam 1) took place as early as possible after admission, i.e. once the patients could be mobilised in a wheelchair and were able to attend to an experiment over a period of approximately 30 minutes (M = 12.2 days, SD = 5.3). The first follow-up examination (Exam 2) was carried out just before the patients were discharged and transmitted to a rehabilitation unit (M = 18.7 days, SD = 5.2). The second follow-up examination (Exam 3) took place in the chronic stage, i.e. not before 6 months had elapsed after stroke (M = 10.6 months, SD = 5.2). At this time, the patients had stayed in a rehabilitation unit for a median time of 70.2 days (range = 118 days). During this period, they had received a conventional therapy program including standard physiotherapy, occupational therapy, and neuropsychological training. The two control groups without spatial neglect (RBD, NBD) were investigated once (RBD: M = 12.0 days since lesion, SD = 7.4). Table 3 gives an overview of the relevant demographic and clinical data of the subject groups.

Apparatus

Using the magnetic field-search technique (Robinson, 1963; cf. Chapter 2.3.1), gaze and head-on-trunk positions were measured separately under two experimental conditions, (i) at rest and (ii) during active exploratory search. Both paradigms were carried out with room lights on and in complete darkness. Patients' gaze positions were measured by a 2D scleral search coil lens. Head-on-trunk positions were recorded with a further solenoid attached to the patients' foreheads. The sampling rate was 100 Hz. Full technical details about the methods used to determine eye and head positions were described in Study 1 (Chapter 4.2.2).

Patients sat upright in a wooden chair or wheelchair within the cubic frame such that the head was positioned centrally (see Figure 8). In both conditions, the head could be freely moved while the trunk was immobilised on the chair by a belt and shoulder straps. A unitary array of black letters (each 1.8° high) on a white ground was presented in a rectangular area of 240° x 80°. The room was normally lightened or completely darkened, depending on the experimental condition (see below). There was no fixation target or any other hint indicating the objective straight ahead position (0°/0°). Eye-in-head positions represent the difference between the corresponding gaze and head-on-trunk positions and were determined by multiplying the rotation matrices of gaze positions with the inverse rotation matrices of head-on-trunk positions. Gaze positions represent combined eye-in-head and head-on-trunk positions. Head-on-trunk and gaze co-ordinates 0°/0° were aligned with the patient's mid-sagittal body axis in the horizontal plane and the individual eye level in the sagittal plane. Eye-in-head co-ordinates were head-centred with co-ordinates 0°/0° aligned with the head's mid-sagittal axis at eye level. Positive values thus indicate locations right of these centres, negative values those on the left.

Table 3.
Demographic and clinical data of the 6 right hemisphere stroke patients with spatial neglect (NEG) and the 12 control patients without the disorder (RBD and NBD).

			Neglect			No neglect (Controls)	
			Acute stage		Chronic stage	Acute stage	
			Exam1	Exam 2	Exam 3	RBD	NBD
Number of patients			6			6	6
Sex			6m			4m, 2f	4m, 2f
Age (years)		*Mean (SD)*	62.7 (12.4)	62.7 (12.4)	63.5 (12.3)	51.8 (13.5)	59.8 (8.3)
Aetiology		Infarct	5			4	
		Haemorrhage	1			2	
Time since lesion (days)		*Mean (SD)*	12.2 (5.3)	18.7 (5.2)	317.2 (156.0)	12.0 (7.4)	
Lesion location			NEG1: Bg NEG2: F, P, T, I NEG3: Bg NEG4: F, P, T, I, Bg NEG5: F, P, T, I, O, Bg NEG6: F, T, I, Bg, Th			RBD1: P RBD2: Bg, I RBD3: Bg RBD4: T, P, I RBD5: F, P RBD6: P, O, Th	
Contralateral paresis		% present	100	83.3	83.3	100	0
Visual field defect		% present	0	0	0	0	0
Neglect							
Letter cancellation (hits)	Left	*Mean (SD)*	2.8 (4.0)	8.7 (10.0)	23.3 (7.3)	29.7 (0.8)	
	Right	*Mean (SD)*	16.0 (10.0)	20.3 (11.1)	29.8 (0.4)	29.3 (0.5)	
Bells test (hits)	Left	*Mean (SD)*	0.7 (0.8)	3.0 (4.3)	10.0 (3.9)	14.2 (0.8)	
	Right	*Mean (SD)*	8.5 (5.4)	10.7 (4.8)	14.7 (0.5)	15.0 (0.0)	
Copying (% omitted)		*Mean (SD)*	60.4 (27.9)	43.8 (40.1)	25.0 (27.4)	0.0 (0.0)	

Note. Neglect: right hemisphere stroke patients with spatial neglect; *No Neglect*: *RBD*, right hemisphere stroke patients without spatial neglect; *NBD*, healthy subjects without brain lesions; *f*, female; *m*, male; *SD*, Standard deviation; *F*, frontal; *P*, parietal; *T*, temporal; *O*, occipital; *I*, insula; *Th*, thalamus; *Bg*, basal ganglia.

Procedure

Rest condition in light and complete darkness. The patients' spontaneous gaze, eye-in-head, and head-on-trunk position was measured at "passive" rest, i.e. without any specific requirements (for detailed description cf. Chapter 4.2.2). Once the patients were seated in the chair and the coils were attached, they were informed that "it will be necessary to wait for a while until the preparations of the apparatus are finished and the experiment can start. Don't care about the prearrangements. Just relax, do nothing, until being informed that the experiment is ready to begin". No further communication took place between the experimenters and the patients while data were recorded for 30 seconds right afterwards in complete darkness, followed by 30 seconds recording in light. The cycle of data acquisition was repeated three times, such that the total recording period in light as well as in darkness was 90 seconds each. After ending data recording, patients were told that "now all technical arrangements were completed and the experiment is ready to start".

Active visual search condition in light. Subsequently, the patients' gaze, eye-in-head, and head-on-trunk movements were recorded during "active" visual search. We employed a task that resembles the clinical exploration task of Weintraub and Mesulam (1985) for the diagnosis of spatial neglect (cf. Chapter 2.1.3). The whole search array covered an area of 240° in the horizontal plane (120° right and left of the body's mid-sagittal plane) and of 80° in the vertical plane (40° above and below the subject's eye level). Patients were blindfolded and told that a single target letter 'A' would now be hidden "somewhere in the entire search array". Immediately after the blindfold was removed, the task was "to actively search the whole array for this target letter 'A' by looking thoroughly in all directions". Data were recorded for 120 seconds under normal room light conditions. Subsequently, patients were blindfolded again.

In fact, during data recording no target letter was presented. This procedure was employed to prevent that a target stimulus attracts the patient's attention and thus influences the pattern of spontaneous distribution of exploratory gaze movements. To maintain the patient's motivation during the experiment, an intermediate trial was implemented in which no data were recorded but the letter 'A' was presented somewhere in the central area of the search array. If the patient did not find the target within 40 seconds, the experimenter identified its location by pointing on it. The active search behaviour of each patient was recorded in two out of three trials. Thus, the total recording period amounts to 240 seconds per patient.

Active visual search condition in darkness. After the visual search condition in normal room light, we recorded gaze, eye-in-head, and head-on-trunk movements while the patients were searching for a non-existing laser spot in complete darkness. In this condition, a red dot (0.5° of visual angle) was reflected onto the inner surface of the cabin by a laser pointer, which was mounted to the frame directly above the patients' head. Each experimental condition started with the spot being pseudo-randomly presented in one of four eccentric positions (i.e. +10°/+10°, +10°/-10°, -10°/-10°, and -10°/+10°). Subsequently, the red dot was extinguished and the patients were asked, "to search for the new location of the spot that is positioned somewhere in the cabin". In fact, the spot was not presented within the next 120 seconds of data recording. Thus, the patients searched in complete darkness, while gaze and head-on-trunk movements were recorded at the same time. Again, this procedure was employed to prevent an influence on the pattern of the distribution of spontaneous exploratory gaze movements.

After 120 seconds of data recording, the scanning period was terminated by presenting the laser spot at a random location on the inner surface of the cabin in order to maintain the patients' motivation during the experiment. If the patients did not notice the dot within the next 40 seconds, the experimenter identified its position verbally and by repeatedly moving the laser pointer. To further maintain the patients' motivation, an intermediate trial was carried out between the first and the third record in which no data were collected. In this step, the red dot was actually presented in the central area of the search array. If the patient did not find the laser spot in the 40 seconds allowed, the experimenter identified its location as described above. According to the visual search condition in light, the total recording period in darkness amounted to 240 seconds for each patient.

"Active and passive neglect behaviour"

In the present eye and head recording set-up, the patients' free, unrestricted gaze positions (= combined eye and head positions) almost resemble those that would be obtained by observing their spontaneous or task-related behaviour in a natural environment (cf. Chapter 2.3.1). Consequently, a deviation of the patients' gaze during unrestricted, active exploration was defined as "active neglect behaviour", a bias of gaze positions at rest as "passive neglect behaviour". Further, active neglect behaviour defines the patients' performance in the clinical visuo-motor tasks, such as cancellation or copying, which allows to calculate individual "neglect severity" scores for the patients' clinical behaviour under normal room light conditions (please cf. Figures 1 & 2, and Chapter 4.1.5).

Repeated measure analyses of variance on the patients' gaze orientation in light thus additionally included the factor 'neglect severity'. This factor was added to study whether the development of the patients' active exploratory gaze movements as well as of their spontaneous gaze orientation at rest is related to the performance measured by standardised clinical tests conducted under normal room light conditions.

For repeated measure ANOVAs, Mauchley's test was used to test for sphericity and to decide whether degrees of freedom have to be corrected with the Greenhouse-Geisser epsilon. All Post-hoc tests were adjusted using the Bonferroni procedure for multiple comparisons. In case of unequal variances as determined by Levene's statistics, we used the Welch's test.

4.4.3 Results

All analyses were carried out separately i) in light and ii) in complete darkness for each single parameter (gaze, eye-in-head, head-on-trunk). No differences were found between the control patients with and without brain lesions (RBD, NBD). Thus, they were merged into a single group of patients without spatial neglect (CON, $n = 12$), which was compared to the patients with spatial neglect (NEG, $n = 6$). The samples were comparable with respect to age (CON versus NEG: $t_{16} = 1.17$, $p = .261$), time since lesion (RBD versus NEG: $t_{10} = 0.05$, $p = .965$), aetiology (RBD versus NEG: Fisher's exact test: $p = 1.00$), and paresis of the contralateral side (cf. Table 3).

<u>Development of active and passive neglect behaviour under normal room light conditions</u>

Figure 13 illustrates the scan paths (= gaze) and Figure 14 the mean horizontal gaze positions (= combined eye and head positions) of the control and the neglect group during active visual exploration as well as at rest ("doing nothing"). In addition, Figure 14 shows the averaged neglect severity as determined by the clinical neglect tests (for calculation cf. Chapter 4.1.5).

In the acute stage of the disorder (Exam 1), we found marked differences between the patients with spatial neglect and the control group for both, active exploratory ($t_6 = 9.25$, $p < .001$) and resting behaviour ($t_5 = 4.51$, $p = .005$). In each condition, the mean horizontal gaze position was close to the mid-sagittal body axis in the control group (active search: $M = -2.7°$, $SD = 7.6°$; rest: $M = -1.4°$, $SD = 4.2°$), while it was markedly deviated towards the ipsilesional side by 55.3° ($SD = 14.4°$) during active visual search and by 30.0°

(*SD* = 16.8°) at rest in patients with spatial neglect. Correspondingly, the omissions made in the clinical neglect test differed markedly between the two groups ($t_5 = 7.03$, $p = .001$).

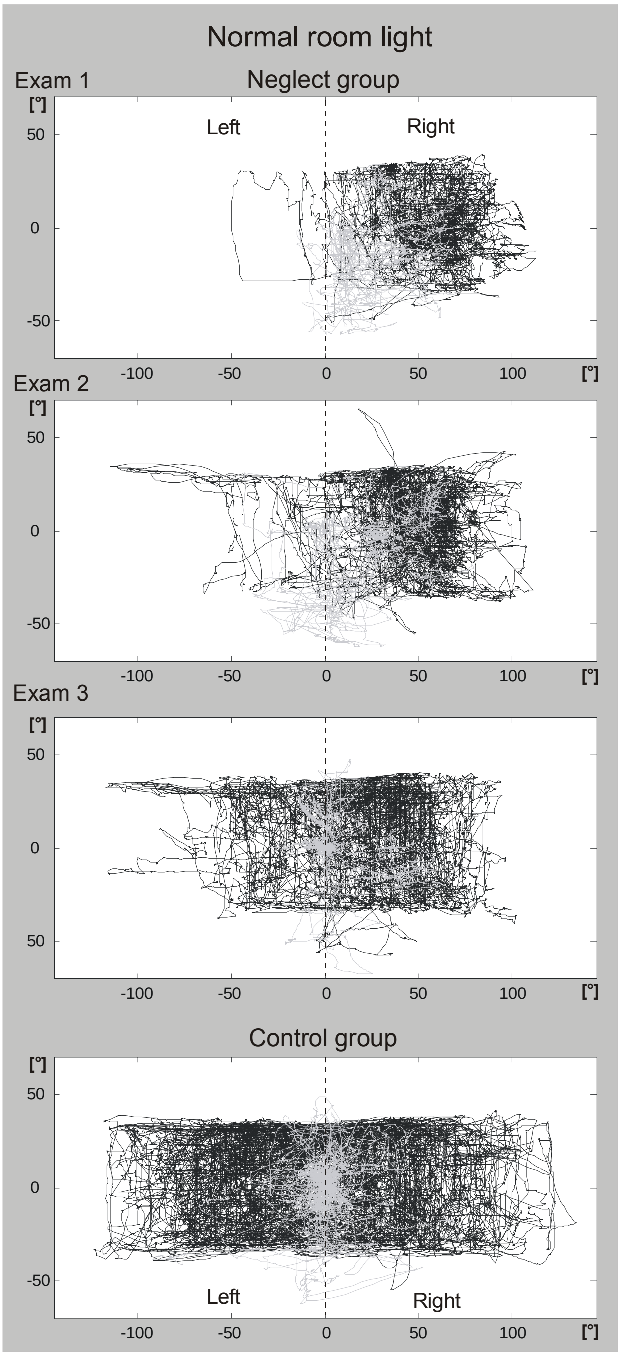

Figure 13. *Time course of active and passive gaze orientation in light. Scan paths (= gaze) of the patients with spatial neglect during "active" visual search (black lines) as well as at "passive" rest (grey lines) for each time of examination (upper 3 panels) compared to the group of control patients without the disorder (lower panel) when room lights were on. In the acute stages of the disorder, the neglect patients showed a marked bias of their active and their passive behaviour towards the ipsilesional, right side (Exam 1 > Exam 2). In the chronic stage (Exam 3), it converged towards the performance of patients without the disorder.*

To analyse the development of active and passive neglect behaviour as measured by the neglect patients' gaze positions in light as well as of the neglect severity, we conducted a two-way repeated measures analysis of variance with 'time' (Exam 1, Exam 2, Exam 3) and 'condition' (active search, rest, severity) as within-subject factors.

Analyses of the simple main effects indicated marked differences for both, the course of recovery ($F_2 = 64.35$, $p < .001$) as well as for the amount of the patients' neglect behaviour in the different conditions ($F_2 = 5.44$, $p = .025$). Post-hoc analyses revealed that neglect patients showed a more rightward deviation during active visual search than at rest in both, the acute as well as the subacute stage of the stroke (Exam 1: $t_5 = 4.53$, $p = .006$; Exam 2: $t_5 = 4.75$, $p = .005$). The differences between active and passive neglect behaviour amounted to 25.3° at Exam 1 and to 22.6° at Exam 2.

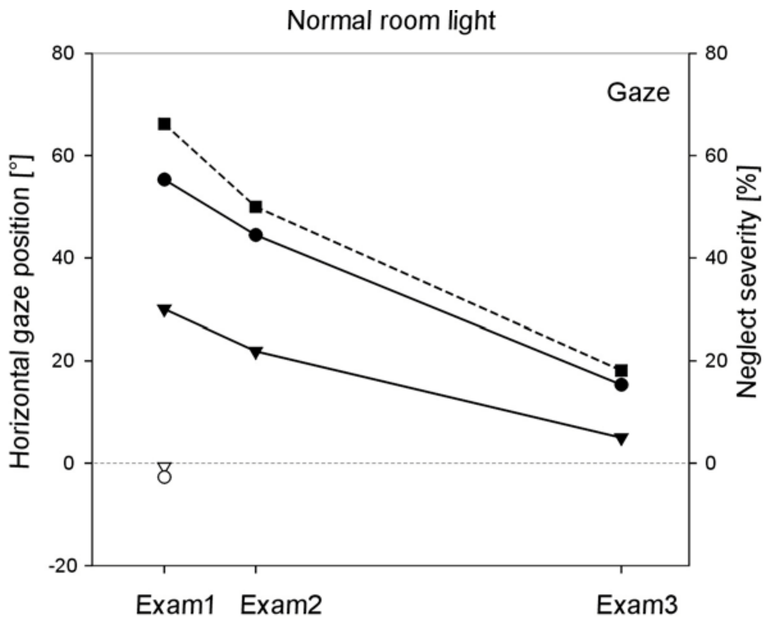

Figure 14. *Mean gaze positions for active and passive neglect behaviour in light. Averaged horizontal gaze position of the patients with spatial neglect during active visual search (closed circles) and at rest (closed triangles) for each time point (Exam 1 to 3) compared to the performance of the patients without the disorder (visual search: open circle; rest: open triangle) when room lights were on. In addition, the averaged neglect severity as measured by the clinical neglect tests is given (closed squares). The doted horizontal line represents the position of the mid-sagittal body axis (0°).*

Post-hoc comparisons on the time course of recovery showed a common decrease of the neglect patients' gaze deviation between the initial (Exam 1) and the follow-up (Exam 3) examination for both, active search ($t_5 = 9.23$, $p < .001$) and rest behaviour ($t_5 = 5.14$, $p = .004$). At the chronic stage, the rest position had improved by approximately 83 percent

(= 25°) of its initial amount, resulting in a residual rightward deviation of 5.0° (*SD* = 16.1°, cf. Figure 14). Within the same period the neglect patients active search behaviour decreased on average by 72 percent (= 40°), which was also the case for the clinical neglect severity (t_5 = 13.87, p < .001).

The performance measured by the visual exploration task (t_5 = 5.72, p = .002) as well as by the clinical neglect test (t_5 = 4.89, p = .005) also improved markedly between the subacute (Exam 2) and the chronic stage (Exam 3) of the disorder. Analyses of the passive behaviour showed a comparable trend (t_5 = 2.52, p = .053). Within this period, the improvement amounts up to 66 percent for the visual search respectively 77 percent for the resting condition.

Eye-in-head and head-on-trunk positions under normal room light conditions

At the first examination (Exam 1), mean eye-in-head and head-on-trunk positions differed markedly between the group of neglect patients and the control group in both conditions (active search: t_{16} = 6.81; t_{16} = 8.38; rest: t_{16} = 4.74; p < .001 each; t_5 = 2.55; p = .048). As reported, mean horizontal eye-in-head and head-on-trunk positions in control patients were close to the their mid-sagittal body axis (cf. Figure 15). In clear contrast, the eye-in-head position in patients with spatial neglect amounted to 16.7° (*SD* = 4.9°) during visual search and to 14.2° (*SD* = 5.4°) at rest. Accordingly, head-on-trunk positions were shifted towards the ipsilesional side, namely about 38.5° (*SD* = 12.8) in the active task and about 15.5° (*SD* = 15.9°) in the passive condition.

Repeated measures ANOVAs with 'time' (Exam 1, Exam 2, Exam 3) and 'condition' (active search, rest) as within-subject factors revealed marked differences for the time course of recovery (eye-in-head: F_2 = 7.93, p = .009; head-on-trunk: F_2 = 9.11, p = .006) as well as a simple main effect of condition (F_1 = 22.98, p = .005) and a significant interaction (F_2 = 8.38, p = .007) for head-on-trunk.

Post-hoc analyses on the time course of eye-in-head and head-on-trunk deviation showed a common decrease between the initial and the second follow-up examination for active search (eye-in-head: t_5 = 6.64, p = .001; head-on-trunk: t_5 = 8.17, p < .001) and for the resting condition (head-on-trunk: t_5 = 4.46, p = .007). In the chronic stage (Exam 3), the patients' passive eye-in-head and head-on-trunk positions at rest had improved by 91 percent respectively 77 percent of the initial amount (see Figure 15), resulting in mean eye and head positions around the mid-sagittal body axis. Within the same period, neglect patients' exploratory eye-in-head and head-on-trunk movements had decreased on average by 88 percent respectively 66 percent, leading to mean eye-in-head positions of 2° and a residual head-on-trunk deviation of 13.2° towards the ipsilesional side.

Post-hoc analyses also revealed that the rightward deviation of the head was more pronounced during active visual search than at rest in both, the acute as well as the subacute stages of stroke (Exam 1: $t_5 = 5.29$, $p = .003$; Exam 2: $t_5 = 4.79$, $p = .005$). The differences between active and passive neglect behaviour amounted to 23.0° at Exam 1 and to 20.4° at Exam 2.

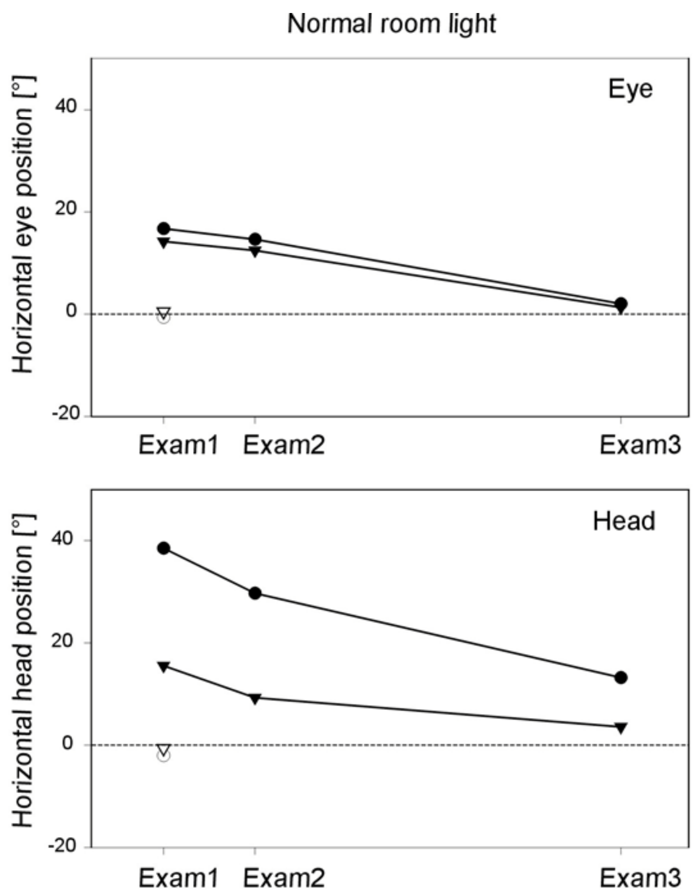

Figure 15. *Mean eye and head positions for active and passive neglect behaviour in light. Averaged horizontal eye-in-head (upper panel) and head-on-trunk (lower panel) positions of the patients with spatial neglect during active visual search (closed circles) and at rest (closed triangles) for each time point (Exam 1 to 3) compared to the performance of the patients without the disorder (visual search: open circles; rest: open triangles) when room lights were on. The doted horizontal line represents the position of the mid-sagittal body axis (0°).*

Development of active and passive neglect behaviour in complete darkness

Figure 16 illustrates the scan paths (= gaze) and Figure 17 the mean horizontal gaze, eye-in-head, and head-on-trunk positions as measured for the control and the neglect group during active visual exploration as well as at rest ('doing nothing') for the three times of examination in complete darkness.

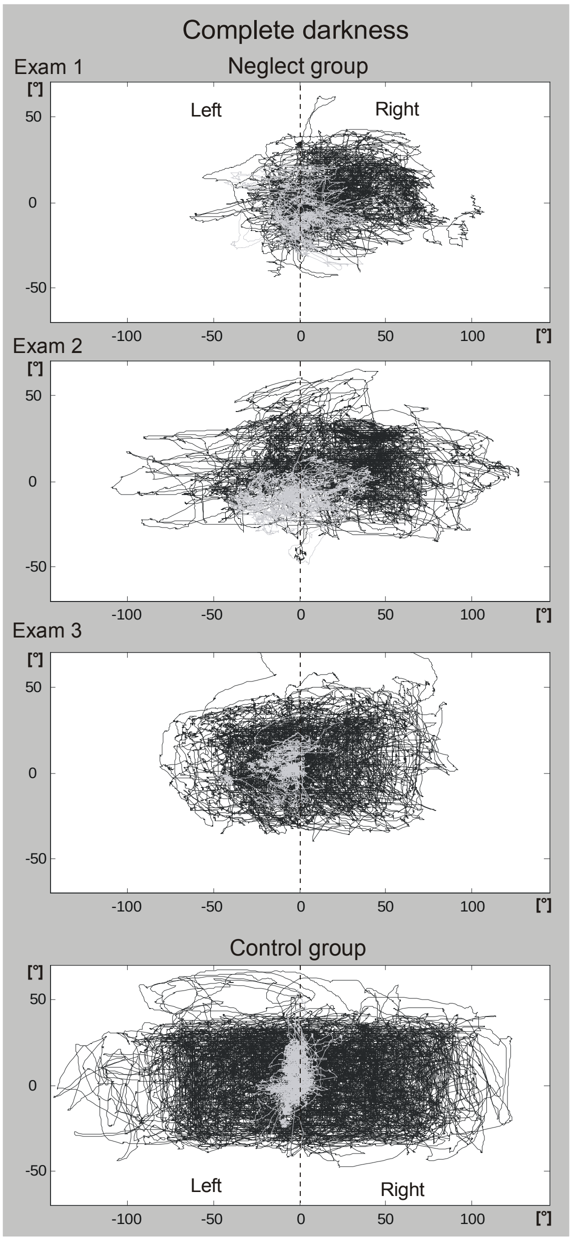

Figure 16. *Time course of active and passive gaze orientation in darkness. Scan path (= gaze) of the patients with spatial neglect during active visual search (black lines) as well as at rest (grey lines) for each time of examination (upper 3 panels) compared to the group of control patients without the disorder (lower panel) in complete darkness. In the acute stages of the disorder, the neglect patients showed a bias of their active search behaviour towards the ipsilesional, right side (Exam 1 > Exam 2). In the chronic stage (Exam 3), it converged towards the performance of patients without the disorder.*

In the acute stage of the disorder (Exam 1), the difference of active search behaviour (= gaze) in complete darkness amount to 21.4° between the patients with spatial neglect and the control group (t_5 = 2.55, p = .049; cf. Figure 17). While active exploratory movements in patients with spatial neglect were biased towards 24.6° (SD = 20.3°) on the patients' ipsilesional side, the mean horizontal gaze positions in patients without the disorder varied around the mid-sagittal body axis (M = 3.2°, SD = 4.8°). In contrast, gaze positions at rest did not differ between the groups. Both, the mean spontaneous gaze position in neglect patients (M = 2.2°, SD = 7.7°) as well as in patients without the disorder (M = -3.6°, SD = 3.9°) was close to the mid-sagittal body axis.

The development of active and of passive neglect behaviour in complete darkness was investigated by a two-way repeated measures analysis of variance with 'time' (Exam 1, Exam 2, Exam 3) and 'condition' (active search, rest) as within-subject factors. Analyses of the simple main effects revealed differences for the course of recovery (F_2 = 4.51, p = .040) and for condition (F_1 = 8.31, p = .034). Subsequent post-hoc analyses showed a more rightward gaze deviation (= combined eye and head positions) during active exploration compared to the resting position in the acute stage as well as a comparable trend in the subacute phase of the stroke (Exam 1: t_5 = 2.84, p = .036; Exam 2: t_5 = 2.54, p = .052). The differences between active and passive neglect behaviour amounted to 22.4° at Exam 1 and to 20.4° at Exam 2. Beyond, no further analyses reached significance. Yet it is remarkable that exploratory gaze positions in darkness showed a decrease of approximately 24° (= 97 %) between Exam 1 and Exam 3.

<u>Eye-in-head and head-on-trunk positions in complete darkness</u>

At Exam 1, eye-in-head positions during active visual search showed slight differences between the patients with spatial neglect and the control group (t_6 = 2.52, p = .047). Comparable to the normal room light condition, the mean horizontal eye position in patients without the disorder was close to the mid-sagittal body axis (M = 0.6°, SD = 3.1°), while it amounted to 9.4° (SD = 8.2°) in the neglect group. In contrast to the condition in light, head-on-trunk positions in complete darkness did not differ statistically between the patients with spatial neglect and the control group neither for active exploration (t_6 = 2.10, p = .085) nor for rest (t_{16} = 1.23, p = .237) in our present sample. Yet, there was a quantitative difference of about 13° at Exam 1 between the mean head-on-trunk positions in patients with spatial neglect and those without the disorder during active visual search.

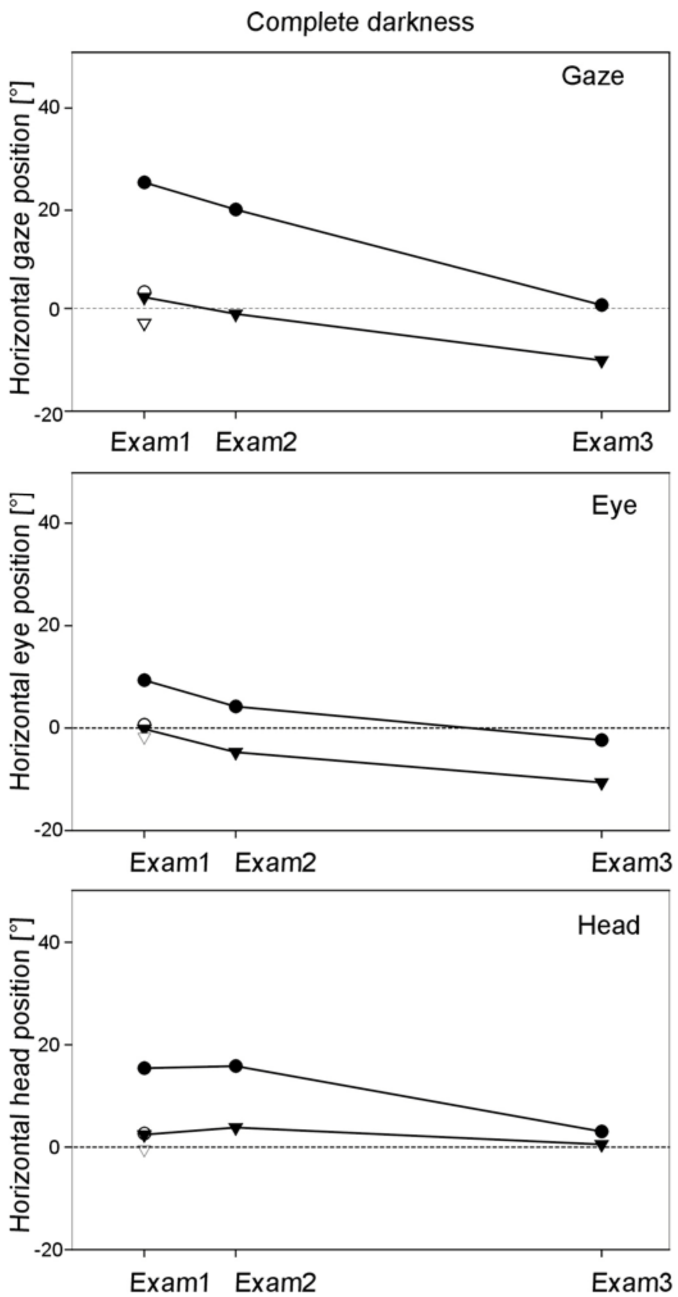

Figure 17. *Mean gaze, eye, and head positions for active and passive neglect behaviour in darkness. Averaged horizontal gaze (upper panel), eye-in-head (middle panel), and head-on-trunk (lower panel) positions of the patients with spatial neglect during active visual search (closed circles) and at rest (closed triangles) for each time point (Exam 1 to 3) compared to the performance of the patients without the disorder (visual search: open circles; rest: open triangles) in complete darkness. The doted horizontal line represents the position of the mid-sagittal body axis (0°).*

Repeated measures analyses of variance revealed differences between the eye-in-head positions regarding the condition (F_1 = 14.91, p = .012). Post-hoc tests showed a more rightward orientation of the eyes that amounted to approximately 9° during active visual search compared to the eye position at rest for each time of examination (Exam 1: $t_5 = 2.84$, $p = .036$; Exam 2: $t_5 = 2.88$, $p = .035$; Exam 3: $t_5 = 2.59$, $p = .049$). According to the neglect patients' eye positions obtained in light, also the eye positions in darkness had commonly decreased in both conditions, leading to an average eye orientation at rest towards the contralateral, left side (Exam 2: $M = -4.7°$, $SD = 10.1°$; Exam 3: $M = -10.6°$, $SD = 9.4°$). Further, the rightward orientation of the head during active visual search was found to be more pronounced at Exam 1 compared to Exam 3 ($t_5 = 4.36$, $p = .007$) with an average amelioration of about 12.4° within the 10 months period.

4.4.4 Discussion

The present study investigated whether a bias during "active" visual search and at "passive" rest (i.e. of active and passive gaze orientation) are independent or related symptoms of spatial neglect. Our main focus was -due to our definition of neglect behaviour- on combined eye and head positions (= gaze) under normal room light conditions. Analysis of the course of recovery over a period of 10 month post stroke revealed a parallel decrease in both behaviours that was accompanied by a comparable decline in neglect severity. The common time course argues for a close relationship between active and passive neglect behaviour. Indeed, the observation of a shared development does not finally prove a *causal* relationship between active and passive neglect and does not necessarily imply a common underlying mechanism. Nevertheless, the parallel decrease in both behaviours is suggestive to assume a close relationship as it was observed in every single patient with spatial neglect of the present sample (cf. also Chapter 5 for discussion).

A further argument for a close relationship between active and passive neglect behaviour is provided by a recent anatomical study focussing on brain lesions in patients with a "passive" deviation of the eyes (Singer, Humpich, Laufs, Lanfermann, Steinmetz, & Neumann-Haefelin, 2006), that is likewise observed from a behavioural point of view in the present work. The authors uncovered a remarkable analogy of the cerebral regions affected in their patient group to the neural correlate of spatial neglect as diagnosed by active tasks like cancellation or copying. They described a network of structurally affected regions in the right hemisphere, including the temporoparietal junction and the basal ganglia as well as perfusion deficits in the right inferior parietal cortex, the supramarginal gyrus, the middle and superior temporal cortex as well as parts of the insula (cf. their Figures 4a and 5). Interestingly, these regions are known to be structurally injured in patients with spatial neglect (Heilman et al., 1983b; Karnath et al., 2001, 2004a, 2004b; Mort et al., 2003; Vallar & Perani, 1986) as well as to be malperfused though structurally intact in cases of subcortical neglect (Karnath et al., 2005; please cf. Chapter 2.1.4).

Previous studies followed the patients' spontaneous eye/head position under normal room light conditions by clinical inspection in the acute and subacute stage (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Tijssen, 1988; cf. Chapter 2.4.4). However, its progress was not related to the co-occurrence of spatial neglect. The average duration of eye deviation in these studies was estimated between 12.5 days (De Renzi et al., 1982) and 18.5 days (Kömpf & Gmeiner, 1989) in patients with right hemispheric stroke. Ringman et al. (2005) conducted a post-hoc analysis on a data subset of a previous multicentre study. Three months post stroke, neither left nor right hemisphere patients showed a spontaneous deviation of the eyes. Yet, the authors did not relate their results to the recovery of spatial neglect in this sample. The study of De Renzi et al. (1982) investigated the co-occurrence of spatial neglect once between day 14 and 18. At this time, all patients with a clinically defined eye or head deviation showed neglect symptoms. However, the disorder was also found in some of those patients whose initial eye/head deviation had already recovered but who had not previously been investigated for spatial neglect. Although the results of De Renzi and co-workers (1982) are not strictly comparable with the present study (different procedures to detect gaze deviation and to test for spatial neglect; cf. Chapter 2.4.3), they bear an interesting analogy, namely the gradual difference in the recovery of eye deviation compared to the recovery of other clinical neglect symptoms.

The present study revealed that both, passive and active neglect behaviour (i.e. passive respectively active gaze orientation) have a parallel time course, but may start at different levels of impairment. One obvious explanation for these gradual differences at stroke onset may be the task difficulty of our exploration task. It required searching for a non-existing target in a very dense array of distractors covering 240° of horizontal space respectively in the *whole room* when the experiment was carried out in complete darkness. Previous studies on active tasks have shown that the rightward bias is reduced by decreasing the number of stimuli in search displays (De Renzi et al., 1989; Husain & Kennard, 1997; Kartsounis et al., 1994; Rapcsak et al., 1989) or during visual exploration in darkness (Hornak, 1992; Karnath et al., 1996). The latter is supported by the present results, showing a reduced degree of active and passive neglect behaviour in darkness compared to normal lightning conditions. Thus, it is feasible that less complex visual exploration tasks would provoke eye/head shift amplitudes that are more comparable in extent to those at rest.

Our results on the spontaneous resting position in darkness offer an interesting perspective for further research on task-specific differences. At present, reports on its development are missed that may help to explain the patients' gaze orientation in complete darkness towards the contralesional, left side as measured 10 months post stroke. Within a wider scope, the observation of Pflugshaupt et al. (2003, cf. Chapter 2.3.4) may be interesting to note, though it derives from exploratory search in light and do not allow for direct comparisons. The authors recorded eye movements in a group of pre-selected, solely recovered neglect patients during time constraint visual search within everyday scenes (size 29°x22°, 7 seconds each). Eleven months post stroke, these patients also showed a slight deviation towards the contralateral, left side regarding the horizontal distribution of fixation frequency. Further, asymmetry quotients (AQ) revealed a higher total fixation duration in favour of the contralesional side in patients with recovered neglect (AQ 0.91) compared to a group of healthy control subjects, who showed a balanced search behaviour (AQ = 1.04; $p = .04$). Unfortunately, no eye movement measures of the patients' performance from the acute stage were included that would allow to study and to compare the course of recovery.

Our present finding on a parallel development of active and of passive neglect symptoms strengthen the view that the characteristic feature of this striking behaviour, namely the marked deviation towards the ipsilesional side, is due to a very elementary disturbance of spatial information processing as already suggested by Study 1 and 2. Under both rest and active task conditions, patients with spatial neglect show a specific bias that might represent a pathological default position of eyes and head at a new origin on the ipsilesional side. This shift towards a new default position may be explained by a disturbance of the transformation process that converts the multimodal sensory input into internal representations of space and that provides us with redundant information about the position and motion of our body relative to external space (cf. Karnath & Dieterich, 2006 and for further discussion Chapter 5).

5 GENERAL DISCUSSION

5.1 Discussion and Conclusions

The present work on patients with unilateral cerebral lesions measured the relationship between spatial neglect and a spontaneous deviation of the eyes and the head by means of standardised recording techniques. The first part of the present work investigated the relation between active and passive neglect behaviour in the acute and subacute stages of stroke. In contrast to previous studies, we determined not only the discrete presence or absence of eye deviation by clinical inspection, but measured the extent of horizontal gaze, eye-in-head, and head-on-trunk deviation in light as well as in complete darkness. In further contrast, we compared the results of patients with acute first-ever stroke as well as of healthy subjects with respect to their spontaneous eye and head position as well as the presence respectively absence of spatial neglect by implementing an experimental setting without any explicit requirements that allows for a precise measure of the patients' resting position.

Study 1 showed that an ipsilesional bias of spontaneous eye and head position regularly occur with spatial neglect when measured on average 13 days post stroke in both, light and complete darkness. This finding argues for a comparable specificity of this symptom as it is reported for the patients' lateralised behaviour in active search tasks. Our main finding was that the eyes and the head in patients with spatial neglect were markedly oriented to the right. Their average gaze position showed an ipsilesional bias of about 30° in light and was reduced but still observable in complete darkness. The extent of this spontaneous deviation in the resting condition under both lightning conditions corresponded well with the position measured when the patients were instructed to "look straight ahead".

Our results from the subacute phase allowed for implementing eye movement recordings in the very acute stage at the patients' bedside. Consequently, *Study 2* asked whether a substantial gaze deviation could also be observed in very acute stroke patients without any symptoms of spatial neglect -as implicitly stated for example by stroke scales but has not been investigated so far (cf. Chapter 2.4.1)- or if it is specific to the disorder even in the very acute stage. In contrast to the first study, measurements were performed as early as possible after stroke onset in an unselected sample with acute left and acute right hemispheric stroke. On average 1.5 days post stroke, we observed that each single patient with spatial neglect and a right-sided lesion showed a marked spontaneous bias of the eyes and the head towards the ipsilesional side. The average deviation of the spontaneous horizontal gaze position in the neglect group was striking with 46° towards the right. Such marked deviation of the eyes and the head was neither observed in left or right hemisphere stroke patients without spatial neglect, nor in healthy subjects. Spontaneous horizontal eye-in-head and head-on-trunk positions in these latter groups varied around the sagittal trunk midline (0°), summing up to an average position very close to this axis.

Spatial neglect – an elementary disturbance of spatial information processing

The present work revealed that a spontaneous "passive" deviation of the eyes and the head is as specific to spatial neglect as is the "active" performance in clinical or experimental tasks traditionally used to uncover the most characteristic, lateralised behaviour in such patients. These findings as well as our observation on a parallel development of active and passive neglect behaviour in Study 3 strengthen the view that the most characteristic component of the disorder, namely the marked deviation towards the ipsilesional side, is due to a very elementary disturbance of human spatial information processing. Under both, rest and active task conditions, such patients show a specific bias that might represent their pathological default position of eyes and head at a new origin on the ipsilesional side. Our results are in line with the assumption that this shift may be explained by a disturbance of the transformation process that converts the multimodal sensory input (visual, vestibular, neck proprioceptive, etc.) into long-lasting, internal representation of space (cf. Chapter 2.2.3). The pathological "default position" observed in the present work might be a consequence of a rotation of these reference frames towards the lesion side. From an anatomical point of view, the superior temporal gyrus, insula, and the temporo-parietal junction seem to be crucial parts of the multisensory system involved in these transformation process and probably constitute the neural basis for orienting and exploring (cf. Chapter 2.1.4). It is assumed that these regions provide us with redundant information about our body position and motion and thus are essentially involved in adjusting our body relative to external space (Karnath & Dieterich, 2006).

In contrast, the present work does not confirm previous assumptions on a spatially lateralised left-to-right gradient of attentional orienting (Kinsbourne, 1977, 1993; Rizzolatti & Berti, 1990; Rizzolatti et al. 1985; cf. Chapter 2.2.1 & 2.2.2). Following this idea, the performance of patients with spatial neglect would be expected to successively deteriorate from the very right to the extreme left side. Studies on eye movement pattern under restricted visual search conditions have been interpreted to favour this view

(Behrmann et al., 1997; cf. Chapter 2.3.2). In contrast, studying the natural course in a set-up that allows for free eye and head movements within a range of ± 140° reveals a peak of exploratory movements within a bell-shaped distribution, but not a lateral gradient with the peak of search activity at the extreme ipsilesional, right side of a given array (please cf. Study 3). Our results further confirm the assumption that the horizontal range in studies like that of Behrmann et al. (1997) is too narrow to detect how the distribution would continue on the outer right side of space (Karnath, 1997). Particularly a study by Niemeier and Karnath (2002) demonstrated that the brain continuously organises and reorganises its representation of the same physical stimulus in correspondence with changing task demands. This finding favours instead of a static model, a more dynamic view of the subjects' representation of the multimodal egocentric reference frames. In line with this assumption, the present results integrate the seemingly contrasting results on visual search behaviour as representing a function of display size and thus appear to be more complementing than contradictory. Moreover, at rest the patients' passive behaviour was also remarkable biased but was located far away from the very right side of space, namely within the area that was previously scanned during visual search, what further clearly argues against a maximum of severity on the extreme right side. Finally, according to Kinsbourne's theory, every unilateral cerebral lesion should provoke signs of spatial neglect. This was neither confirmed by previous nor by the present results (cf. Studies 1 to 3 and Chapter 2.1.4).

Although Posner's theory (cf. Chapter 2.1.1) may explain why patients with spatial neglect are impaired in directing their attention towards the contralesional side, it presumably does not account for the phenomenon that a bias of exploratory search is also present in complete darkness as observed in the present studies. The idea of Pouget and Driver (2000) who explained the ipsilesional bias and graded deficits in neglect patients by a pathological gradient caused by partial loss or dysfunction of similar cell populations is also opposed by our findings. Their neural model of monkeys cannot explain the consistent findings on a right hemisphere dominance in patients with spatial neglect, which has again been replicated particularly by Study 2. Among all stroke patients of the present studies, we did not observe spatial neglect caused by left hemisphere lesions, but we were able to investigate a balanced sample of right hemisphere patients with and without the disorder. This is in line with previous research on the incidence of the disorder following left hemisphere stroke, showing that spatial neglect occurs as asymmetrically after right hemisphere stroke (cf. Chapter 2.1.2; Bowen et al., 1999; Mesulam, 2002; Pedersen et al., 1997), as for example aphasia after left hemisphere lesions. In a prospective, community-based study, 85 percent of the patients who suffered from spatial neglect had a right hemisphere lesion (Pedersen et al., 1997). However, as patients exist with aphasia after right hemisphere stroke, we expect to find patients with spatial neglect after left hemisphere lesion in other samples or samples of larger size. Based on the present findings, we predict that such neglect patients would show a spontaneous eye and head deviation towards the left side, comparable to the marked rightward deviation observed in each of the neglect patients of the present study.

Clinical impact for the diagnosis of spatial neglect

As shown in Chapter 2.4.1, identification of stroke patients should be based on brief and easy to observe predictors as provided for example by various stroke scales. In this context, the spontaneous orientation of the eyes and the head as observed in the present work might be of interest. In fact, the patient's initial gaze position is known to serve as acute clinical sign for stroke during prehospital evaluations even before admission to the stroke unit. One of the most common stroke scales, the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989) was developed to identify stroke patients and measure stroke severity. Even the two shortened versions of the NIHSS, consisting of 8 respective 5 items (sNIHSS-8 and sNiHSS-5), included the initial gaze position and thus generally support its clinical value in the very acute stage for the triage of acute stroke patients (Tirschwell et al., 2002). However, the patients' gaze is not related to the diagnosis of spatial neglect so far (cf. Chapter 2.4.1).

Until now, it seemed as if this sign of steering the eyes towards the side of the brain lesion occurs with both, right-sided as well as left-sided stroke. Already in 1865 Jean Louis Prévost reported that "in all cases [of acute hemiplegia] I have observed, the two ocular axes were always deviated to the side opposite the paralysis, thus the two eyes looked towards the damaged hemisphere" (Prévost, 1865, p. 649). Moreover, he pointed out that the deviation of the eyes and the head "can be an invaluable indicator for the [stroke] diagnosis" (Prévost, 1865, p. 649). The present work does not only confirm Prévost's (1865) observation that the initial gaze deviation in stroke patients is directly related to hemisphere lesions and therefore is a valid predictor of acute stroke. The results also add a crucial modification/supplement to his initial report on patients with acute hemiplegia, such that they clearly argue for a direct link between a marked eye and head deviation and right-sided lesions in patients with acute hemispheric stroke *and* spatial neglect. Moreover, it was presently shown that the same account to later stages of the stroke (cf. Study 1 and 3). Prévost's sign and spatial neglect thus seem to reflect the same phenomenon, namely an orientational bias towards the lesion side. The present results on a total of 72 patients revealed that this ipsilesional deviation occurs predominantly with unilateral right-sided stroke, thus indicating that the underlying function is represented asymmetrically in the human hemispheres (for review cf. Karnath & Dieterich, 2006).

The implemented procedure of "doing nothing" is quite comparable to that on stroke units, when clinicians initially look at the patients' eye and head position in order to detect hemispheric lesions. Our results on patients with hemispheric stroke thus may further have implications for both, acute stroke diagnosis as well as for neuropsychological assessment. As acute language disorders strongly argue for a stroke in the left hemisphere, our data suggest that a marked horizontal eye and head deviation observed in the very early phase (~1.5 days) is a clear sign for spatial neglect and thus typically right-sided lesions. Yet, both assumptions would undoubtedly have to be validated as soon as possible by appropriate measures, i.e. by standardised clinical neglect tests respectively MRT/CT scans in order to avoid a false diagnosis.

Also in later phases, i.e. about 12 and 19 days post stroke all patients with spatial neglect but none of the controls showed a marked deviation of the eyes and the head towards the ipsilesional, right side. Thus, an accompanying evaluation of the horizontal eye and head position in stroke patients could help to facilitate and validate the initial diagnosis of spatial neglect in addition to the traditional paper-and-pencil tests. Again, it is important to mention that eye and head deviation may also occur with e.g. epileptic seizures, brainstem, and cerebellar lesions (cf. Chapter 2.4.2). These pathologies, however, have not been addressed in the present work and thus are not included in our present conclusions about hemispheric stroke.

From the patients' perspective, the observation of their gaze orientation may serve as a brief and convenient way to detect the disorder in the very acute stage of the stroke, i.e. in a situation when standardised neuropsychological testing is too exhausting and is complicated by impaired consciousness or, particularly after left hemisphere stroke, by potential language disorders. Based on the present results, we conclude that the detection of the patients gaze in acute stroke may help to identify patients with spatial neglect early after symptom onset, which is important with respect to an early rehabilitation and adequate clinical treatment (cf. Chapter 2.1.3).

Parallel time course of active and passive neglect behaviour

The second part of the present work investigated the relation between active and passive behaviour in the course of recovery. Based on the first two studies showing that the striking ipsilesional bias in patients with spatial neglect is not only apparent in tasks that address the "active" behaviour but also in the spontaneous resting position, it seemed as if both aspects characterise the disorder. However, it remained open whether these changes are independent or related symptoms of spatial neglect. *Study 3* thus measured the development of the patients' gaze deviation during "active" visual search as well as at "passive" rest in the course of recovery. In addition to the resting condition ("doing nothing"), we implemented an active search condition resembling the cancellation task of Weintraub and Mesulam (1985). The latter is traditionally used for the diagnosis of spatial neglect in a clinical context (cf. Chapter 2.1.3). Eye and head recording analyses covering a period of about 10 month post stroke revealed a parallel decrease of rightward gaze orientation in both conditions, which was accompanied by a comparable decline in neglect severity as measured by clinical tasks. This common time course argues for a close relationship between active and passive neglect behaviour under normal room light conditions as well as in complete darkness. Of course, the observation of a shared development do not finally prove a causal relationship between active and passive neglect behaviour and also do not necessarily imply a common underlying mechanism (see Chapter 5.2 as well). However, the common decrease in both behaviours is suggestive to assume a close relationship. In fact, a marked deviation under both rest as well as active task conditions, which had declined in parallel over time, was observed in every single patient with spatial neglect of the present sample. Beyond, this relation is underlined by the lack of dissociation between the symptoms.

To date, no follow-up study on active or passive neglect behaviour has been conducted that would allow for comparisons to our present long-term study. Thus, we here report on analogies to previous one-time examinations of visual exploration in spatial neglect or to observational studies, that followed eye and head deviation in the acute and subacute stages independently from the diagnosis of spatial neglect (cf. Chapter 2.3.4 & 2.4.4).

Regarding the degree of rightward deviation, one-time examinations that allowed for unrestricted free exploratory search in light or darkness might be interpreted to correspond to our results. In line with our present Exam 1 (12 days post stroke: mean = 55°) and Exam 3 (10 months post stroke: mean = 15°), a study by Karnath et al. (1998) revealed mean gaze positions of about 41° towards the right side when measured on average 2.4 months post stroke. Accordingly, gaze positions in darkness generally showed a smaller ipsilesional deviation of about 15° (Karnath & Fetter, 1995; Karnath et al., 1996). Repeatedly, these studies revealed a symmetrical bell-shaped distribution with a central peak on the right side of the mid-sagittal body axis but no continuously increasing gradient of saccadic eye movements from the left to the right side as it was likewise observed in the present work.

Beyond, solely studies using smaller display sizes had been conducted that were not directly comparable to our present results but show the expected trend of recovery towards the mid-sagittal plane. Eye movements of patients with chronic neglect showed a right-sided maximum around 18° when measured on average 12.7 months post stroke (Behrmann et al., 1997), whereas recovered neglect patients showed no ipsilesional bias during visual search 30 months after symptom onset (Pflugshaupt et al., 2004). Dividing our patients by their performance in the clinical neglect tasks (although this was not the focus of the present work) resembles these findings. Ten months after stroke onset, patients with persistent neglect as defined by clinical tasks showed a rightward bias of about 26.7° in light, while those who had already recovered searched around 4.0°, and thus had converged towards almost "normal" positions around the mid-sagittal body axis.

So far, the development of the patients' spontaneous eye/head position at rest was not related to the co-occurrence of spatial neglect. However, some previous studies followed the eye/head orientation by clinical inspection in the acute and subacute stage (cf. Chapter 2.4.4). Our results did not only confirm those studies estimating a longer duration of eye/head deviation between 14.9 and 17.6 days after right hemisphere stroke (e.g. De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Tijssen, 1988), but also suggest that a marked bias may persist beyond the subacute period. Actually, our patient sample still showed a pronounced gaze deviation of about 22° towards the right side when measured on average 19 days after symptom onset. In line with previous studies (De Renzi et al., 1982; Kömpf & Gmeiner, 1989; Tijssen, 1988), our findings thus argue against the conclusion that a bias of the eyes/head vanishes within minutes, hours, or few days (Okinaka et al., 1952; Steiner & Melamed, 1984). However, since the later studies did not diagnose or report about symptoms of spatial neglect, any attempt to explain the different time courses would remain speculative.

Yet, our results bear an interesting analogy to the study of De Renzi and co-workers (1982) who did not follow the course of recovery, but investigated the co-occurrence of spatial neglect once between day 14 and 18. At this time, all patients with a clinically defined eye or head deviation showed neglect symptoms. Thus, both studies argue for a gradual difference in the recovery of gaze deviation compared to the recovery of symptoms as diagnosed by clinical neglect tests. Consequently, Study 3 clearly opposes the assumption of a review article stating that a possible deficit of initial eye and head orientation in the acute stage recovers fast compared to spatial neglect (Fink & Heide, 2004, p. 398). A main finding of the present work is that a spontaneous deviation of the eyes and the head is directly linked and specific to spatial neglect. Thus, the patients' passive neglect behaviour is not a distinct symptom that may solely co-occur with traditionally defined "active" neglect symptoms, as it is the case for disorders like extinction or impaired working memory (cf. Chapter 2.1.1). In fact, we found a gradually different, but parallel recovery of gaze positions during active *and* passive conditions as well as of neglect severity, arguing for related symptoms that both characterise spatial neglect and specify the disorder even beyond the very acute stage. In contrast to Fink and Heide's (2004) conclusion, our data showed that a deviation of the eyes and the head will not recover faster but still is obvious in some patients up to 10 months post stroke, though to a lesser degree than during active exploratory search. Importantly, it has to keep in mind that this previous conclusion did not refer to quantitative data but to discrete, clinical observations.

Based on the gradually different, but parallel development of active and passive neglect behaviour, we suggest that a profound bias in passive orienting at the acute stage may serve as reliable criterion for severe neglect. However, the question if the patients' spontaneous gaze deviation may predict chronic symptoms has not been addressed in the present work. The predictive value of the patients' initial gaze positions might be an interesting topic for future research on a larger sample size and sub-groups matched by their clinical neglect severity.

Task-specific effects and other influences on active and passive neglect behaviour

We found differences regarding both, the task (active versus passive) as well as the lighting condition (light versus darkness). Study 3 showed that passive and active neglect behaviour has a parallel time course that may start at a different level of impairment. One obvious explanation for these gradual differences may be the difficulty of our complex exploration task requiring searching for a non-existing target within a dense array of distractors that covers 240° of horizontal space. Previous studies on active tasks (e.g. cancellation, exploration, reaction time) have shown that the rightward bias is reduced by decreasing the number of stimuli in search arrays (De Renzi et al., 1989; Husain & Kennard, 1997; Kartsounis & Findley, 1994; Rapcsak et al., 1989) or during visual exploration in darkness (Hornak, 1992; Karnath et al., 1996). Thus, it is feasible that less complex search tasks would reveal a more comparable shift of eye/head position during active and passive conditions.

Further, the smaller bias of passive gaze during the resting condition may also be due to the lack of external requirements, i.e. the absence of any behavioural instruction. Actually, spatial neglect is considerably influenced by external factors. In this context it should be noted that both conditions were studied within the same visual array that surrounded the patients and allowed for free eye and head movements respectively in complete darkness. Thus, environmental influences have been kept constant and could not have affected the patients' behaviour within the tasks. However, it may be considered whether a direct demand on the patients' active search skills (given while standing straight behind the patient and asking to actively search the whole letter array) would have further enhanced the patients' basal orientation bias towards the right side that was already apparent at rest. Vice versa, the smaller bias of passive gaze may be explained by the lack of external, task-specific requirements. The stimulative nature of the visual surrounding at rest was almost at zero, although the same external sensorial stimuli as provided for the search condition could have addressed the patients' attention. The reduced bias found for the non-task-related, passive behaviour thus could also be interpreted such that the absence of a task-related, stimulative visual context diminishes the impact of the -in the rest condition- extraneous visual stimuli on the right side and uncovers the basal bias of the patients' egocentric orientation. It thus seems as if a demanding visual context (comparable to incoming sensory stimuli) on the ipsilesional side may play an additional role in shifting the eyes and the head towards it and in enhancing neglect on the contralateral side. This assumption is for example supported by the marked differences between gaze positions in complete darkness compared to those under normal room light conditions.

Regarding the effects of the different lightning conditions, our results on free exploratory search behaviour within a horizontal range of 240° are in line with previous studies using a comparable search field either with or without a visual context. In darkness, the rightward deviation of active neglect behaviour was markedly reduced compared to that in normal room light. This corresponds well to former studies, reporting a larger degree of rightward exploratory eye movements in normal room light (about + 41°; Karnath et al., 1998) than in complete darkness (about + 15°; Karnath & Fetter, 1995; Karnath et al., 1996; Karnath, 1997). Interestingly, Hornak (1992) who measured eye movements in darkness within a quite smaller array (~ 70°) than the Karnath group had done (100°), reported on a rightward deviation of the eyes around 15° as well. This finding might be due to the entirely smaller deviation in darkness that may "circumvent" the effect of display size reported for exploratory search in light. Yet, regarding future studies focussing on search behaviour in complete darkness, we still would like to argue for display sizes beyond 70°. Although the mean rightward deviation at our initial investigation centred at 25°, the range of exploratory movements within our patient group still amounted to 112°.

Within the different lightning conditions, gradual differences in the degree of rightward deviation might of course be due to the time interval between stroke onset and eye movement recordings. In the present work, the patients' eye and head deviation already had decreased within 1 week. While the mean gaze position in light amounted to 30° when measured ~12 days post stroke, it was found at 21.9° on day ~19 after symptom onset (cf. Figure 14). Initial gaze positions of very acute patients recorded ~1.5 days post stroke were even more pronounced with 46° towards the ipsilesional side. Of course, this time course is not surprising, since all symptoms usually improve during the period of stroke recovery. However, regarding the question of a common development of active and passive neglect behaviour (cf. Study 3), it appears to be useful to gain first insight into whether both behaviours will recover in parallel and to the same amount or if they may dissociate from each other over time (see above).

Based on previous research and ours, it thus can be concluded that the degree of rightward deviation is a function of display size, the stimuli and task characteristics, as well as of the course of recovery (cf. also Chapter 2.3.2, 2.3.3). Our results further confirm the assumption that neglect can be modulated to some degree by changing the attentional demands of a task for example by altering the lightning condition. However, since the effect of such contextual differences were not explicitly investigated with the present design they do not allow to draw conclusions about the underlying mechanisms that may lead to an enhancement of the deficits in light and an attenuation in darkness. Our preliminary results on the development of the passive neglect behaviour in chronic stages of the stroke however might stimulate ongoing research on the basal mechanisms that cause such differences.

Behavioural similarities in passive orienting between spatial neglect and vestibular (dys)function

The present observation that stroke patients with spatial neglect exhibit a horizontal bias of spontaneous eye and head orientation corresponds well to previous research on the function of the human vestibular system. This relation becomes especially important within the theoretical framework of spatial neglect that was first described by Karnath (1997; cf. Chapter 2.2.3) and that is clearly supported by the present work (see above). Actually, the egocentric reference system is highly susceptible to manipulations of its multi-sensory input, as will be shown in the following for the vestibular channel.

Experiments with *healthy subjects* revealed that asymmetrical vestibular stimulation of one vestibular organ, for example by cold water, induces a shift of the average horizontal eye position towards the stimulated side with the nystagmus (Abderhalden, 1926; Jung, 1953; Karnath et al., 1996; Karnath, Himmelbach, & Perenin, 2003b). Consequently, the lateral bias of the subjects' eye position is towards the right with right-sided stimulation and towards the left with left-sided application under this procedure. Using a comparable setting as the present Study 3, namely searching for a non-existing target in complete darkness, Karnath and co-workers (1996) showed that cold water irrigation of the left vestibular organ provokes a marked shift of exploratory eye movements in healthy subjects. This bias was observed towards the stimulated, left side and was further characterised by an almost total lack of spontaneous saccades beyond the mid-sagittal plane, i.e. towards the right side of space (cf. their Figure 1, p. 336). Obviously, the effects of vestibular stimulation on healthy subjects' search behaviour fit well with the visual search performance shown by our patient sample with spatial neglect (cf. Figure 13). In contrast, the same healthy subjects showed the usual, balanced search behaviour in line with the body axis when no caloric stimulation was applied (Karnath et al., 1996). A further consequence of this procedure is a shift of spontaneous head orientation around the yaw axis. Cold caloric stimulation of the right vestibular organ provoked a deviation of spontaneous head orientation of about 20° to 30° towards the right side (Karnath et al., 2003b; cf. their Figure 5, p. 235).

Interestingly, an intervention targeting the vestibular channel in healthy subjects provokes characteristic symptoms that have likewise been observed by the present work, when measuring eye and head positions in patients with spatial neglect at rest as well as during exploratory search (cf. Figures 13 & 16). In our patients, this bias was not only apparent with active motor behaviour (exploring, copying, reading, etc.) but also at rest, i.e. when "doing nothing". This behavioural similarities may strengthen the view that asymmetric function of the vestibular system and the horizontal bias of eye and head position in stroke patients with spatial neglect are closely related (for review see Karnath & Dieterich, 2006).

The tight connection is further confirmed by the compensatory effects on the ipsilesional deviation in *patients with spatial neglect* that are typically observed during stimulation of one vestibular organ (Karnath et al., 1996; Rode et al., 1998; Rubens, 1985; Vallar, Papagno, Rusconi, & Bisiach, 1995). Actually, left-sided vestibular stimulation in these patients results in a transient shift of exploratory eye movements towards the neglected side (Karnath et al., 1996). Thus, it seems as if there are comparable (vestibular) effects on healthy individuals and neglect patients, i.e. a leftward shift of exploratory eye movements that might be explained by a temporary shift of the whole body-centred reference system towards this side. This bias is likely to be caused by a transient interference of the vestibular channel, which is one crucial part of the multimodal sensory system that constitutes our internal spatial representations in relation to external space.

Anatomical similarities in passive orienting between spatial neglect and vestibular (dys)function

Further similarities between passive orienting in spatial neglect and vestibular (dys)function concern anatomical findings. Traditionally, injury to the right inferior parietal lobule (IPL) and temporo-parietal junction (TPO) had been considered the best predictor for spatial neglect (Heilman et al., 1983b; Mort et al., 2003; Vallar & Perani, 1986). Recently, four studies found the superior temporal gyrus (STG), the planum temporale, and the insula in the right hemisphere to be predominantly involved in neglect patients' impaired processing of spatial information (cf. Chapter 2.1.4 & Figure 3; for review see Rorden et al., 2006). On subcortical level, it was further observed that spatial neglect following lesions in the right basal ganglia induce perfusion deficits in just these cortical areas, namely in the STG, the IPL, and the TPJ, as well as in the inferior frontal gyrus (IFG; Karnath et al., 2005). Moreover, in spatial neglect the underlying mechanism is known to be as asymmetrically represented in the non-dominant, usually right hemisphere, as is language ability in the dominant hemisphere. This accounts for the observation that the characteristic, lateralised behaviour of neglect patients most commonly occurs with right-sided stroke (Bowen et al., 1999; Pedersen et al., 1997).

Likewise cortical activation pattern in humans during vestibular stimulation are not symmetrically distributed in the left and the right hemisphere, but mainly rely on the side of vestibular manipulation as well as on the subjects' handedness (Bense et al., 2003; Dieterich et al., 2003). According to these determinants, cerebral activation is enhanced on the side of the stimulated ear as well as in the non-dominant, usually right hemisphere. Thus, maximum activation is found when the non-dominant (right) hemisphere is ipsilateral to the stimulated vestibular organ, i.e. in the right hemisphere of right-handers during caloric irrigation of the right ear, while it is markedly reduced in their dominant, left hemisphere (Dieterich et al., 2003; cf. their Figure 4, p. 1002). Beyond this laterality, vestibular stimulation leads to distinct temporo-parietal activation pattern in the anterior and posterior insula as well as in the STG, the IFG, the IPL, the precuneus, and the anterior cingulum (Dieterich et al., 2003). Thus, it seems as if both, spatial neglect and vestibular processing at cortical level show a dominance in the non-dominant hemisphere and involve common brain areas.

The latter conclusion recently revealed support by a cortical, electrical stimulation study in humans. Searching for the *human equivalent* of the parieto-insular vestibular cortex described in monkeys (PIVC), Kahane, Hoffmann, Minotti, & Berthoz (2003) retrospectively investigated a subsample of patients with epilepsy who had undergone stereotactic intracerebral electroencephalogram recordings before surgery, and who had reported on vestibular signs, such as sensations of own body rotation concerning themselves or their surrounding environment. Electrical stimulation of 44 different temporal and parietal loci revealed an area in the temporo-peri-sylvian cortex from which mainly an illusion of own body rotation around the yaw axis was elicited (cf. their Figure 2, p. 621). This area, the so-called "temporo-peri-sylvian vestibular cortex" (TPSVC) extends above and below the sylvian fissure and mainly involves the STG, the middle temporal gyrus, and the parietal operculum. Within these regions, most of the 260 patients (82 %) described a sensation of bodily motion, while the illusion of rotation clearly dominated and was concretely described by the three major planes (yaw, pitch, roll). Stimulation of the parietal operculum was particularly reported to induce pitch plane illusions, while MTG and STG stimulation preferentially elicited sensations of primarily *head and whole body rotation* around the longitudinal body axis, i.e. in the horizontal plane. The authors thus confirmed the pioneer work of the Penfield group (Penfield, 1957; Penfield & Jasper, 1954; Penfield & Rasmussen, 1957), who had observed illusions of dizziness and rotary movements of the body particularly with electrical stimulation of the STG in patients with epilepsy.

Regarding the specificity of an eye/head deviation for spatial neglect this research is of particular interest, since just these areas in the temporal cortex -especially the STG- were found to be lesioned in a large group of patients with impaired spatial exploration and orientation abilities (n = 78; cf. Karnath et al., 2004a & Figure 3). Further, a rotation of the body-centred reference system around the patients' mid-sagittal body axis is suggested to underlie the lateralised behaviour in patients with spatial neglect (cf. Chapter 2.2.3 & Figure 7).

In the scope of our present findings and their relation to the vestibular system, it is further important to note that the PIVC has been proposed as an integration centre of the multisensory (vestibular) cortex in monkeys (Grüsser, Pause, & Schreiter, 1990a, 1990b; Guldin & Grüsser, 1996). Such integrative function may also account to its putative human equivalent, the TPSVC, described by Kahane and co-workers (2003). These cortical regions obviously are involved in multimodal (vestibular) processing and show a dense relation to areas critical for spatial orienting (cf. Chapter 2.1.4).

Beyond, Kahane et al.'s study (2003) is of particular interest for the present work since it addresses the phenomenon of a modified body-centred orientation from a perspective that is not obviously linked to spatial neglect at first glance. In fact, Kahane's findings on stimulation effects on the STG appear to be closely related to the main result of the present study, namely to a rightward shift of spontaneous eye and head orientation around the mid-sagittal body axis in neglect patients from both, a behavioural as well as an anatomical point of view.

To conclude, observations deriving from experiments on vestibular stimulation in healthy subjects and in stroke patients as well as from electrical stimulation of human cortex may indicate that the STG is a critical site for converting sensory input into longer-lasting spatial representations and thus for adjusting the subject's "default position" of eye and head orientation as reported here. Moreover, asymmetric function of the vestibular system and the horizontal bias of eye and head position in patients with spatial neglect seem to be closely related from a behavioural as well as from an anatomical point of view. Yet, considerations on the common mechanisms leading to spatial neglect and/or vestibular dysfunction have not been targeted by the present work and need to be validated by further investigations.

Implications for the rehabilitation of spatial neglect

Considering the rehabilitation of spatial neglect, it might be interesting that former clinically oriented approaches encouraged patients with left-sided neglect to direct their gaze towards the contralateral side, for example by asking them to find a red line marked on the left margin of a reading or search task. Initially, these attempts may have temporarily altered or even improved the patients' scanning behaviour. However, the success remained mainly task-specific and usually showed little generalisation to the complex natural environment beyond the training situation, which usually do not provide the patients with cues reminding them to look towards the left side (Robertson & Marshall, 1993).

Assuming an impaired representation of space in patients with spatial neglect that is caused by an erroneous transformation process of multimodal sensory input (cf. Chapter 2.3.3), it is not surprising that a cueing procedure seeking to encourage patients to simple "look" leftwards does not lead to long-lasting effects. Approaches that are more promising thus involve techniques, which particularly focus on manipulations of vestibular, neck proprioceptive, or visual input, i.e. on those channels that provide us with multimodal information for adjusting the position of our body in relation to external space. These methods include for example caloric stimulation of the vestibular organ (Rubens, 1985; Vallar, Bottini, Rusconi, & Sterzi, 1993), neck muscle vibration (Johannsen, Ackermann, & Karnath 2003; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002), or prism adaptation (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Rossetti et al., 1998). The later approach uses prismatic lenses to induce a rightward horizontal displacement of the patients' visual fields. A recent study reported on a long lasting amelioration of neglect symptoms due to this procedure, while a standard rehabilitation treatment revealed no specific improvement in patients with spatial neglect (Frassinetti et al., 2002).

The promising results of therapies targeting the patients' egocentric space representation by specifically stimulating basal sensory input channels further emphasise the present assumption that spatial neglect is due to a very elementary disturbance of spatial information processing, which leads to profound behavioural changes in "normal" passive orienting and active exploring, but fortunately can improve in a majority of patients over time.

5.2 Summary of Contributions

The present studies were the first to measure the degree of *spontaneous* eye and head orientation in stroke patients with and without spatial neglect by means of quantitative recording methods in the acute stages as well as in the course of recovery. Although clinical experience and observational studies may have suggested an association between this striking symptom of passive orienting and spatial neglect, we argued for the need of verification by systematic, quantitative comparisons. This seemed particularly relevant, because it was formerly concluded that hemispheric stroke per se leads to a deviation of the eyes towards the lesion side, i.e. regardless of spatial neglect (cf. Chapter 2.4.2). Further, only two observational studies actually focussed on spatial neglect and its relation to the patients' eye position so far, while others had mainly addressed extinction, i.e. a disorder that indeed may co-occur with the patients' lateralised behaviour, but constitutes a discrete symptom that can even dissociate from neglect (cf. Chapter 2.1.1). These two observations came to opposite conclusions, favouring respectively rejecting a direct relation between neglect and a deviation of the eye/head (cf. Chapter 2.4.3).

Our data contribute to these ambiguous findings by quantitative comparisons on a total of 51 patients with circumscribed cerebral stroke and of 21 neurological patients without brain lesions. We found that a marked spontaneous horizontal deviation of the eyes and the head as observed on average 1.5 days post stroke is not a symptom associated with any acute cerebral lesions per se, nor is a general symptom of right hemisphere lesion, but rather is a *specific* sign of spatial neglect. Thus, our results suggest a modification of Prévost's (1865) original assumption that eye and head deviation in the acute stage occurs symmetrically with both left- and right-sided stroke. Also, the statements in present neurological text books, saying that stroke patients usually steer the eyes towards the side of the brain lesion may be reconsidered in the light of the present data. Moreover, we showed that the patients' passive neglect behaviour is *not* a distinct symptom that may solely co-occur with traditionally defined "active" neglect symptoms, as it is the case for disorders like extinction or impaired working memory (cf. Chapter 2.1.1), but rather is directly related to it. Consequently, the present data allow to conclude that spatial neglect is characterised by a deviation of the eyes and the head during both "active" visual search *and* at "passive rest".

Further, our data allow for conclusions on the hitherto unknown development of these symptoms in the course of recovery. Based on clinical observation it has been assumed that a possible deviation of the eyes in patients with spatial neglect improves fast compared to its traditionally measured active components (cf. Chapter 2.4.4), favouring distinct rather than related phenomena that may even dissociate over time. In clear contrast, we observed a gradually different, but parallel recovery of gaze positions during active *and* passive conditions as well as of neglect severity. A deviation of the eyes and the head thus will not recover faster but still is obvious in some patients up to 10 months post stroke, though to a lesser degree than during active exploratory search. These findings again clearly argue for related symptoms, which both characterise spatial neglect and specify the disorder even beyond the very acute stage.

Our data also provide preliminary evidence to suggest a consideration of the patients' gaze in acute stroke scales in order to test not only oculomotoric function following hemispheric stroke, but also to evaluate a main characteristic of spatial neglect. While the "neglect" items in stroke scales are no valid parameters to measure the characteristic symptoms of spatial neglect, the patients' "gaze" positions do not play a role in the diagnosis of the disorder within these clinical scoring systems to date (cf. Chapter 2.4.1). Possibly, the patients gaze would be a more valid criterion for a preliminary estimate of the presence or absence of visual neglect than other items that may dissociate, or may at most accompany rather than characterise the disorder (e.g. anosognosia and extinction; cf. Chapter 2.4.1). Particularly this topic might be interesting to be addressed by future studies on larger samples that again would be needed to be investigated as soon as possible after symptom onset.

The present work further emphasise that the characteristic feature of spatial neglect, i.e. the marked ipsilateral deviation, is due to a very elementary disturbance of the spatial information process that converts multimodal sensory input into longer-lasting spatial representations and provides us with redundant information about the position and motion of our body relative to external space (cf. Chapter 2.2). Crucially, this erroneous transformation is assumed to induce a rotation of the patients' whole egocentric reference frame towards the lesion side. This assumption was repeatedly confirmed by the present work. The third study showed that the characteristic bias in exploratory search is due to a shift of the entire search distribution towards the ipsilesional side with decreasing frequencies at the extreme left and right margins (cf. Figure 6), rather than to a left-right gradient with a maximum number of omissions at the ipsilateral side and a minimum at its outer contralateral positions. This observation applies to both acute as well as chronic stages of the stroke.

Contrasting other models of spatial attention, our data thus favour the view that spatial neglect leads to a shift of spatial orientation to a new location at the ipsilateral side from which patients carry out their exploratory movements equally towards the left and right side. Under both rest and active task conditions, our patients showed a specific bias that might represent their pathological "default position" of eyes and head at a new origin on the ipsilesional side. In fact, it is observable while "doing nothing" as well as during active search, and is enhanced in a visible context but may be still apparent in complete darkness. While the position of eyes and head in subjects without neglect is in line with trunk orientation, this default position is shifted to a new origin in patients with spatial neglect. This shift may be understood as a pathological adjustment of the subject's normal resting position at an individually different, but characteristic since always spatially lateralised, location on the ipsilesional side.

5.3 Methodological Considerations

Presumably because of the limited sample size and study period, spatial neglect was only found with right hemispheric stroke. This is in line with reviews and lesion studies, showing that neglect predominately occurs with right-sided lesions, and rarely following left-sided stroke (cf. Chapter 2.1.1 & 2.1.4). Thus, our results do not allow to draw conclusions for the rare case of a patient with a left-sided lesion *and* spatial neglect who may be admitted to the stroke unit within 0 and (on average) 1.5 days after the onset of neurological symptoms. Within this short period after stroke, eye and head deviation may possibly also occur with left hemisphere lesions. If this indeed would be the case, the present results would indicate that a deviation after left-sided stroke recovers very fast (within 1.5 days on average), while a bias of eyes and head associated with right hemispheric lesions and spatial neglect remains.

In the light of the present results, the absence of any marked ipsilesional deviation in our group of patients with very acute left hemispheric stroke is consequently not surprising, since none of these patients suffered from spatial neglect. Although previous observational studies reported on very acute eye/head deviation following left hemisphere stroke, it should be considered that they investigated its co-occurrence with extinction or other phenomena but not with visual neglect (cf. Chapter 2.4.3; Ringman et al., 2005; Tijssen, 1988). Thus, to date it remains entirely open whether a marked eye/head deviation in very acute stroke (i.e. below 1.5 days on average) also may be specific to left hemisphere lesions *and* spatial neglect or whether it can occur independently. This question thus has to be targeted by future research. At present, we were able to demonstrate the absence of a marked deviation of the eyes and the head towards any specific side in a sample of 16 very acute left hemispheric patients (~1.5 days from symptom onset). Although we found some, moderate deviations they were balanced towards both sides (cf. Figure 12) and thus do neither serve as an indicator for the hemisphere affected (as suggested previously), nor for spatial neglect.

The present work was designed to study patients with *hemispheric* stroke, but not with brainstem or cerebellar lesions, etc. Moreover, we pointed out that in spare cases of haemorrhagic stroke (mostly in the thalamus), who all showed a shift of midline structures on CT scans as well as clinical signs of rostral brain stem dysfunction, also a contralateral deviation of the eyes may be detected (Tijssen, 1994). In accordance with this, we certainly do not conclude that eye and head orientation per se is a valid predictor to identify which hemisphere is affected by the stroke. Actually, this may be a false localising sign. The first step always has to be medical imaging in order to diagnose and characterise abnormalities of the central nervous system. However, despite these mandatory investigations, we suggest a modification of the general assumption that eye and head deviation per se is an indicator of large hemisphere lesions. Saying that it could be an indicator for the presence of spatial neglect as well, may be a useful preliminary modification of the current clinical practice.

Further, our present data on visuospatial neglect do not allow for conclusions on the relation between a marked gaze deviation and other interpretations of the neglect syndrome (cf. Chapter 2.1.1 & 2.2.2). Some of them emphasise that neglect is a collection of different symptoms, which can be doubly dissociated as for example visual perception and imagery. A patient may suffer from visual neglect without having any trouble in describing familiar places from memory. Our data cannot account for possible impairments in the latter case, since we focussed on the neglect patients' characteristic attentional bias in the visual modality. Consequently, the clinical validity of a passive gaze deviation is presently confined to the main characteristic of patients with spatial neglect, namely their lateralised visuospatial behaviour. Thus, our findings can hardly be discussed in the scope of other aspects concerning the neglect syndrome (e.g. mental imagery, auditory neglect, etc.).

A major difficulty of the second study was that we had to require the patients to attend to the experiment and to be able to perform traditional paper-and-pencil tests very soon after onset of neurological symptoms. Consequently, not every patient admitted to the stroke unit could be included. Nine severely impaired patients could not participate because of a very low level of consciousness or severe aphasia. Accordingly, like in each study on acute stroke, also our very acute sample does not consist of serial cases but had to account for a subsample of severely impaired patients. This may be interpreted as possible bias of patient selection due to the EOG method used to record eye orientations quantitatively, but this problem has also been reported by observational studies. As a possible effect of such inevitable selection, we may not overcome a criticism of a possible underestimation concerning the prevalence of gaze deviation in left-hemisphere patients and thus most probably of the incidence of right-sided spatial neglect. Despite this, it is rather unlikely that our main conclusions would have been changed substantially, regarding the results of our remaining sample of 51 very acute patients who were investigated on average 1.5 days after symptom onset. Nevertheless, the present results have to be further validated by a bigger sample size as well as by the attempt to investigate the patients even earlier, in order to especially clarify whether a marked eye and head deviation indeed will occur in left-sided stroke patients with spatial neglect. Future research on this topic thus may seek to implement eye-recordings or comparable methods as well as diagnostic procedures that may be suitable to include more patients before day 2 or 3. Based on the present results that revealed a tight link between both symptoms, one may now be allowed for applying for example a reduced number of standardised neglect tests that would still be appropriate to detect spatial neglect but would reduce the requirements on the patients' capacity. Regarding the study by Simon et al. (2003), a deviation of the eyes as detected in MRT/CT scans could for example be useful to define the patients' orientation of the eyes without depending on their participation in potentially exhausting calibration procedures, and thus may be an appropriate method in patients with a very low level of consciousness.

A secondary point to be mentioned is our conclusion that a potential deviation of the eyes may be important in detecting neglect in the very acute stages of stroke when patients may not be able to perform traditional paper-and-pencil tests. Of course, this concerns a future consideration of our results, but could not have been accounted for the present study in which we needed to implement a valid control for the presence or absence of spatial neglect by precisely such standardised tests.

The present work focussed on behavioural not anatomical aspects, regarding the relation between a passive gaze deviation and the presence of spatial neglect as measured by active tasks. In doing so, we observed a direct and systematic connection between both behaviours. Our results on the present sample of hemispheric stroke patients actually showed that a marked, systematic deviation of the eyes and the head towards the lesion side was only due to the effects of spatial neglect and right hemispheric lesions. Of course, other features may be related to an altered orientation of the eyes such as the function of the ocular eye-fields in the frontal lobes or other pathologies than spatial neglect. However, such relations were not in the scope of the present work and must be subjected to studies that focus on both, anatomy and behavioural outcome using appropriate neglect tests and lesion detection methods in a large sample that allows for conclusions on an anatomical level (see below).

The common time course argues for a close relationship between active and passive neglect behaviour. However, the conclusion that a parallel improvement in active and passive neglect is suggestive of a common underlying mechanism for both, gaze deviation and spatial neglect, has to be taken cautiously and need further verification. Generally, all symptoms tend to improve during the period of stroke recovery. Thus, only the observation that, for example, hemiparesis and aphasia will recover in patients with left-sided stroke is little evidence of a common underlying mechanism for motor and language function. Consequently, the tendency of all brain functions to recover after the stroke confines our conclusion and necessitates future research. However, regarding the question of a common development, we gained first insight into whether active and passive neglect behaviour will recover in parallel or tend to dissociate. Indeed, several hypotheses on the recovery of gaze deviation and spatial neglect are conceivable, including an independent, almost dissociative development, which was clearly disapproved by the present follow-up study. Moreover, our patients clearly showed less improvement of hemiparesis, which had not recovered between the second and third investigation, while both characteristics of spatial neglect developed in parallel over time. Based on our present results, it could thus be argued that to date there is no positive evidence to assume different underlying neural mechanisms for apparently associated symptoms. Yet, this might be a challenging starting point for future investigations.

5.4 Future Research

In addition to the upper mentioned considerations, ongoing research could continue our investigation of a tight link between gaze deviation and spatial neglect due to hemispheric lesions. Currently it seems as if a spontaneous deviation of the eyes and the head underlies the asymmetric behaviour in patients with spatial neglect. However, the direction of causality may also be the other way round. The challenging question thus will be whether a spontaneous gaze deviation is indeed the cause or rather the consequence of spatial neglect.

Future studies may also contribute to our findings on a quantitative relation between the degree of gaze deviation and the severity of spatial neglect within a larger sample, particularly in order to investigate whether the individual degree of ipsilesional gaze orientation in fact may be predictive of chronic neglect.

Beyond the present focus, a challenging question would be whether eye-head co-ordination is affected in patients with spatial neglect. Though our results on a *static* condition have to refrain from drawing representative conclusions on such *dynamic* aspects, this topic of eye and head co-ordination might be interesting to be targeted by future studies.

Our results on the spontaneous resting position in darkness offer an interesting perspective for future research on task-specific differences in spatial neglect. At present, reports on its development are missed that may help to explain the patients' gaze orientation in complete darkness towards the contralesional, left side as measured 10 months post stroke. Moreover, since the effects of contextual differences were not explicitly investigated with the present design they do not allow to draw conclusions about the underlying mechanisms leading to an enhancement of the deficits in light and an attenuation in darkness. Our preliminary results on the development of the passive neglect behaviour in chronic stages of the stroke under varying lightning conditions, however, might stimulate ongoing research on the basal mechanisms leading to these differences.

Finally, an interesting aspect that was not addressed by the present work is lesion location. According to our present results, we assume that spatial neglect and a spontaneous deviation of the eyes and the head are directly linked and thus are caused by similar hemispheric lesions. Based on our study on 140 patients (Karnath et al., 2004a; cf. Figure 3), we suggest an essential role of the right superior temporal gyrus for the occurrence of spatial neglect and thus for a passive deviation of the eyes in patients with unilateral cerebral stroke. However, to date a study on spatial neglect, that considers both, behavioural and anatomical aspects of eye and head deviation as well as of spatial neglect, is missed. Subsequently to our report on a direct relation between the behavioural symptoms, such an investigation will need larger samples in order to take into account whether the different patient groups are comparable for example regarding handedness, volume and nature (infarct or haemorrhage) of the lesion. Further, such studies may clarify if and how the lesion site correlates with the severity of eye and head deviation in patients with spatial neglect. These results should also be related to the literature on the anatomy of conjugate eye deviation (e.g. due to lesions in frontal eye fields), which had not addressed the co-occurrence with spatial neglect so far, but might be a challenging perspective. In this context, it finally may be interesting to learn whether there are differences between the lesion locations of the two presently documented characteristics of spatial neglect - namely active search and passive resting behaviour - regarding their recovered respectively chronic manifestations in patients with hemispheric stroke.

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Hiermit erkläre ich, dass ich die zur Promotion eingereichte Arbeit mit dem Titel "On the relation between active and passive behaviour in patients with spatial neglect – Insight from acute stroke and the course of recovery" selbständig verfasst, nur die angegebenen Quellen und Hilfsmittel benutzt und wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe.

Die Daten der vorgelegten Dissertation wurden bereits teilweise in wissenschaftlichen Journalen veröffentlicht (Studie 1 und 2) bzw. befinden sich derzeit im Begutachtungsprozess (Studie 3). Die Daten der Studie 2 sind zudem Teil der medizinischen Doktorarbeit meiner Mitautorin Rebekka D. Proß.

Ich habe bisher an keiner anderen Universität einen Antrag auf Zulassung zum Promotionsverfahren gestellt und keine Promotionsverfahren oder entsprechende Prüfungsverfahren abgebrochen oder abgeschlossen.

Es sind mir keine strafrechtlichen Verurteilungen, Disziplinarmaßnahmen oder Straf- bzw. Disziplinarverfahren anhängig.

Esslingen, im April 2008

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Fruhmann Berger, M., Johannsen, L., & Karnath, H.-O. Time course of eye and head deviation in spatial neglect. *Submitted.* [Study 3]

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