

Aus dem Zentrum für Neurologie Tübingen
Neurologische Klinik und Hertie-Institut für klinische Hirnforschung
Abteilung Kognitive Neurologie
Ärztlicher Direktor: Professor Dr. H.-P. Thier
Sektion Neuropsychologie
Leiter: Professor Dr. Dr. H.-O. Karnath

**Eye and head deviation
in acute hemispheric stroke
and its relation to spatial neglect**

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Rebekka Dorothee Proß
aus
Tübingen

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Dekan:

1. Berichterstatter:

2. Berichterstatter:

Professor Dr. I. B. Autenrieth

Professor Dr. Dr. H.-O. Karnath

Professor Dr. H. Wilhelm

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Abbreviations

CED	Conjugate eye deviation
CON	Healthy control
CON_all	Healthy controls and patients without neglect
DC	Direct current
EOG	Electrooculography
Exam.	Examination
FEF	Frontal eye fields
GD	Gaze deviation
ISA	Intracarotide sodium amylobarbiton
RBD	Right brain damaged patient
LBD	Left brain damaged patient
LED	Light emitting diodes
n	Number
N+	Patient with neglect
N-	Patient without neglect
N.g.	Not given
T.n.p.	Testing not possible

1. Introduction

Cerebral stroke leads to many different kinds of neurological impairment, e.g. hemiparesis, hemihypesthesia, aphasia, etc. Some of them are only discovered by careful examination, others already attract attention at the first sight. One of these latter, striking symptoms is the spontaneous orientation of the patient's head and eyes to one side (figure 1). Observing stroke patients in a spontaneous resting position without being addressed or examined, we quite frequently find them looking into one direction most of the time. This behaviour is not necessarily due to visual or auditory stimuli, which attract the patient's attention, but can also be observed in situations without distraction. This symptom has been termed "conjugate eye deviation", although only a part of the symptom, i.e. the position of the eyes, is described by this term. The occurrence of a conjugate eye deviation (CED) is not restricted to brainstem or hemispheric stroke. It is also seen in patients with cerebral tumors or epileptic seizures. As we focussed on patients with hemispheric stroke in this study, the following illustrations of conjugate eye deviation are confined to this topic.



Figure 1

Example of the spontaneous eye and head orientation of a right brain damaged patient towards the ipsilesional side. One could have the impression, that the patient was fixating a certain target situated on the right side. However, the room was empty with only the photographer standing directly in front of the patient.

1.1. Definition of conjugate eye deviation (CED)

As described above, CED is a sustained shift of the patient's horizontal eye-in-head position towards the affected hemisphere, usually accompanied by a rotation of the head (Goodwin and Kansu, 1986; Tijssen, 1988) towards the same side. CED is further accompanied by defective eye movements (De Renzi et al., 1982; Goodwin and Kansu, 1986; Tijssen, 1988) in the direction of the non-damaged hemisphere. Eye movements are impaired to varying extent: some patients are not able to move their eyes away from the ipsilesional canthus, others barely attain the midline and some move their eyes to the contralesional canthus, but they are, even with great effort, not able to hold this position for a time. The severity of this (partial) gaze paresis is equal for smooth pursuit and saccadic eye movements (Tijssen, 1988). Along with the varying degrees of gaze paresis, the extent of the shift in the horizontal eye-in-head position also varies from very outstanding eye positions to only slight deviations from the midline. The direction of eye deviation is, as stated above, normally towards the side of the damaged hemisphere. The rare exceptions of this rule, i.e. contralateral conjugate eye deviations, will be discussed later on (see chapter 5.2.3.).

1.2. Previous studies on CED and their results

Although CED following hemispheric stroke is a striking symptom, only few studies have been performed on this topic (Prévost, 1868; Okinaka et al., 1952; De Renzi et al., 1982; Mohr et al., 1984; Steiner and Melamed, 1984; Tijssen, 1988; Kömpf and Gmeiner, 1989; Simon et al., 2003). CED was mentioned in further studies (Aring and Merritt, 1935; Walshe et al., 1977; Kelley and Kovacs, 1986; Horowitz and Tuhim, 1997; Chung et al., 2000; Lawrence et al., 2001), but as they contain little information and partly were made in a different subpopulation of stroke patients (e.g. only in patients with hemianopia), we will

focus on the first mentioned eight studies (see Table 1), in which CED following hemispheric stroke was the main topic.

Simon et al. (2003) investigated the presence of CED in CT scans by measuring the angle between the radio-opaque lens and the mid-sagittal axis of the head. In all other previous studies, CED was diagnosed following clinical examination. The clinical assessment of CED holds some difficulties. One concerns the criteria for the diagnosis of CED, where some studies investigated the single eye-in-head position and others demanded an impairment of contralateral eye movements or a rotation of the head to set the diagnose. Additionally, the clinical diagnosis of CED suffers from poor interobserver agreement (Edwards et al., 1995), because there is no universal cut-off value between a normal and a deviated eye position. Furthermore, the diagnosis is influenced by the time of examination, as CED is known to be a transient symptom, *“tending to disappear within a few days, a few hours or even a few minutes”* (Okinaka et al., 1952). Under these conditions, the results of the different studies seem to be little comparable, which is reflected by the wide range of stated prevalences between 16 and 50 %. However, all studies agree, that CED is seen more frequently following stroke of the right than of the left hemisphere (right-to-left ratio approximately 2:1). A similar hemispheric asymmetry is also observed for the persistence of CED: while it's mean duration in left brain damaged subjects is stated between 4.5 (Tijssen, 1988) and 8.6 days (De Renzi et al., 1982), it is estimated at 14.9 (De Renzi et al., 1982) to 17.6 days (Tijssen, 1988) in patients with damage of the right hemisphere. Moreover, there's a difference between the hemispheres concerning the severity of CED (more severe following right brain damage (De Renzi et al., 1982)) and the extent of underlying lesions, which are larger in the left than in the right hemisphere (De Renzi et al., 1982; Mohr et al., 1984; Tijssen, 1988), but in both hemispheres are usually larger than lesions not leading to CED (Kelley and Kovacs, 1986). The clinical findings about the hemispheric asymmetry for CED are supported by experimental results of Meador et al. (Meador et al., 1989), who investigated CED following intracarotid sodium

Table 1: Previous studies on conjugate eye deviation (CED) and their results

Authors	Year	n total	n with ipsilateral CED	duration	prognosis	CT and/or autopsy	Side of lesion R:L ratio	Predominant location of lesions	Size of lesion
Prévost	1868	n.g.	54	several days	n.g.	51	68:32	basal ganglia region	n.g.
Okinaka et al.	1952	77	24 (31%)	transiently, tending to disappear within a few days, hours or minutes RBD: mean 14.9 LBD: mean 8.6	n.g.	24	n.g.	capsula interna	n.g.
De Renzi et al.	1982	436	120 (28%)	RBD: mean 14.9 LBD: mean 8.6	higher rate of death, higher frequency of severe neurological symptoms	47	60:40	R: post-Rolandic; L: entire Sylvian artery territory	L>R
Steiner and Melamed	1984	n.g.	42	several hours to 11 days 57% subsided in 48 hours 90% present no longer than 5 days	disappearance of CED unrelated to outcome in case of other neurological manifestations	33	55:45	frontal lobes	n.g.
Mohr et al.	1984	531	86 (16%)	In 9 cases CED for more than 20 days: patients had large lesions	n.g.	n.g.	R>L	frontal = parietal	L>R
Tijssen	1988	n.g.	74	RBD: mean 17.6 days (1-65), LBD: mean 4.5 days (1-14). Longlasting CED associated with large lesions	associated with severe disability and higher rate of death	64	64:36	R: subcortical fronto-parietal L: fronto-temporo-parietal	L:R = 3:2
Kömpf and Gmeiner	1989	48	24 (50%)	mean 18.5 (1-90) days	n.g.	24	67:33	temporo-parietal and dorsal subcortical frontal	massive damage
Simon et al.*	2003	115	43 (37%)	n.g.	no correlation with NIHSS	115	R>L	anterior circulation	n.g.

N = number, RBD = right brain damaged subjects, LBD = left brain damaged subjects, n.g. = not given, NIHSS = National Institutes of Health Stroke Scale. *Only patients with ischemic stroke CED assessed by means of CT scans.

amylobarbiton (ISA) injections. Besides the asymmetry found for the occurrence, severity and duration of CED, they stated, that the occurrence of CED was significantly affected by cerebral lateralization.

1.3. The pathophysiology of CED

1.3.1. Outline of reported hypotheses

The pathophysiological mechanism leading to CED is topic of controversial discussions. While Prévost (Prévost, 1868) proposed that CED might be the result of asymmetric eye muscle contraction due to an imbalance of hemispheric activation, Pedersen and Troost postulated damage of the frontal eye fields (FEF) with the consequence of a contralateral saccadic palsy to be responsible for CED (Pedersen and Troost, 1981). The latter hypothesis was accepted, until Tijssen stated that CED is accompanied not only by an impairment of saccadic but also of smooth pursuit eye movements and that lesions of temporo-parietal and subcortical regions seem to be more essential for the occurrence of CED than lesions of the FEF (Tijssen, 1988). In current textbooks, CED is attributed to damage of cortical centres of eye movement control or their descending pathways at different levels (Poock and Hacke, 2001).

1.3.2. CED and spatial neglect

Besides these assumptions, Tijssen (1988) suggested that the neglect syndrome might play a role in the pathogenesis of CED. Spatial neglect is a lack of awareness of space and of objects on the side contralateral to a subject's brain injury. It is preferentially observed after right brain damage. Patients typically ignore contralesionally located people or objects. When searching for targets, patients direct their eye and hand movements towards the ipsilesional side, leading to neglect of the contralateral side (figure 2).

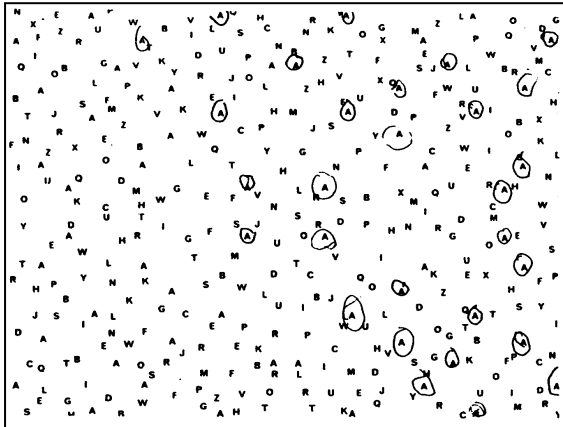


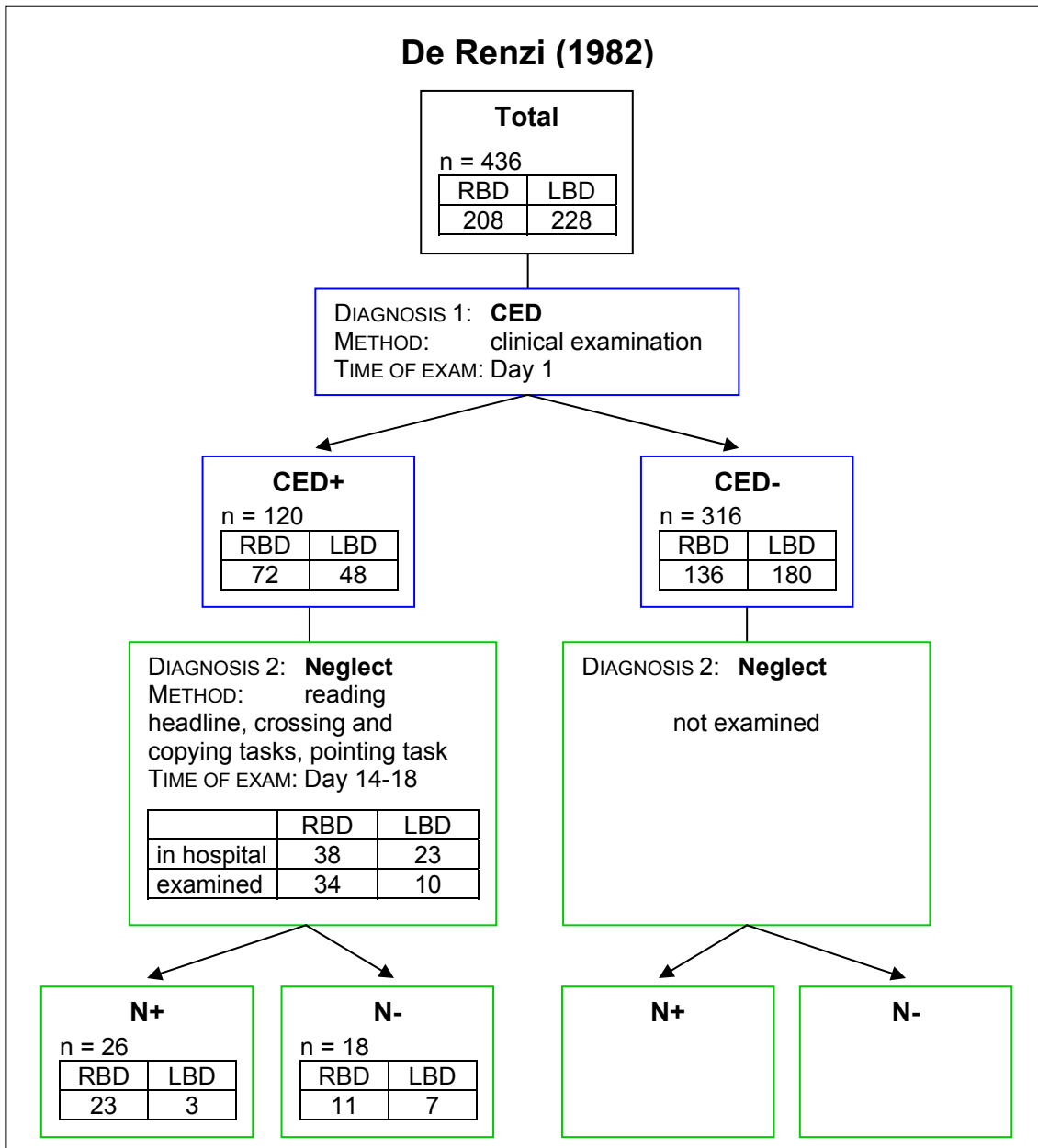
Figure 2

Letter cancellation test performed by a patient suffering from spatial neglect. The patient was instructed to cancel all letters „A“ on the whole sheet of paper. When he indicated to be ready, he was instructed twice again to take a second look at the whole sheet of paper to find every letter „A“. Despite these instructions, the patient failed to cancel 31 of 60 targets, 25 of them lying within the left half of the paper.

The existence of a relationship between CED and neglect is discussed controversially. Although there are only four studies (De Renzi et al., 1982; Tijssen, 1988; Kömpf and Gmeiner, 1989; Fruhmann Berger and Karnath, 2005) dealing with this topic, each possible opinion is supported by one of them: there is no relationship between CED and neglect (Kömpf and Gmeiner, 1989), CED leads to neglect (De Renzi et al., 1982), neglect causes CED (Tijssen, 1988; Fruhmann Berger and Karnath, 2005). As a relationship between both symptoms would have clinical implications, for example a simplification of the diagnosis of spatial neglect, the current project aimed to clarify, if there is a systematic relationship between these symptoms or not. For comparison with the present study, the different methods and results of the four studies mentioned above will be illustrated in the next sections (see also figures 3-6).

1.3.2.1. Investigations on the relationship between CED and spatial neglect

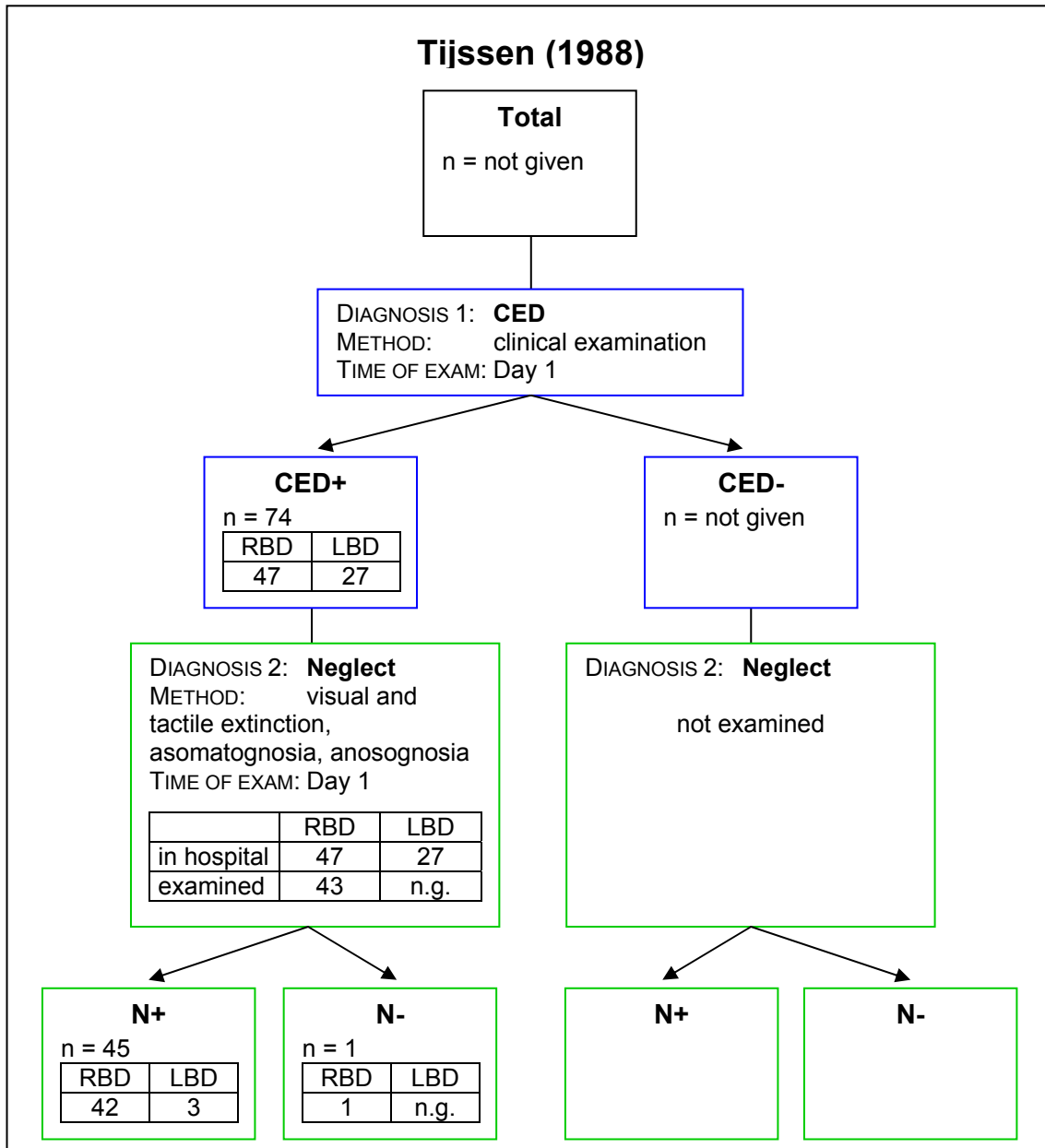
De Renzi et al. (1982) investigated 120 patients with CED. Neglect was considered present whenever stimuli or parts of stimuli located on the side contralateral to the lesion, were neglected in one or more of the following tests: reading the fullwidth headline of a newspaper, crossing ten small circles, copying ten drawings, or pointing at a row of seven girls and boys in a magazine photograph. These tests were carried out 14-18 days after stroke.

**Figure 3**

De Renzi et al. (1982). RBD = right brain damaged subjects, LBD = left brain damaged subjects, n = number, CED = conjugate eye deviation, EXAM. = examination, N = spatial neglect.

Even after that time not all patients were able to perform at least one of the tests because of severe neurological impairment. Finally, 10 of 23 left brain damaged patients, who were still in the hospital, could be examined. Three of them were considered as suffering from spatial neglect. Out of the 38 right brain damaged patients, who were still in hospital, 34 could be examined. Neglect was diagnosed in 23 of them. Interestingly, all patients who still suffered from CED at the time of examination for neglect, suffered from neglect as well. In 15 patients who's CED had already recovered, neglect was diagnosed and in further 18 patients no neglect was present. For the latter group, it remains open, if there had been no neglect symptoms at all or if neglect already had recovered. It is also unknown, whether neglect may occur in patients who did not suffer from CED, because only patients with CED were examined. De Renzi et al.'s conclusion, that neglect was the result of an imbalance in oculomotor orientation, is mainly based on the similar hemispheric asymmetry found for the occurrence of neglect and CED.

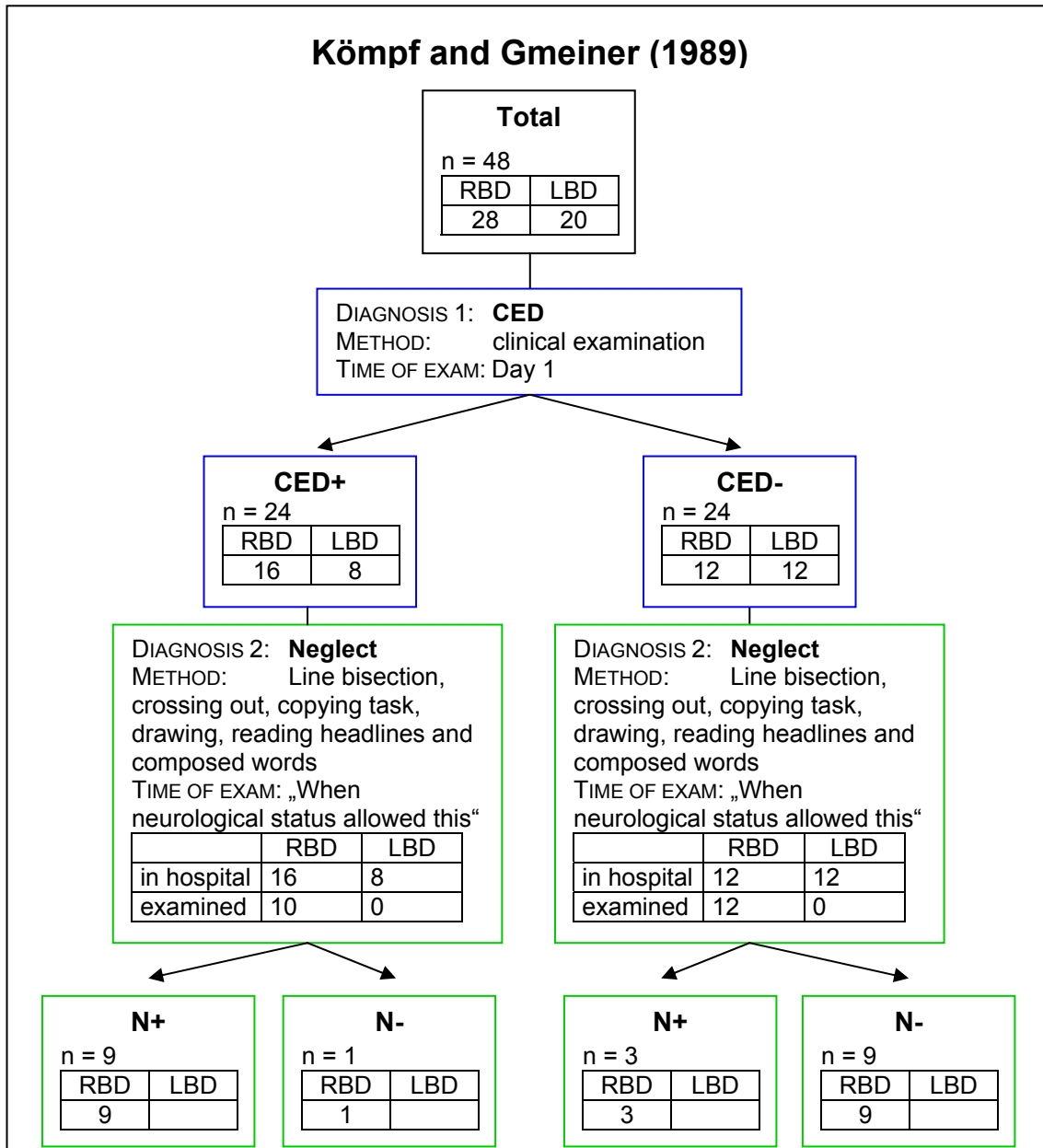
In Tijssen's (1988) study, 74 CED patients were examined. They were considered to suffer from "spatial neglect" if visual or tactile extinction, asomatognosia or anosognosia were diagnosed. None of the common neglect tests was carried out. The examination took place at the day of admission to the hospital, i.e. at the same time, as CED was diagnosed. Tijssen faced the same problem as De Renzi and coworkers (De Renzi et al., 1982): a great number of patients, mainly patients with a lesion in the left hemisphere, could not be examined. Nevertheless asomatognosia could be diagnosed in 3 of the left brain damaged patients. In addition, 98% of the right brain damaged subjects, i.e. 42 of the 43 patients, that could be investigated, showed one or more of the upper mentioned symptoms. Tijssen concluded, that neglect might play an important role in the pathogenesis of CED. The relationship between neglect and CED in left brain damaged patients remained uncertain, as well as the question, if neglect may occur in patients who never showed CED, remained open.

**Figure 4**

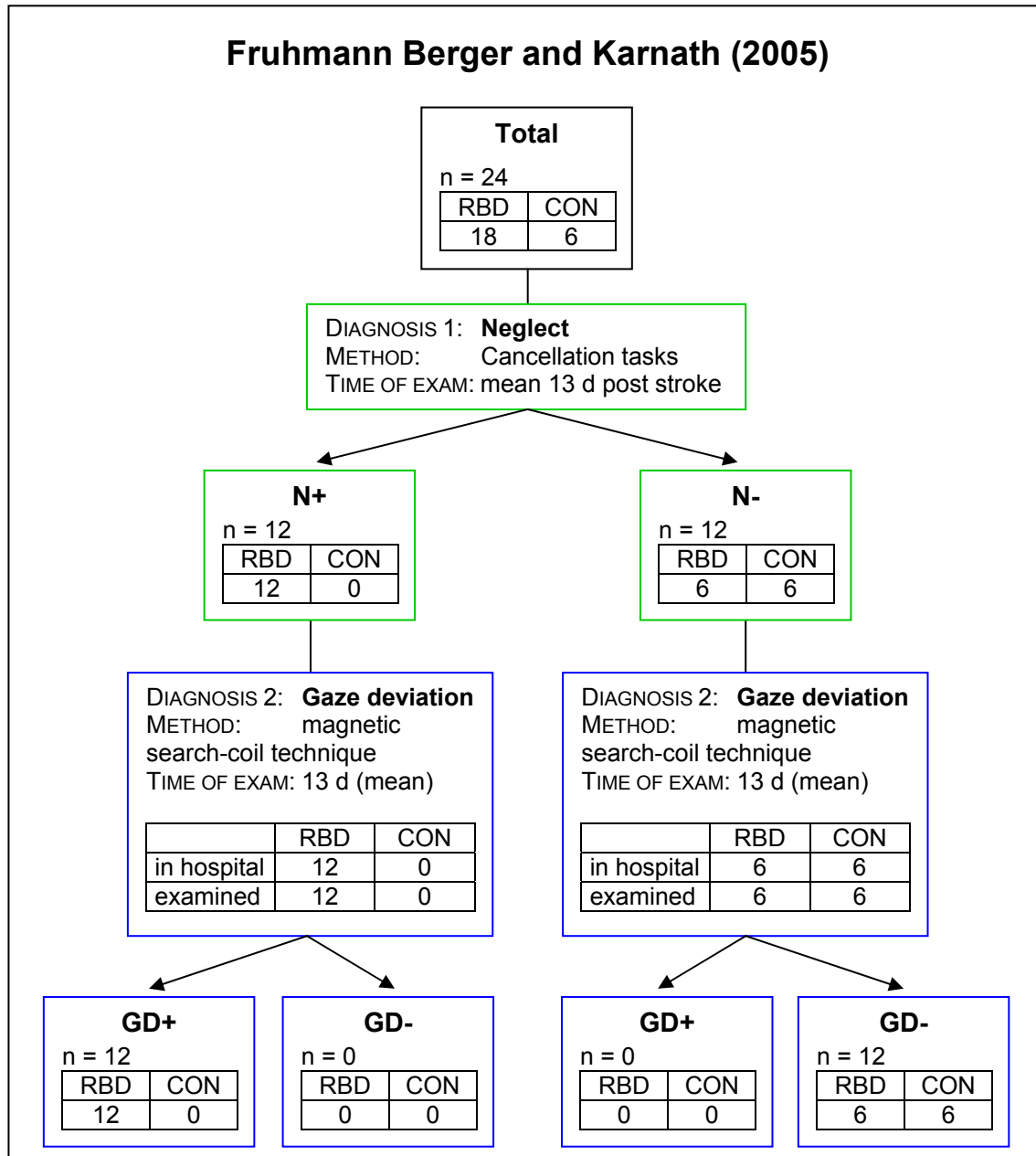
Tijssen (1988). RBD = right brain damaged subjects, LBD = left brain damaged subjects, n = number, CED = conjugate eye deviation, EXAM. = examination, n.g. = not given, N = spatial neglect.

Kömpf and Gmeiner investigated 48 stroke patients, 24 of them suffering from CED. Neglect was assessed by observing the clinical behaviour and by means of six tests: line bisection, crossing out, a copying task, drawing, reading headlines and composed words. Neglect was diagnosed if patients had more than one pathological test. The tests were carried out "*when neurological status allowed this*" (p. 50). In consequence of severe language impairment, none of the left brain damaged patients of this study could be investigated. In the group of right brain damaged subjects, 9 suffered from neglect and CED at the same time, one had CED but no neglect and 3 did not suffer from CED but showed neglect. Interpreting these results, Kömpf and Gmeiner stated that neglect was not the result of an oculomotor imbalance and CED cannot be interpreted as representing visual neglect. They lend further support to this thesis from the fact, that marked CED was also observed in some patients in coma.

In contrast to the studies above, Fruhmann Berger and Karnath asked, if spatial neglect is predominantly linked with active behaviour, e.g. searching targets, or if it is also obvious in situations without explicit requirements, i.e. in the patient's spontaneous eye and head orientation. They investigated the spontaneous eye and head orientation of 12 right brain damaged patients with spatial neglect and 12 control subjects (six right brain damaged patients without neglect and six subjects without any brain damage). Neglect was diagnosed, when patients fulfilled the criterion in at least two of the following tests: the letter cancellation task, the bells test, or a copying task. Gaze, eye-in-head, and head-on-trunk positions were recorded by the magnetic search coil technique. To allow participation in this set up, patients needed to be in a stable state. Recordings therefore were carried out approximately 13 days after stroke (mean = 13.3 days). They revealed, that the spontaneous eye and head orientation of neglect patients differed significantly from that of controls. It was deviated about 30° (gaze position) towards the right side. Fruhmann Berger and Karnath interpreted this gaze deviation as pathological adjustment of the subject's

**Figure 5**

Kömpf and Gmeiner (1989). RBD = right brain damaged subjects, LBD = left brain damaged subjects, n = number, CED = conjugate eye deviation, EXAM. = examination, N = spatial neglect.

**Figure 6**

Fruhmann Berger and Karnath (2005). RBD = right brain damaged subjects, CON = control subjects without brain damage, n = number, GD = gaze deviation, EXAM. = examination, N = spatial neglect.

normal resting position to a more rightward position, due to spatial neglect. As no left brain damaged subjects were investigated, it remained open, whether or not such a shift is linked to only right hemispheric stroke and neglect.

1.3.2.2. Critical aspects of the investigations on the relationship between CED and spatial neglect

Looking at the methods of these studies, we encounter several weaknesses. One issue concerns the diagnosis of CED. As mentioned in 1.2., the clinical assessment of CED leads to a diagnosis, which strongly depends on the person examining the patient. Although being used in most of the studies, clinical assessment of CED does not seem to be a suitable method to set the diagnose. Other weaknesses concern the diagnosis of spatial neglect. Some studies investigated CED patients only, resulting in a lack of information to the question, whether neglect might occur also in patients without CED. Other studies did not employ valid criteria. They investigated e.g. the presence of anosognosia or extinction and then set the diagnosis of spatial neglect (Tijssen, 1988). Though these symptoms often occur simultaneously with neglect, their presence does not grant, that patients additionally suffer from spatial neglect (Bisiach et al., 1986; Driver, 2003; Karnath et al., 2003a). In contrast, cancellation tasks are the commonly accepted diagnostic tool for neglect. Reflecting the spatial distribution of exploration movements, cancellation tasks address the specific deficit of patients suffering from neglect, i.e. the shift of exploratory movements to the ipsilesional side when searching for a target. Studies employing cancellation tasks (De Renzi et al., 1982; Kömpf and Gmeiner, 1989; Fruhmann Berger and Karnath, 2005) have the weakness, that they were not able to investigate patients in the acute state of disease and that they did not examine left brain damaged patients or only few of them because of aphasia.

1.3.2.3. Conclusions

Summarising the results of the upper mentioned studies, the existence of a relationship between CED, respectively gaze deviation, and neglect is likely but remains uncertain, especially in patients with left brain damage. For clarification,

there is a need of a study employing valid methods for the diagnosis of both CED / gaze deviation and neglect and investigating right and left brain damaged patients in the early stage of disease.

In the following, the term “conjugate eye deviation” will be replaced by “gaze deviation” (GD), as the latter describes the symptom of interest more precisely: a shift of the spontaneous eye plus head orientation, resulting in a deviation of gaze.

2. Aims of the study

In the present study, we tend to clarify the relationship between gaze deviation (GD) and neglect in patients with hemispheric stroke.

We thus investigated all unilateral, left as well as right hemispheric stroke patients, submitted within a 9 month period to the University hospital of Tübingen, with respect to (i) their spontaneous eye and head position and (ii) spatial neglect.

To obtain valid diagnoses, we

- employed commonly used neglect tests and
- assessed spontaneous eye positions with an objective, quantitative method (electrooculography, EOG) after defining a normal range of eye-in-head, head-on-trunk and gaze positions.

Moreover we

- assessed GD and neglect as soon as possible after stroke to register even short lasting GD,
- carried out both examinations in a short interval to avoid dissociation caused by recovery between examinations,
- had a follow up examination of all patients showing neglect,
- put particular effort in the investigation of all stroke patients admitted to the Neurology Department of the University hospital of Tübingen, i.e. left as well as right brain damaged patients.

To be able to make a detailed statement about the relationship between GD and neglect, we not only observed their simultaneous occurrence but also compared their qualities. We investigated, if there is a systematic relation between the degree of GD and the severity of neglect and we compared the persistence of both symptoms.

3. Methods

3.1. Subjects

We investigated all patients with hemispheric first-ever stroke that were consecutively admitted to the University hospital of Tübingen between March and November 2004. Patients who came to the hospital more than four days after onset of symptoms, who died or were transferred to another hospital before examination was terminated were excluded from the study.

We intended to examine patients as soon as possible after admission to the hospital in order to register even the short lasting eye deviations. In fact it was not possible to investigate each patient within the first days after stroke because of critical state, severe impairment of consciousness, severe aphasia, apathia, etc. In order to keep the interval between stroke and examination comparable, we focussed on patients in whom complete examination was possible in the first three days after stroke. Demographic and clinical data of these 33 patients are presented in Table 2. In nine further patients complete examination was not possible within the first three days after stroke. They thus were excluded from the study.

In order to define a normal range of spontaneous eye-in-head, head-on-trunk, and gaze positions we also investigated 15 neurological control subjects (CON) without brain damage. All subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the ethics committee of the University of Tübingen.

3.2. Clinical investigation

Clinical investigations were carried out as soon as possible after onset of symptoms. Patients, in which neglect was diagnosed, had a follow up examination 4-6 days after the first examination.

Table 2: Demographic and clinical data of patients and healthy controls

		RBD	LBD	CON
Number		16	17	15
Sex		7f, 9m	6f, 11m	11f, 4m
Age (years)	Mean (SD)	60.63 (12.52)	63.94 (10.03)	59.87 (11.80)
Etiology		13 Infarct	12 Infarct	
		3 Hemorrhage	5 Hemorrhage	
Time since lesion to examination (d)	Mean (SD)	1.44 (0.90)	1.65 (0.86)	
Level of consciousness (GCS)	Mean	3.7 – 6 – 5	3.9 – 5.9 – 4.4	
Visual field deficit	% present	18.75	11.76	
Gaze paresis	% present	25.00	0	
Eye muscle paresis	% present	0	0	
Paresis of contralesional side	% present	81.25	52.94	
....strength arm	Mean (SD)	2.82 (2.04)	3.63 (2.00)	
....strength leg	Mean (SD)	3.75 (1.76)	4.20 (1.78)	
Somatosensory loss	% present	37.50	29.41	
Extinction				
....visual	% present	31.25	11.76	
	% t.n.p.	12.50	23.53	
....tactile	% present	12.50	11.76	
	% t.n.p.	31.25	35.29	
....auditory	% present	25.00	5.88	
	% t.n.p.	18.75	29.41	
Aphasia	% present	12.50	82.35	

RBD = right brain damaged subjects, LBD = left brain damaged subjects, CON = control subjects, GCS = Glasgow Coma Scale, SD = standard deviation, t.n.p. = testing not possible, d = days.

3.2.1. Neurological examination

All patients underwent neurological examination. Level of consciousness was assessed using the Glasgow Coma Scale (Jennett and Teasdale, 1977). Visual field defects were diagnosed on base of standardized neurological examination. Pupillar reactivity to light, quality of smooth pursuit movements (saccadic smooth pursuit or spontaneous nystagmus) and saccadic eye movements were investigated. Gaze paresis was diagnosed if the subject's eyes were not able to follow a slow moving object towards the contralesional side. If the subject stated diplopia while gazing towards one side and his eyes moved disconjugatedly in this direction, eye muscle paresis was diagnosed. The ability of head movements in both directions was assessed and the oculoccephalic manoeuvre was performed. The latter was considered normal if bulbi moved fully in the angle of the eyes in both directions. Somatosensory loss was recorded if the patient stated less sensation of the same tactile stimulus at one side. The degree of paresis of upper and lower limbs was scored according to the usual clinical ordinal scale with 0 to 5 points, where "0" indicates no visible muscle contraction and "5" reflects normal strength of movements. Patients were also investigated for visual, tactile and auditory extinction. For this purpose, ten stimuli on either side and ten bilateral stimuli were presented in a pseudo-random order. Stimuli in the visual modality were movements of the investigator's index fingers in the right and / or left visual hemifield of the patient. Auditory and tactile stimulation were conducted with the patient's eyes closed. Tactile extinction was tested by applying short fingertips on either the right and / or left hand or shoulder of the patient. The auditory modality was tested using the clicking sound of two ball pens. Extinction in the respective modality was considered present if the patient reported more than 90% of the unilateral stimuli on each side correctly but failed to perceive the contralesional stimulus in $\geq 50\%$ of bilateral trials. Aphasia was assessed conducting a bedside examination that evaluated spontaneous speech, picture naming, auditory comprehension of single words and whole sentences.

3.2.2. Neuropsychological examination

Spatial neglect was assessed by means of four tests: the “Letter cancellation” task (Weintraub and Mesulam, 1985), the “Bells test” (Gauthier et al., 1989), “Albert’s test” (Albert, 1973) and a copying task (Johannsen and Karnath, 2004). Patients were classified as suffering from spatial neglect when they fulfilled the criterion in at least two tests.

In the letter cancellation task, 60 targets „A“ are distributed amid distractors on a horizontally orientated 21 x 29.7 cm sheet of paper. 30 targets are distributed on the right and 30 on the left half of the paper. Patients were asked to cancel all of the targets. They were classified as suffering from spatial neglect if they omitted at least 4 targets more on one side of the paper than on the other side. The bells test consists of seven columns each containing 5 targets (Bells) and altogether 40 distractors. Three of the seven columns (i.e. 15 targets) are on the left side of a horizontally orientated 21 x 29.7 cm sheet of paper, one is in the middle and three columns (i.e. 15 targets) are on the right side. Again patients were asked to cancel all targets. Spatial neglect was diagnosed if the difference between omissions on one side and the other was more than 5 targets. Albert’s test consists of seven columns of targets (lines) without distractors. Three columns, each containing 6 targets, are on the right half of a horizontally orientated 21 x 29.7 cm sheet of paper, one column with 5 targets is in the middle, and three columns, each with 6 targets, are on the left side of the paper. Patients had to cancel all targets. They were classified as suffering from spatial neglect if the difference between omissions on the right and the left side was larger than one. In the copying task, patients were asked to copy a multi-object scene consisting of four figures: a tree, a house, a car, and a fence. Two of the figures were located in each half of a horizontally orientated 21 x 29.7 cm sheet of paper. Omission of at least one of the contralesionally located features of each figure was scored as 1, omission of a whole figure was scored as 2. One additional point was given when figures located on the contralesional side were drawn on the ipsilesional side. Neglect was indicated by a score higher than 1 (12.5% omission). The maximum score was 8 points.

A percentage omission score was calculated. The number of undetected targets was divided by the maximum number of targets. This quotient was multiplied by 100 yielding a percent omission. A high score thus reflects a high number of omissions, a low score indicates fewer omissions. That was carried out for each test separately and percentage omission scores subsequently were averaged over all neglect tests performed by a subject.

3.3. Apparatus

Eye-in-head position was measured by electrooculography (Schott, 1922; Meyers, 1929). Electrooculography (EOG) is based on the physiological corneo-retinal potential difference (Mowrer et al., 1936) which induces an electrical field in the neighbouring anatomical structures. Changes in this electrical field are due to eye movements or change of illumination and can be measured by electrodes placed near the orbits (figure 7). If the intensity of illumination is kept constant, signal output is proportional to the angle of eye movements until 30° and reflects the eye-in-head position with an accuracy of 1-2° (Büchele et al., 1980).

We recorded horizontal eye movements with surface Ag/AgCl electrodes placed at the outer canthus of each eye and at the forehead as reference (figure 8). The skin was cleaned thoroughly at the contact points with abrasive paste before electrodes were applied in order to reduce the electrical resistance of the stratum corneum and improve the quality of recordings. All signals passed a lowpass filter (20-30 Hz) to eliminate high frequency noise before they were amplified by a direct current (DC) amplifier with an adjustable gain from 1000 to 10000. The sample rate was 70 Hz. Data and information about calibration and disturbances during the recording period (see below) were stored on hard disk for offline analysis.

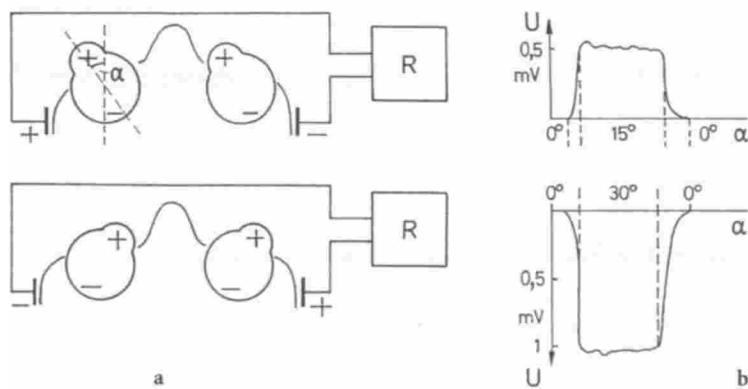


Figure 7

Operating mode of EOG recording. The eyeballs with their electrical fields, the bitemporal Ag/AgCl electrodes and a recording apparatus (R) are illustrated on the left side (a) of the figure. The drawing on the right side (b) illustrates the change in the detected voltage (U), which depends on the visual angle (α) of the eye movement.

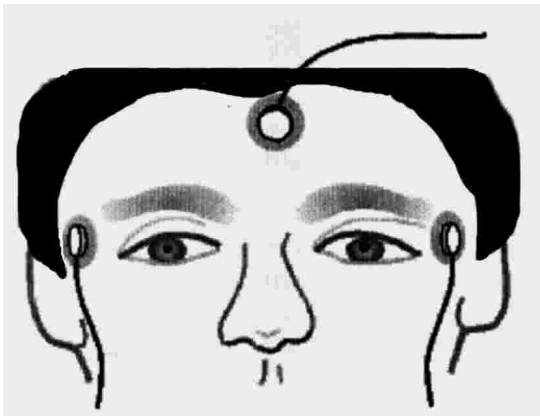


Figure 8

Bitemporal EOG Recording. Ag/AgCl electrodes are placed at the outer canthus of each eye and one at the forehead as reference.

The signal was calibrated by measuring the voltage corresponding to a defined position of the eyes. For this purpose the subject was asked to look at two light emitting diodes (LEDs) displayed on a black cardboard 30cm in front of the subject at an interval of 5.29 cm. The first LED was positioned in the mid-sagittal axis of the subject's head, reflecting the eye-in-head position of 0°. The second LED was placed at 10° visual angle on the right side for right brain damaged subjects, while it was at 10° on the left side for left brain damaged

subjects. The fixation period of each LED was marked in the data for offline analysis.

We recorded spontaneous horizontal eye positions over 180s. The mean value of these positions reflects the subject's spontaneous eye-in-head position.

Head-on-trunk position was measured by a standard graphometer circle: one leg was brought in line with the sagittal midline of the head, the other with the orientation of the shoulders so that the head-on-trunk position could be determined in degrees. Gaze position was calculated by combining eye-in-head and head-on-trunk position.

Positive values for gaze, eye-in-head, and head-on-trunk positions indicate a shift to the right side of the mid-sagittal head and/or body axis. Negative values indicate a turn of eyes and/or head to the left side.

3.4. Procedure

During the recording of the spontaneous eye-in-head and head-on-trunk position, illumination was kept constant. The subjects were seated in an upright position in either a wheelchair or their bed with the possibility to move their head freely. The aim of the study was to measure the spontaneous orientation of gaze, eye-in-head, and head-on-trunk, i.e. the orientation in a resting situation while doing "nothing". After the initial calibration was carried out, subjects therefore were instructed to rest in a comfortable position, keep the eyes open and remain seated without talking. The investigator was positioned out of the patient's sight behind the wheelchair or bed of the patient and no further instructions were given. EOG data were recorded for 90s and the subject's head position was measured by a graphometer circle. The whole procedure was repeated such that the total recording period was 180s. If there were any disturbances while data were recorded, e.g. the patient closed his eyes, started to talk or to move his trunk, this period was marked and excluded of the data. When the recording interval that remained after disturbances were eliminated,

was shorter than 45 seconds, data were excluded from the analysis and the whole procedure was repeated.

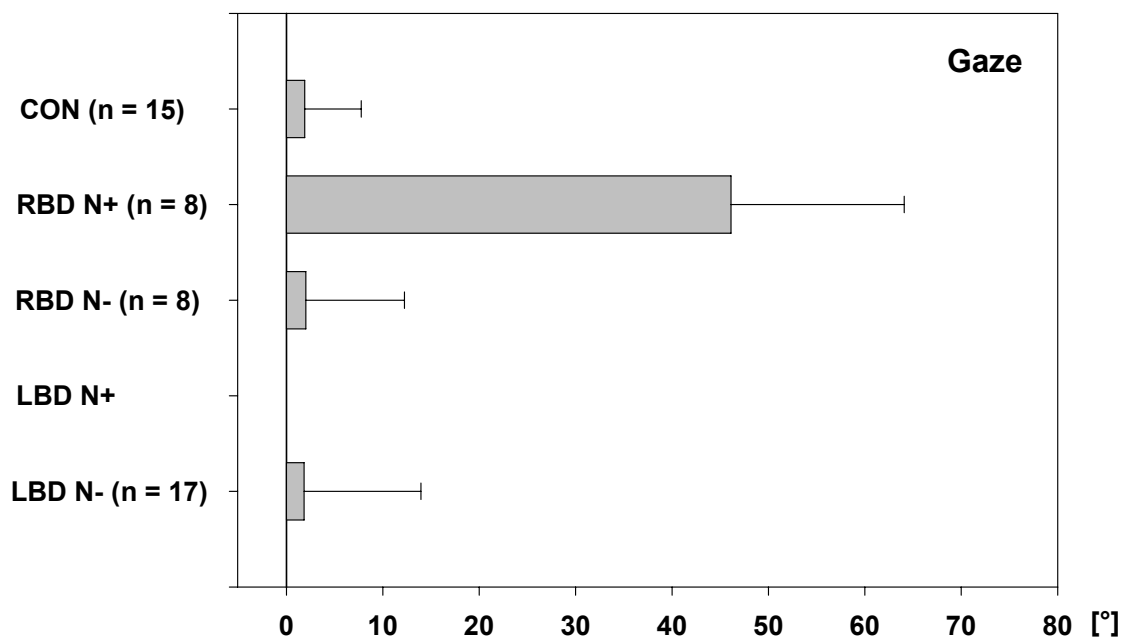
4. Results

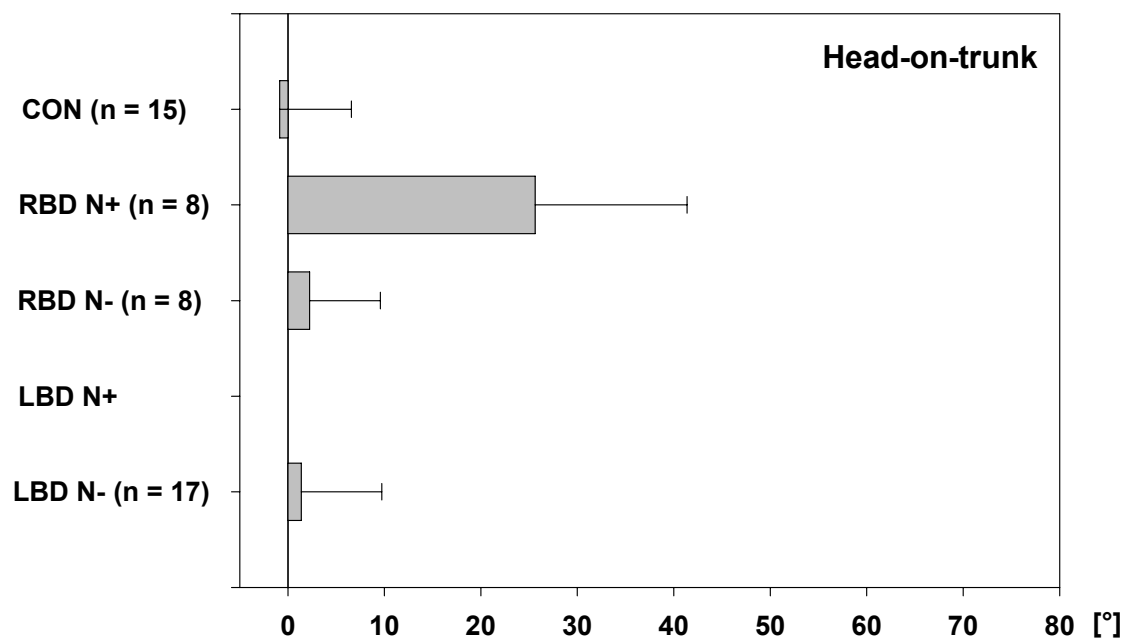
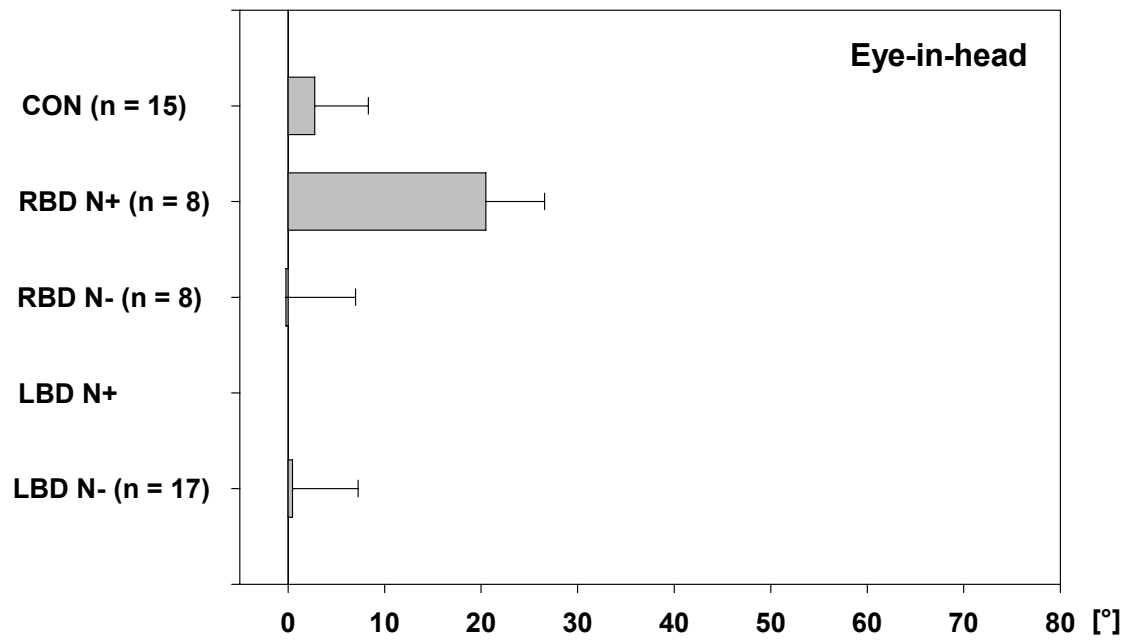
4.1. Gaze, eye-in-head, and head-on-trunk positions

Figure 9 illustrates spontaneous gaze, eye-in-head, and head-on-trunk positions for all patients with neglect (N+), patients without neglect (N-) and healthy subjects (= control subjects, CON). Spatial neglect was present in 24% of the patients. All of them suffered from right hemisphere stroke. Our sample did not include any left brain damaged patient with spatial neglect.

Figure 9

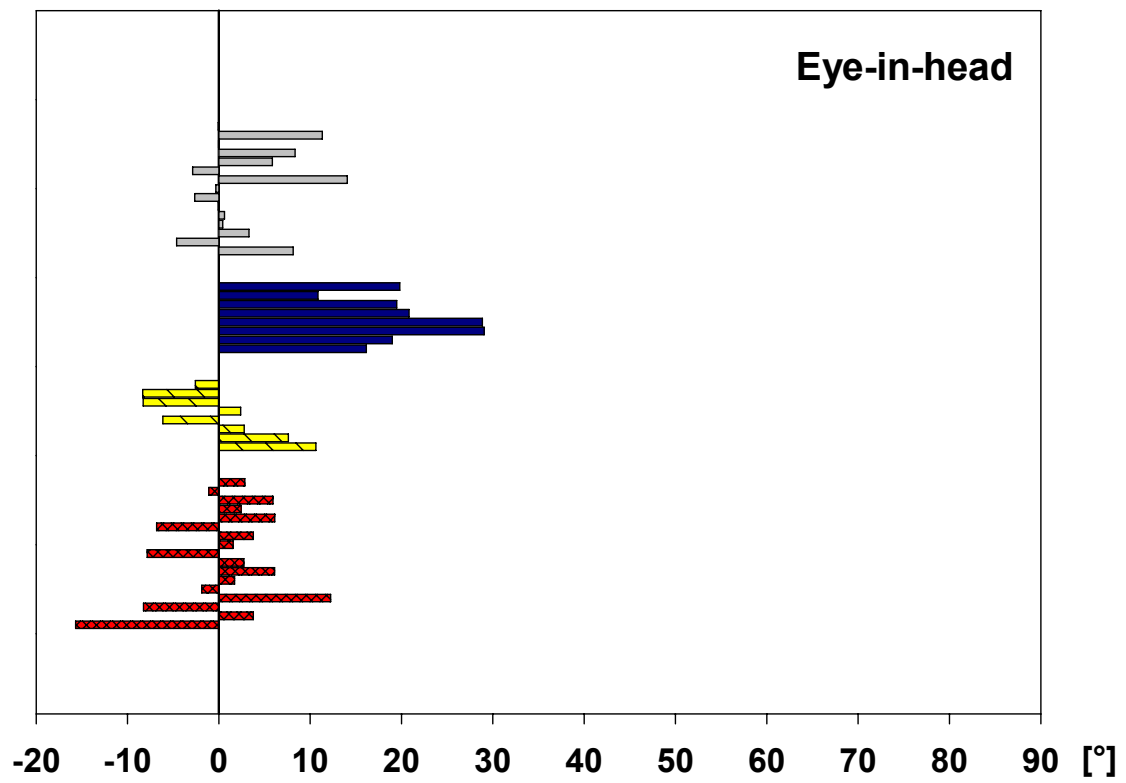
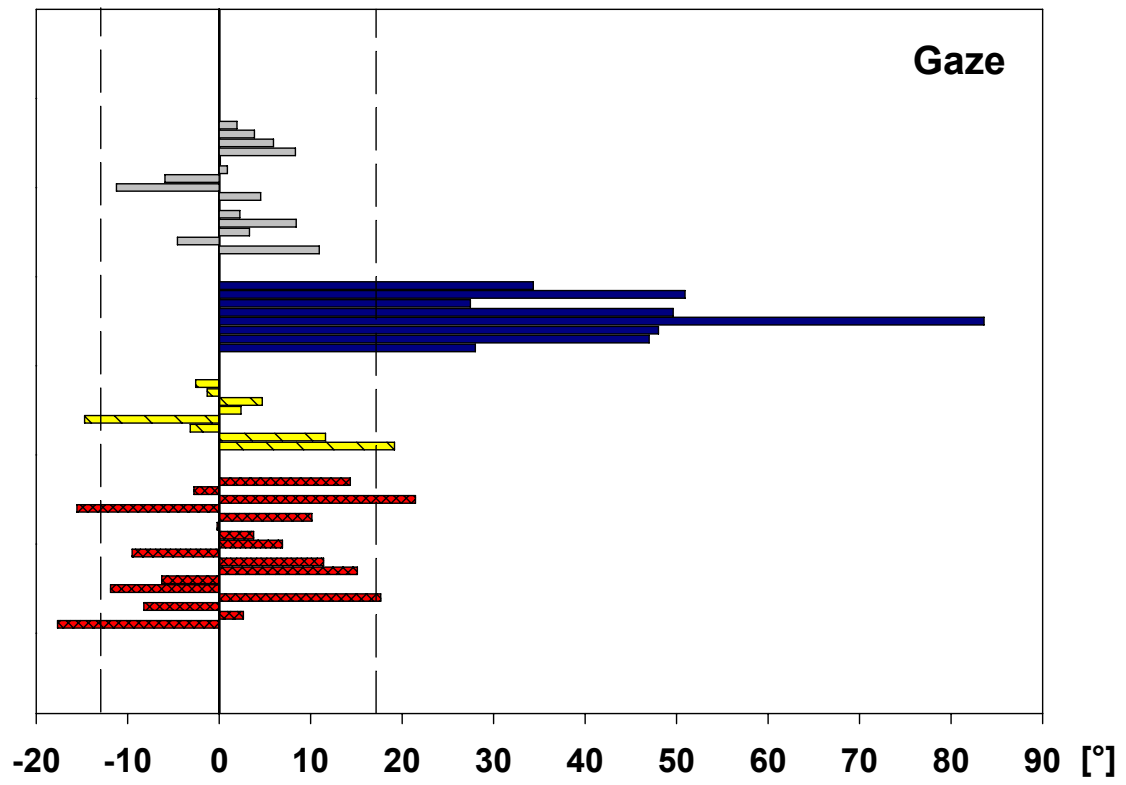
Mean horizontal position (and standard deviation) in degree of visual angle for spontaneous gaze, eye-in-head, and head-on-trunk positions. CON = control subjects, RBD N+ = right brain damaged patients with neglect, RBD N- = right brain damaged patients without neglect, LBD N+ = left brain damaged patients with neglect, LBD N- = left brain damaged patients without neglect. The number of patients included in each group is given in brackets.





To investigate, whether there is a relevant difference for gaze, eye-in-head and head-on-trunk positions between the different groups (CON = control subjects, RBD N+ = right brain damaged patients with neglect, RBD N- = right brain damaged patients without neglect, LBD N- = left brain damaged patients without neglect), we conducted a one-way ANOVA for each of the three parameters between all groups, which revealed significant differences (gaze: $F_3=32.835$, eye-in-head: $F_3=20.845$, head-on-trunk: $F_3=15.372$, $p<0.001$ each). Following the question if spatial neglect might be the crucial factor leading to these differences, for posthoc analysis we first compared the groups of patients without spatial neglect (CON, RBDN-, LBDN-). Conducting a one-way ANOVA for each of the three parameters between these groups, we found no relevant differences between control patients without brain lesions and stroke patients without neglect (gaze: $F_2=0.001$, $p=0.999$; eye-in-head: $F_2=0.757$, $p=0.476$; head-on-trunk: $F_2=0.520$, $p=0.599$). We thus grouped the data of the patients without neglect. This group will be titled CON_all ($n=40$). Comparing RBDN+ and CON_all, we conducted unpaired t-tests. We found a huge difference between the average gaze, eye-in-head, and head-on-trunk positions in neglect patients compared to the whole group of controls (gaze: $t_{46}=-10.15$, $p<0.001$; eye-in-head: $t_{46}=-7.85$, $p<0.001$; head-on-trunk: $t_8=-4.36$, $p=0.003$).

To classify spontaneous gaze positions as normal versus pathological, we defined normal gaze positions as every position within the 99% interval of gaze positions of healthy controls. Gaze positions of less than -13° or more than $+17^\circ$ thus were classified as pathological, i.e. as “gaze deviation (GD)”. Employing these cut-off values, GD occurred in 42 % (14 of 33) of patients, including 3 patients with contralateral gaze deviation. In line with the results of previous studies, GD is more frequently following right brain damage (63 %) than left brain damage (24 %).



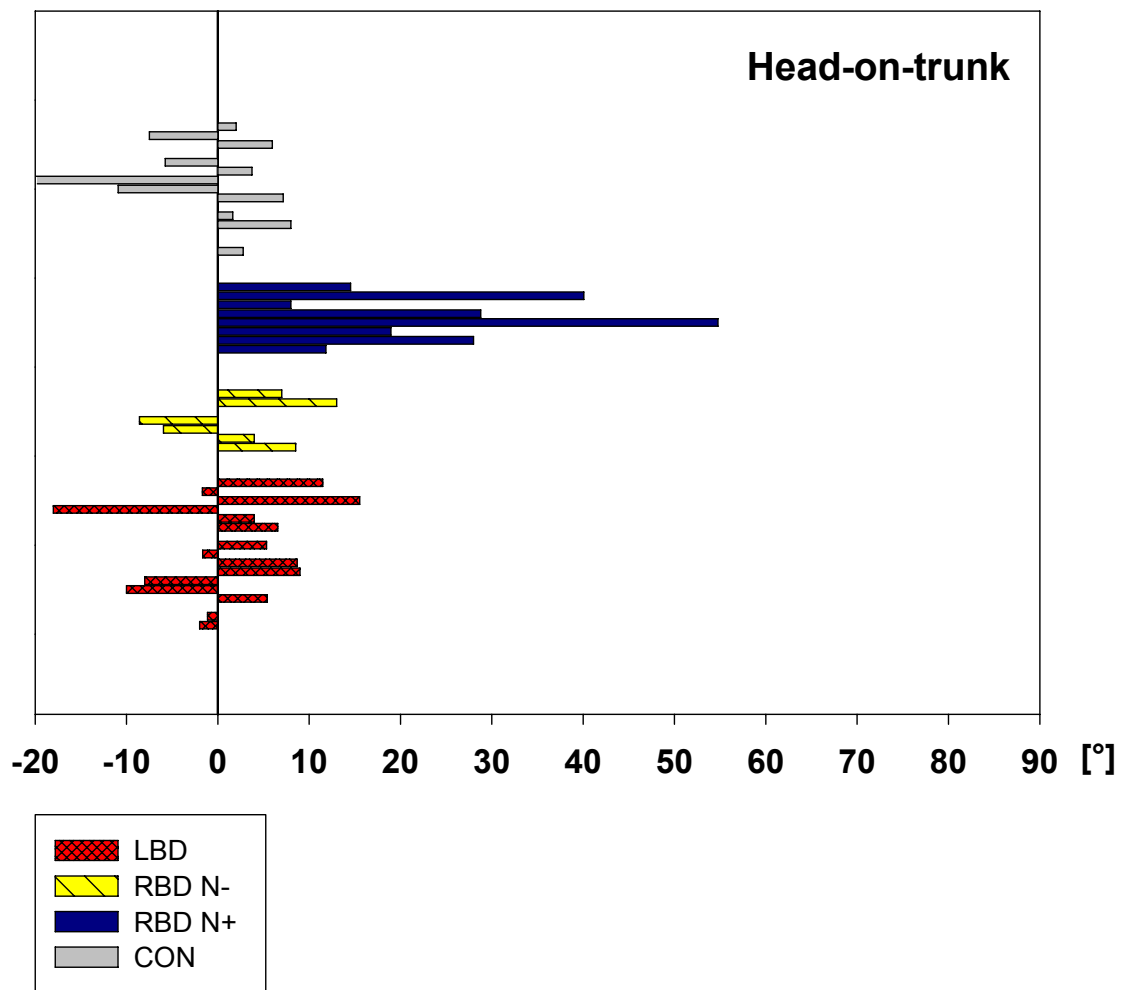


Figure 10

Horizontal gaze position of each subject ($n = 33$), illustrated for LBD N- ($n = 17$), RBD N- ($n = 8$), RBD N+ ($n = 8$), and CON ($n = 15$). Dashed lines indicate the limits of “normal gaze positions” (interval within ± 2.58 standard deviations, based on the values of healthy subjects).

4.2. Relationship between gaze deviation and neglect

Figure 11 presents the different groups of patients, organised by the presence of neglect and GD. When GD occurred, it was combined with neglect in 57 % of cases. The other 43 % of GD patients did not show spatial neglect. In contrast, neglect never occurred on its own but always was combined with GD. We found a clear correlation between the occurrence of spatial neglect and gaze deviation ($\phi=0.659$).

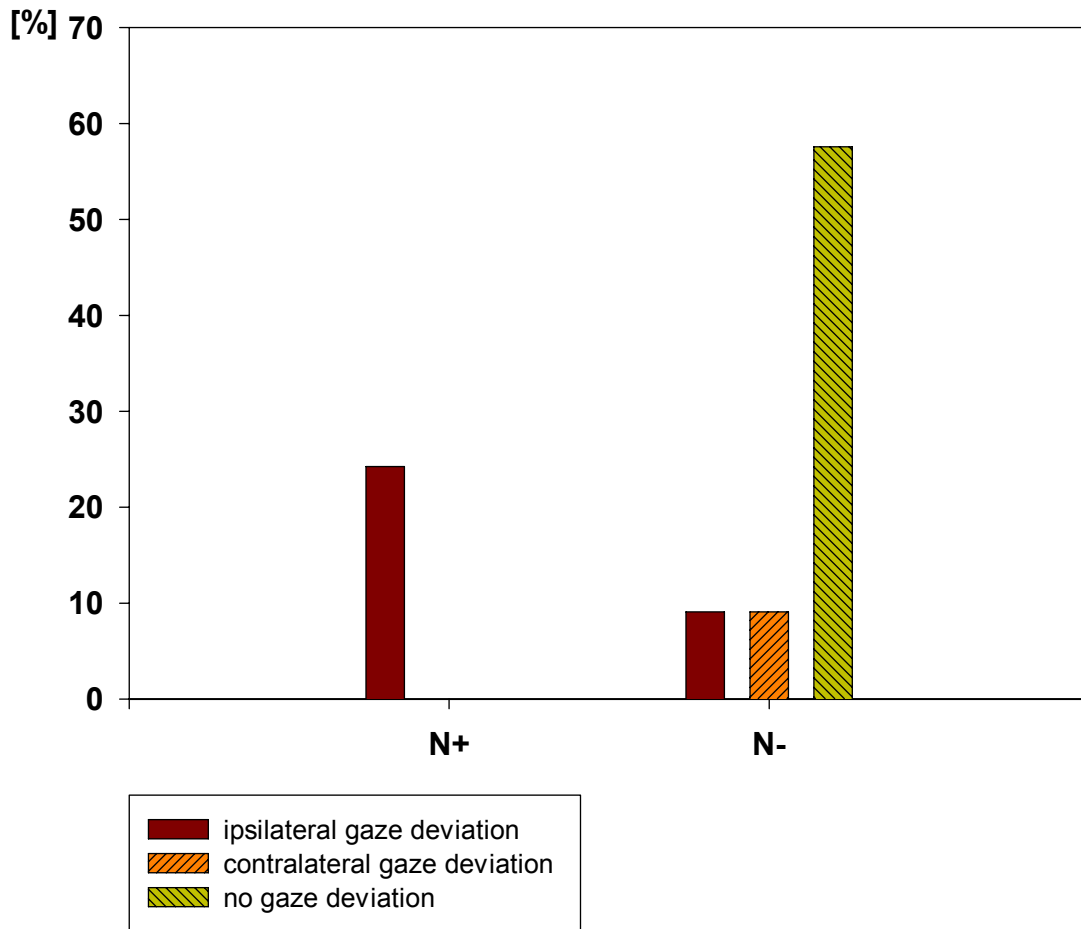


Figure 11

Percentage of subjects with neglect and / or GD in the whole group of patients. GD+ = gaze deviation, GD- = no gaze deviation, N+ = neglect, N- = no neglect. Yellow bars indicate not deviated gaze, orange bars represent a contralateral gaze deviation and red bars indicate ipsilateral gaze deviation.

Regarding the marked difference between the mean gaze position of neglect patients versus all other patients, one could have expected a stronger relation between GD and neglect. The present result can be understood more easily considering the individual results (figure 10). Though the mean values of LBD N- and RBD N- varied around 2° , some of these patients show gaze positions which just go beyond the borderline of non-deviated gaze as defined by the criterion. In contrast, gaze positions of *all* neglect patients *clearly* extend the range of normal gaze positions (mean gaze position in RBDN+ = 46°).

4.3. Extent of gaze deviation and severity of neglect

In consequence to the finding, that all patients with neglect showed a substantial gaze deviation, one could ask whether severe neglect is accompanied by more pronounced gaze positions than milder neglect. For illustration of the correlation between the extent of GD and the severity of neglect, the horizontal gaze position and the severity of spatial neglect were plotted in figure 4 for each patient with neglect. The severity of spatial neglect is represented by the percentage of omissions in all neglect tests performed by a subject. Due to the small sample size in the neglect group ($n = 8$), we did not calculate a regression analysis. Figure 12 illustrates, that there was no markable relationship, as some patients with very high percentages of omission show less deviation of gaze than other patients with lower percentages of omission.

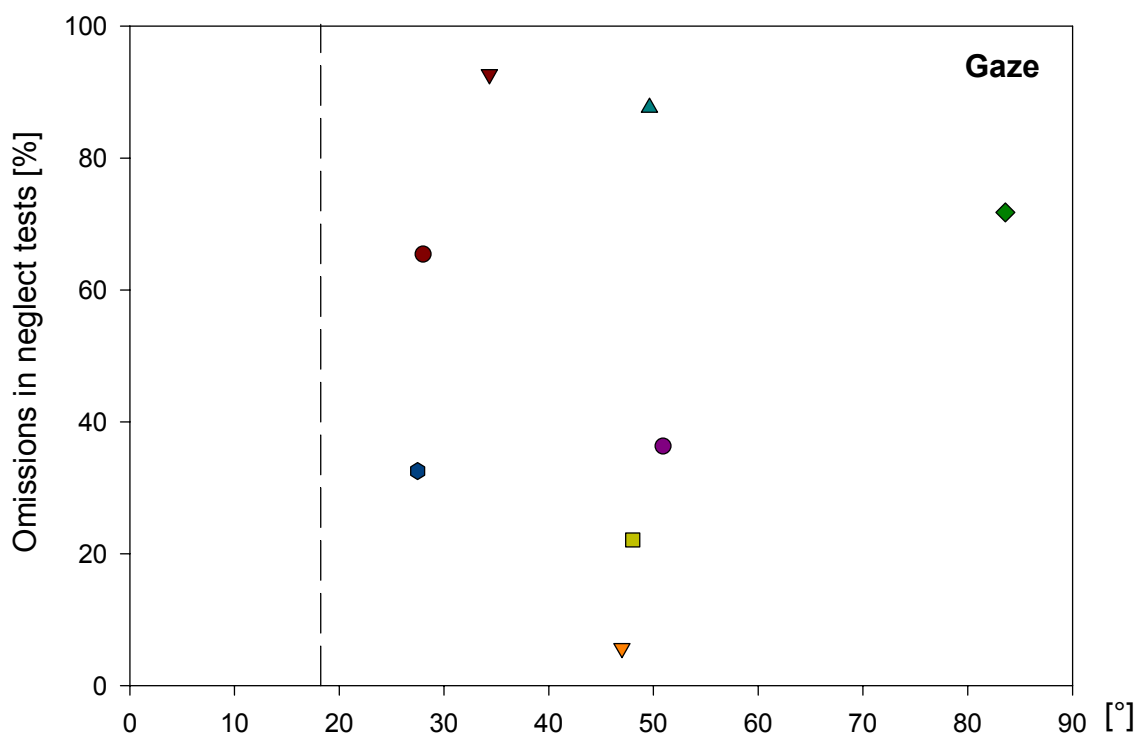


Figure 12

Horizontal gaze position and severity of spatial neglect (represented by the percentage of omissions in neglect tests) for neglect patients ($n = 8$). All values correspond to the data of the first examination, which was carried out 0-3 days after stroke.

4.4. Persistence of gaze deviation and neglect

We further asked, whether GD and neglect might recover simultaneously or not. For this purpose, all patients who have initially been diagnosed to suffer from spatial neglect and who have still been in the hospital were re-evaluated 6-8 days post stroke. Figure 13 illustrates the time course of neglect symptoms and the corresponding horizontal gaze position for each neglect patient (n = 5).

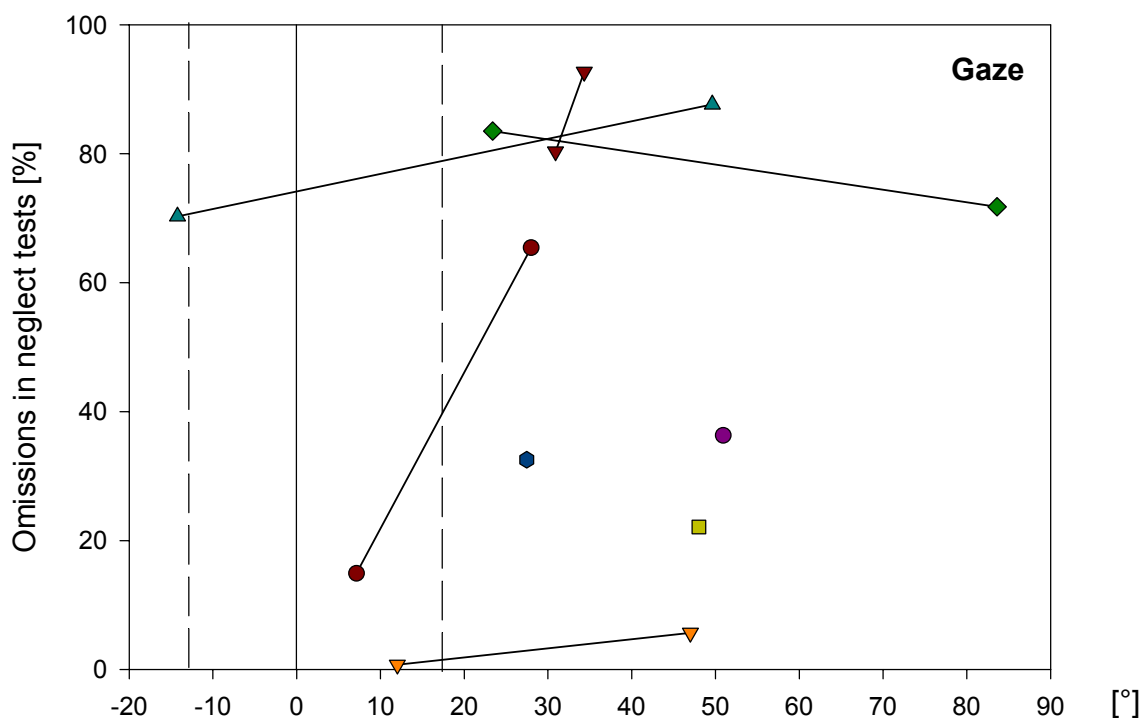


Figure 13

Horizontal gaze position and severity of spatial neglect (represented by the percentage of omissions in neglect tests). The results of each patient are illustrated by two symbols of the same colour, which are connected by a line.

The average horizontal gaze position of neglect patients at the first versus the second examination was compared conducting a t-test for paired samples. The analysis revealed significant changes in the horizontal gaze position ($t_4=3.19$, $p=0.033$). In the second examination, horizontal gaze positions were less

pronounced or recovered, compared to the first examination. Only two patients were left with the diagnosis of GD. Neglect on the other hand did not improve significantly, comparing the average percentages of omission at both times of examinations using the Wilcoxon matched pairs test ($Z=-0.944$, $p=0.345$). Nevertheless, signs of neglect decreased in individual patients (figure 5).

Considering a relationship between GD and spatial neglect, it would be interesting to know, whether the proportion of the decrease of the eccentric gaze position to the recovery of neglect is comparable in all patients. This proportion represents the course of recovery and would be an indicator for a strong relation of both symptoms, if it is comparable between the different patients. Table 3 gives the percentages of decrease of neglect and of the horizontal gaze position for each patient. For calculation, the value of the first examination was set to “100%”. The proportion between recovery of symptoms is reflected by the ratio given in column 4. Due to the small sample size we did not conduct any further analysis to compare these ratios. However, regarding their wide range, we did not find a striking similarity.

Table 3

	Gaze (decrease in %)	Neglect (decrease in %)	Decrease Gaze / Decrease Neglect
Patient 1	74.36	77.21	0.96
Patient 2	74.42	87.28	0.85
Patient 3	72.02	-16.35	-4.41
Patient 4	128.66	19.82	6.49
Patient 5	10.28	13.31	0.77

Percentages of decrease of neglect and the horizontal gaze position for each patient, calculated with the value of the first examination set to “100%”. Column 4 illustrates the ratio between column 2 and 3.

4.5. Relationship between the horizontal gaze position and the time of examination

Keeping in mind the results of previous studies, one could suggest, that the horizontal gaze position might be influenced by other factors than by the presence of spatial neglect.

For example, the time of examination could be such a factor (see introduction). As the mean time since lesion is similar for patients with and without gaze deviation (GD+ = 1.71 days, GD- = 1.42 days), it is evidently not the crucial factor for the deviated gaze positions of patients in our study.

5. Discussion

5.1. Discussion of methods

Keeping in mind the methodical weaknesses of previous studies (see 1.3.2.2.) concerning the time of examination, the diagnosis of neglect, the investigation of left brain damaged patients and the diagnosis of GD, the methods of the present study will be discussed in the following sections.

5.1.1. Time of examination

Concerning the time of examination, we focussed on patients in whom complete examination was possible 0-3 days after stroke. We decided in favour of this short interval to avoid recovery processes. As cancellation tasks and the assessment of spontaneous eye and head positions require a certain degree of consciousness and understanding, investigation was not feasible or only after a longer time interval in 9 patients. Excluding them from the analysis, our data contain a potential (but not avoidable) bias, in the way that the results of the most severely impaired patients had no influence on our data. Nevertheless, the present data reflect the symptoms of stroke patients in the acute state more precisely than data of previous studies.

5.1.2. Diagnosis of neglect and examination of left brain damaged patients

We employed commonly used and accepted cancellation tasks to diagnose neglect. Dealing with aphasic patients, in whom examination via cancellation tasks is difficult, Albert's test was a helpful tool. Due to less sensitivity (Ferber and Karnath, 2001), it is not used as frequently as the Bells test, Letter cancellation test, or the copying task. Nevertheless we employed it, as the task is easy to explain. In this way, we managed to investigate nearly all admitted left brain damaged stroke patients. Some of them had little language understanding but performed tests by imitating the task demonstrated by the investigator on another worksheet. In consequence, only 2 of the 9 patients mentioned above

were excluded because they did not manage to perform any neglect test due to severe aphasia.

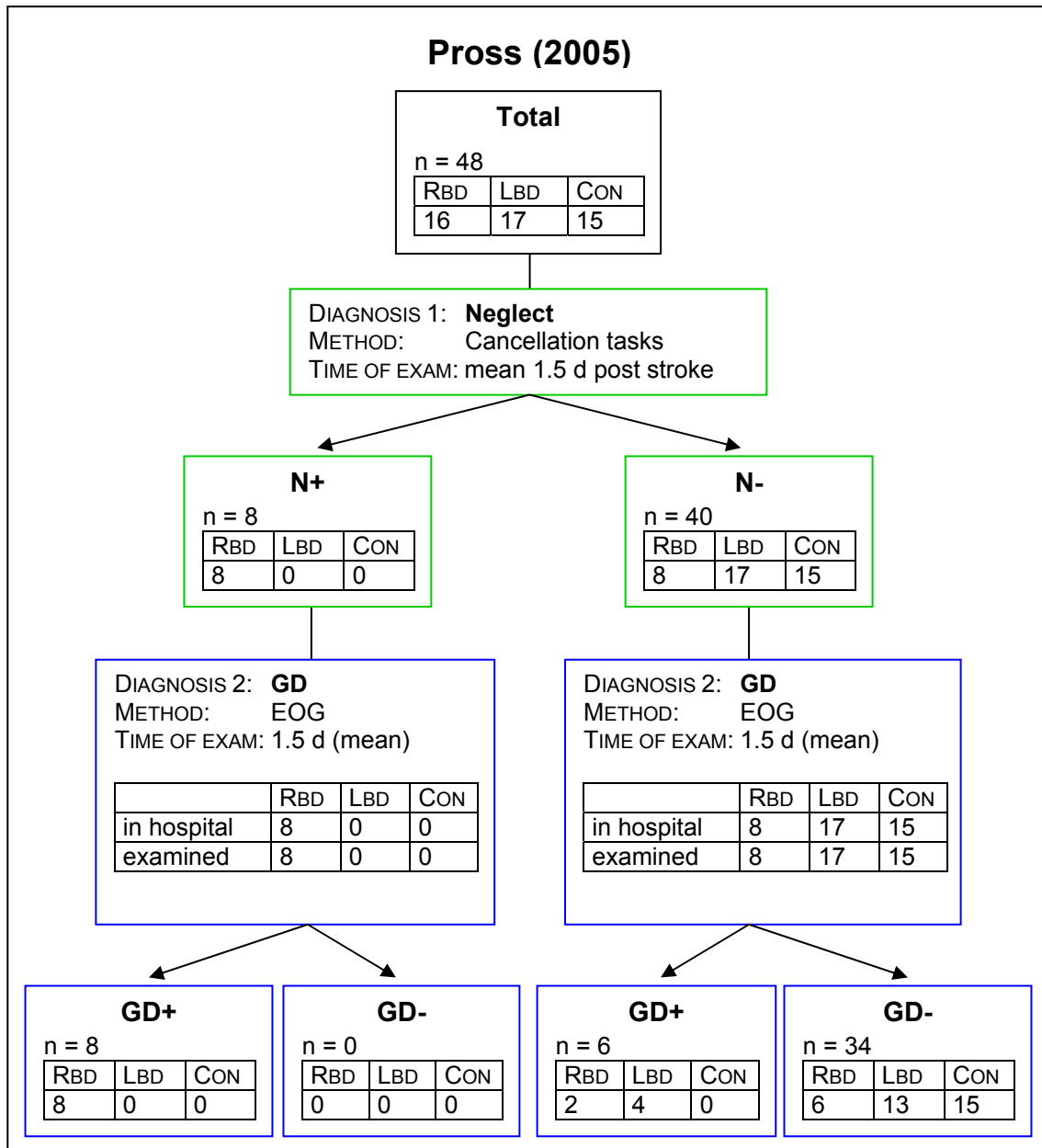


Figure 14

Pross (2005). RBD = right brain damaged subjects, LBD = left brain damaged subjects, CON = control subjects without brain damage, n = number, GD = gaze deviation, EXAM. = examination, N = spatial neglect, EOG = electrooculography.

5.1.3. Diagnosis of gaze deviation

Previous studies diagnosed CED / GD by means of clinical observation (see 1.2.). We decided, to assess GD objectively and in a quantitative way. Since we planned to investigate patients as soon as possible, we aimed to examine them in the intensive care situation of the local stroke unit. Methods requiring a large experimental set up or transport of the patient thus were not suitable. Electrooculography (EOG) seemed to be the adequate method for this situation. EOG is easy to transport and to apply. It can be used in patients sitting in a wheelchair or even in their bed and does neither require much space (which would not have been possible under the local circumstances) nor much effort of the patient. Other methods which might be more precise in the detection of eye movements (e.g. magnetic search coil technique, eye tracking systems, etc.) would not have been suitable in the present situation. Concerning the accuracy, there are different factors influencing the precision of the measurement. Some of them are related to the set up of the examination, others belong to the technique of electrooculography. Factors of both kinds will be explained in the following.

Carrying out the assessment of spontaneous gaze, eye-in-head, and head-on-trunk positions in the local stroke unit, we faced disturbances related to the activity of other patients and the nursery caring for them. In consequence, some recording periods were influenced by visual distraction (someone coming in etc.) or sudden auditory stimuli. These periods were excluded from the analyses. Nevertheless, the basic noise level could not be changed, i.e. interference following auditory distraction could not be fully eliminated. However, control subjects were examined in a quiet room without auditory distraction. Intending to assess eye *and* head positions, the patients' head was not fixated. Under these circumstances, the precision of the EOG calibration deteriorated although patients were instructed not to move their head while the calibration was carried out. Though there was no possibility to reduce these interference factors, their influence is restricted because they occurred in both directions.

EOG data are based on the measurement of changes in an electrical field due to the corneo-retinal potential difference. As the surrounding structures are not electrically neutral but in parts produce a potential difference for themselves, artefacts are known to influence measurement, e.g. muscle artefacts or EEG artefacts. Moreover, artefacts due to blinking and vertical eye movements occur when eye movements are recorded in the horizontal plane only. All of these artefacts are of small extent and did not have to be corrected as they were distributed equally in both directions around the actual gaze position. A further problem, which goes along with direct current (DC) recording of eye movements, is the instability of the baseline. It is caused by changes in the electrodermal activity. To avoid strong influence of this interference factor, we corrected data by linear subtraction of baseline changes. Although baseline changes were not fully linear, most of its influence could be reduced by this approximate correction.

In summary, we can conclude that there were various factors influencing the measurement, which led to a wider range of values, i.e. to an increase of variance, but not to a systematic bias in one or the other spatial direction or to a bias in only one of the groups.

5.2. Discussion of results

5.2.1. Summary of results

Investigating the spontaneous orientation of gaze in hemispheric stroke patients, we found a substantial difference between the mean horizontal gaze position of neglect patients compared to patients without neglect. Despite that, there was no correlation between the severity of neglect and the horizontal gaze position of the patient. Additionally, no relation between the extent of recovery of neglect and GD was found. GD also occurred in patients without neglect. However, this deviation was not as striking as in neglect patients.

5.2.2. Mean horizontal gaze positions in patients with versus without neglect

In line with the results of Fruhmann Berger and Karnath (2005), we found the average horizontal gaze position in RBD patients with neglect to be markedly different from the spontaneous orientation of gaze in RBD patients without neglect and healthy subjects. Moreover, the average gaze position of LBD patients without neglect was similar to the positions of RBD patients without neglect and controls and therefore also clearly different from that of neglect patients. Compared to the study of Fruhmann Berger and Karnath, the mean horizontal gaze position in neglect patients in our study was even more pronounced (46° compared to 30°). This difference is probably due to the time of examination, as recovery starts in the first days after stroke (De Renzi et al., 1982). Fruhmann Berger and Karnath investigated patients approximately 13 days after stroke while the mean time since lesion in our study was 1.4 days for neglect patients and 1.6 days for patients without neglect.

5.2.3. Gaze deviation – Prevalence. Contralateral gaze deviation.

42% of the patients suffered from GD, as defined by the criterion (see 4.1.). This value lies within the upper range of reported prevalences (between 16 and 50%). Comparing our results with those of other studies, it is surprising, that there are 3 patients (9%) showing a contralateral deviation of gaze. In references to this topic, only few patients suffering from contralateral eye deviation following supratentorial stroke are described (Keane, 1975; Pessin et al., 1981; Sharpe et al., 1985; Tijssen, 1994). Tijssen (1994) reported 5 cases out of 133 patients (4%) showing these so-called “wrong-way eyes”. Contralateral gaze deviation usually occurs following hemorrhages, most of them located in the thalamus. Taking into consideration the expanding character of hemorrhages, Tijssen (1994) suggested damage of descending oculomotor pathways from the contralateral hemisphere at midbrain level to cause this phenomenon. In contrast, thalamic hemorrhage was present in only one of our patients, while two of them had ischemic lesions. Looking at figure 5, we observe that gaze values of GD patients without neglect are distributed

equally in both directions, i.e. there are 3 patients with GD to the ipsilateral and 3 patients with GD to the contralateral side. The extent of GD in both directions was also similar and not severe. Based on these observations, one can assume, that in the present study, GD in patients without neglect is rather due to dispersion caused by recording conditions (see 5.1.3.) than to a pathological mechanism.

In contrast to previous studies, our data do not show a ratio of 2:1 between GD following right versus left hemispheric stroke. Excluding the slight deviations of gaze, which might be due to recording conditions (see above), there is no gaze deviation following left brain damage at all. The factor leading to this result could be the fast recovery of CED following left brain damage. It is known to disappear earlier than CED following right brain damage. Though examinations were carried out as soon as possible, we can not assure, that recovery did not take place before. However, another reason for the missing of strong gaze deviations towards the left side might be that there are no left brain damaged neglect patients.

5.2.4. Gaze deviation and spatial neglect – Co-occurrence. Severity. Persistence.

Gaze deviation was present in all patients suffering from spatial neglect. The deviation of gaze shown by these patients was of large extent. A gaze deviation of comparable severity in patients without neglect was neither observed in examinations 13 days after stroke (Fruhmann Berger and Karnath, 2005), nor in the present examination of patients in the acute state after stroke. Nevertheless, the extent of gaze deviation is not related to the severity of spatial neglect. The absence of this relation can be interpreted in different ways. Either there is no relation between the extent of gaze deviation and the severity of neglect or there is a relation which could not be shown because of methodical restrictions. Such methodical restrictions are e.g. the sample size, which does not allow to discover nonlinear relations, the accuracy of gaze position recording and the precision of the percentage omission score in cancellation tasks to reflect the strength of neglect. The latter one is influenced by the alertness of the patient,

in the way that the severity of neglect might be overestimated in some patients with reduced alertness. On the other hand, the severity of neglect might be underestimated in patients with very severe neglect, as the size of the paper limits the maximal available score of severity.

The independent improvement of GD and neglect shown in the follow-up examination is in line with the result of De Renzi et al. (1982). Investigating CED patients for neglect 14-18 days after stroke, they found that all patients suffering from CED at that time also showed neglect. Additionally, neglect was diagnosed in patients whose CED clinically had already recovered. Though being less precise than our results (see 1.3.2.2.), the findings of De Renzi et al. showed the same tendency: despite the simultaneous occurrence, the improvement of GD and of neglect over the course of time seem to be independent.

5.2.5. Is there a relationship between gaze deviation and spatial neglect?

Summing up the results of our study, we ask once again whether or not there is a systematic relationship between GD and spatial neglect. One could question the existence of a relation arguing that symptoms that improve independently probably do not have a causal relationship. The absence of a relation between the extent of GD and the severity of spatial neglect also points against a close relationship of both symptoms, but it can also be interpreted as the consequence of methodical difficulties (see 5.2.4.). Moreover, the occurrence of mild GD in patients without neglect and the appearance of GD following brainstem lesions could be interpreted against the existence of a relation between both symptoms. But one should ask, if GD following brainstem stroke really is the same symptom as GD following hemispheric stroke. As we did not investigate patients with brainstem damage, comparisons are difficult. Lesions of the paramedian pontine reticular formation (PPRF) in the brainstem are known to result in a transient contralateral eye deviation and a permanent gaze palsy to the ipsilateral side (Masuhr and Neumann, 1998). The degree of eye deviation following brainstem lesions is not known, as no quantitative measurement was carried out. Up to now, eye deviations following stroke in general have been interpreted as a symptom resulting from damage to cortical

centres of eye movement control or their descending pathways at different levels. Though eye deviation is thought to be a homogeneous entity, there is no evidence for this. It could also result from different causes. One argument against the uniformity of this entity is that an additional rotation of the head, which is present in most CED patients with hemispheric stroke, is not described following brainstem lesions. To clarify whether eye deviation following hemispheric and brainstem damage really are comparable, a quantitative measurement of GD would be helpful.

On the other hand, the substantial difference between the mean horizontal gaze position of neglect patients compared to the mean values of all other groups of stroke patients is a strong argument for the existence of a relationship between GD and neglect. There was no patient who suffered from neglect but not from gaze deviation. Furthermore, none of the patients without neglect showed a similar extent of gaze deviation as patients with neglect. The difference between the strongest gaze deviation in patients without neglect and the mildest gaze deviation in patients with neglect was 6° , i.e. more than one standard deviation. This difference between gaze positions in single patients comparing patients with and without neglect in addition to the markedly different mean values strongly point to a relationship of GD and neglect. Unfortunately, the present unselected sample of 33 patients did not contain left brain damaged patients with spatial neglect. This is consistent with the notion that spatial neglect occurs asymmetrically after right hemisphere stroke as aphasia is observed after left hemisphere lesions. On the other hand, the data also did not contain patients with a gaze deviation to the left side, which is of comparable extent as the gaze deviation of right brain damaged neglect patients. One could interpret the absence of a strong gaze deviation to the left side and the absence of left brain damaged neglect patients as a further (indirect) sign for a relationship between GD and spatial neglect.

Further indication on a relationship between both symptoms comes from the similar effects of unilateral stimulation of the vestibular system on GD and on symptoms of spatial neglect. Asymmetric vestibular stimulation, e.g. by application of cold water in the external auditory canal of one ear, in healthy

subjects is known to result in a shift of the spontaneous horizontal eye-in-head position (Abderhalden, 1926; Jung, 1953) towards the stimulated side and nystagmus towards the other side. Moreover, there was one study which reported a rotation of the head of about 20-30° towards the stimulated side (Karnath et al., 2003b) under vestibular stimulation. These studies give the impression that cold caloric stimulation in healthy subjects leads to a symptom which is similar to the gaze deviation observed in stroke patients: a shift of the spontaneous eye and head orientation towards the stimulated side. In stroke patients with GD, eye and head deviation temporarily decrease while stimulating the contralesional vestibular apparatus with cold water (Tijssen, 1988). The patients' eyes transiently are positioned in the mid-sagittal orbital axes or even in the contralesional canthus of the eyes. The degree of head rotation also diminishes respectively recovers in the sense that the orientation of the patients' head is in line with that of the trunk. Caloric stimulation of one vestibular organ not only has compensatory effects on GD but also on the clinical signs shown by patients with spatial neglect (Rubens, 1985; Vallar et al., 1995). Conducting exploration tasks like the letter cancellation test, patients with spatial neglect normally show a shift of the centre of exploratory movements (Karnath et al., 1998). In patients with left sided neglect, this centre of exploration is shifted towards the right side. Stimulating their left vestibular organ while tests are conducted, the spatial distribution of exploratory movements changes remarkably. The maximum of explorations shifts back to the midline and the spatial distribution of exploratory movements during stimulation is comparable to those of healthy subjects (Karnath et al., 1996). These similar effects of vestibular stimulation on gaze deviation and neglect indicate a close relation of both symptoms. Moreover, their relation to asymmetric function of the vestibular system is obvious.

In conclusion, the present data and previous findings argue for a close relation between gaze deviation and spatial neglect in the way that right brain damaged patients with spatial neglect show a strong deviation of gaze towards the right side.

5.3. Consequences of the present results

5.3.1. Consequences for the diagnosis of gaze deviation

The idea of the current project was to investigate the relationship between two symptoms: neglect and gaze deviation. In need of a criterion for the diagnosis of GD, we decided to investigate healthy control subjects. Finally, we would like to ask whether the chosen criterion is suitable. Does it reflect the pathology of the symptom? Besides the marked gaze deviation of patients with spatial neglect, figure 10 shows some cases of slight gaze deviation. These latter deviations are distributed equally towards the ipsi- and contralesional side. Considering the results of former studies (e.g. the reported prevalence of eye deviations towards the contralesional side), one can assume that these deviations are caused by dispersion due to recording conditions rather than by a pathology. In contrast, all neglect patients showed a marked deviation of gaze. Their gaze positions were distributed in a range from 28° to 84°. Due to the systematic relationship between gaze deviation and spatial neglect, it would be possible to suggest a new criterion for the diagnosis of gaze deviation in future examinations, calculated on the basis of the pathologic gaze positions of neglect patients. However, this idea does not seem to be useful because of the small sample size and the wide range in which gaze positions of neglect patients were distributed in this sample. Instead of proposing a precise cut-off criterion, we thus rather like to offer a guide-line. Taking into consideration the mean horizontal gaze position of neglect patients found by Fruhmann Berger and Karnath (30°) and the present data, we would like to suggest that all gaze positions larger than 30° are related to spatial neglect.

5.3.2. Consequences for the diagnosis of spatial neglect

So far, the diagnosis of neglect requires the performance of various cancellation tests. Facing the severe impairment of patients, their implementation in the acute state of disease is often difficult. After stroke, consciousness is impaired in many patients and their alertness is markedly reduced. Attending cancellation

tasks therefore is of great effort for them and they often are not able to perform tests completely. Furthermore, the performance of cancellation tasks demands good vision and, most importantly, comprehension of the task. A huge percentage of left brain damaged stroke patients suffer from aphasia. Verbal instructions often fail and patients are not able to perform cancellation tests. In the acute state of disease, diagnosis of neglect thus requires great effort of patients and investigators. However, the present data offer a tool which can help clinical neurologists to diagnose neglect in the early state of disease, when the patient yet is not able to perform cancellation tasks. Patients suffering from right hemispheric stroke, in whom a deviation of gaze towards the right side of more than 30° can be observed, most probably also suffer from spatial neglect.

5.4. Perspectives

Confirming the existence of a relationship between gaze deviation and neglect, our study leads to further questions. One point of interest is the existence of a relation between the extent of GD and the severity of spatial neglect, which should be addressed by a study with a large sample size.

Discussing the results, we asked whether gaze deviation following brainstem and hemispheric stroke is a homogeneous entity or whether it consists of two different symptoms with different causes (see 5.2.5.). CED / GD following brainstem stroke was not yet examined in a quantitative way. It would be interesting to investigate whether this symptom consists of similar parts (shift of the eye-in-head position *and* rotation of the head) and has a similar extent as GD following hemispheric stroke. A quantitative measurement of both symptoms could help to decide whether or not “gaze deviation” really is a homogeneous entity.

5.5. Conclusion

Investigating unilateral, left as well as right hemispheric stroke patients with respect to (i) their spontaneous horizontal gaze position and (ii) spatial neglect, we found the spontaneous gaze position of patients with neglect to be markedly different from that of patients without neglect. Our finding has clinical implications: hemispheric stroke patients showing a marked deviation of gaze larger than 30° in the acute stage of disease (0-3 days after stroke onset) suffer from spatial neglect. This relationship might help clinical neurologists to derive the diagnosis of spatial neglect more easily in the early state of disease, when it is still difficult to perform elaborate clinical testing of the patients.

6. Abstract

Conjugate eye deviation (CED) is a striking symptom following hemispheric stroke. However, the term “eye deviation” describes only a part of the symptom: a sustained shift of the patient’s horizontal eye-in-head position towards the lesioned side. Observing carefully, one recognises that the patient’s head is also orientated towards the side of the brain lesion in most cases. Such a simultaneous deviation of eye and head positions is described more precisely by the term “Gaze deviation” (GD). Up to now, the pathophysiology of GD remains unclear. In this context, a relationship between GD and spatial neglect is object of controversial discussions. The aim of the present study was to clarify whether or not there is a systematic relation between both symptoms. We investigated an unselected sample of 33 consecutively admitted patients with unilateral first-ever stroke. The patient sample consisted of 16 patients with right hemispheric stroke (RBD) and 17 patients with left hemispheric stroke (LBD). In addition, 15 non-brain-damaged control subjects (CON) were investigated. Patients were examined with respect to (i) their spontaneous orientation of gaze and (ii) spatial neglect. Examinations were carried out in the early state of disease, i.e. in an interval of 0-3 days after stroke. To allow a reliable diagnosis of gaze deviation, we used a quantitative method for the assessment of horizontal eye-in-head and head-on-trunk positions. Eye-in-head positions were recorded by electrooculography while the head-on-trunk positions were measured by a graphometer circle. Spatial neglect was diagnosed in 24% of patients. All of them suffered from a strong deviation of gaze. A gaze deviation of similar extent was not observed in any other group of patients. There was a substantial difference between the mean horizontal gaze position of neglect patients versus patients without neglect and healthy controls. The results of the present study indicate a close relation between gaze deviation and spatial neglect. This finding has clinical implications. So far, it was difficult to derive the diagnosis of spatial neglect in the early state of the stroke since patients are severely impaired and not able to perform standardised paper-and-pencil tests. In need of a first estimation it might be helpful for clinical neurologists to consider that right hemispheric stroke patients who suffer from a marked deviation of gaze (i.e. $> 30^\circ$) most probably also suffer from spatial neglect.

7. Zusammenfassung

Schlaganfälle der Großhirnhemisphären gehen mit verschiedenen Symptomen einher. Ein häufiges und auffälliges Symptom ist die konjungierte Blickdeviation (gaze deviation, GD). Patienten mit einer Blickdeviation zeigen eine spontane Wendung der Augen zur Seite der geschädigten Hemisphäre sowie eine Orientierung des Kopfes zur selben Seite. Die Pathophysiologie dieses Symptoms ist noch unklar. Umstritten ist insbesondere eine Beziehung der Blickdeviation zur Neglectsymptomatik. Ziel dieser Studie war es daher zu klären, ob es eine Beziehung zwischen diesen Symptomen gibt. Im Zeitraum von neun Monaten untersuchten wir alle Schlaganfallpatienten mit erstmaligem, unilateralem Schlaganfall. Bei 16 von diesen 33 Patienten betraf der Schlaganfall die rechte Hemisphäre (right brain damaged, RBD). 17 Patienten hatten eine Läsion der linken Hemisphäre (LBD). Wir untersuchten zusätzlich 15 Kontrollpersonen ohne Hirnschädigung (controls, CON). Die Untersuchung fand 0-3 Tage nach Beginn der Symptomatik statt. Sie umfasste eine Messung der spontanen Augen- und Kopfposition sowie Tests zur Diagnose von Neglect. Die spontane Augenposition wurde mittels Elektrookulographie ermittelt, die Kopfposition wurde mit einem Winkelmesser bestimmt. Insgesamt 24% der Patienten hatten einen Neglect. Gleichzeitig zeigte jeder dieser Patienten eine ausgeprägte Blickdeviation, die in dieser Stärke in keiner anderen Patientengruppe beobachtet werden konnte. Die mittlere Blickposition aller Neglectpatienten unterschied sich signifikant von der Blickposition der Patienten ohne Neglect und der Patienten ohne Hirnschädigung. Dieser Befund deutet auf eine enge Beziehung zwischen Blickdeviation und Neglect hin. Daraus ergeben sich Konsequenzen für die Diagnostik von Neglect. Sie war bisher im akuten Stadium des Schlaganfalls nur schwer möglich, da die Patienten zu stark beeinträchtigt sind, um konventionelle Papier-und-Bleistift Verfahren zu bearbeiten. Für eine frühzeitige klinische Einschätzung der Neglectsymptomatik kann es daher hilfreich sein zu wissen, dass rechshemisphärisch geschädigte Patienten mit einer starken Blickdeviation (größer als 30°) mit hoher Wahrscheinlichkeit eine Neglectsymptomatik aufweisen.

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Lebenslauf

Persönliche Daten

Name	Rebekka Dorothee Proß
Geburtsdatum	29.10.1979
Geburtsort	Tübingen

Schulischer Werdegang

1986– 1990	Pliensau-Grundschule Esslingen
1990– 1999	Mörike Gymnasium Esslingen

Freiwilliges Soziales Jahr

1999– 2000	Aupair in Spanien
------------	-------------------

Studium

2000	Beginn des Medizinstudiums an der Eberhard Karls Universität Tübingen
2002	Physikum
2003	1. Staatsexamen
2003 – 2005	Promotion in der Sektion Neuropsychologie an der Neurologischen Universitätsklinik Tübingen
2005	2. Staatsexamen
2005 – 2006	Praktisches Jahr Innere Medizin, Klinikum Esslingen Chirurgie, Klinikum Esslingen Neurologie, Marienhospital Stuttgart
2006	3. Staatsexamen am 21.11.2006