

Neuroimaging of eye position reveals spatial neglect

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Conjugate eye deviation describes the tonic horizontal deviation of the eyes in acute stroke patients. Here we investigate whether measuring patients' eye-in-head position in clinical magnetic resonance imaging or computed tomography scans obtained at admission shows a specific relationship to spatial neglect. We investigated 124 continuously admitted subjects with unilateral, first-ever left- or right-sided stroke. To control for the possibility that the degree of eye deviation is related to lesion size rather than spatial neglect, overall lesion volume was used as a covariate in the statistical analysis. Horizontal eye-in-head deviation on clinical brain scans appeared to be associated with spatial neglect rather than with brain damage *per se*. In contrast to the subject groups without the disorder, the patients with spatial neglect showed an eye-in-head position that was significantly deviated towards the ipsilesional right. Evaluation of eye-in-head position on clinical scans thus may be an additional helpful tool for diagnosing spatial neglect, particularly in the very early period of the stroke.

Keywords: spatial neglect; conjugate eye deviation; temporal cortex; attention; neuroimaging; stroke; human

Abbreviations: CED = conjugate eye deviation; VLBM = voxelwise lesion-behaviour mapping

Introduction

Spatial neglect is a typical consequence of right hemisphere brain lesions. The disorder is not only of theoretical interest for brain processes involved in spatial orienting but also has important clinical implications, as it leads to prolonged inpatient periods and impaired functional recovery (Kalra *et al.*, 1997; for review Karnath and Zihl, 2003). Spatial neglect causes a marked exploration and orienting bias in favour of the patients' ipsilesional right side and neglect of items located on their contralesional left. A prominent clinical sign of spatial neglect is the spontaneous eye and head deviation towards the ipsilesional side. This sign is

apparent even under conditions when patients 'do nothing', i.e. without any active behaviour (Fruhmann-Berger and Karnath, 2005).

A tonic horizontal deviation of the eyes in stroke patients termed conjugate eye deviation (CED) has already been described in the early literature (Prévost, 1865). Subsequent investigation of this phenomenon reported a higher occurrence (Mohr *et al.*, 1984; Steiner and Melamed, 1984; Kömpf and Gmeiner, 1989; Simon *et al.*, 2003) and a longer duration (De Renzi *et al.*, 1982; Tijssen, 1988; Ringman *et al.*, 2005) after right than after left hemispheric stroke. Patients presenting with this sign showed larger lesions compared with stroke patients without CED (Kelley and Kovacs,

1986; Singer *et al.*, 2006), involving the right inferior parietal lobule, right middle and superior temporal gyri as well as parts of the insula and basal ganglia in the right hemisphere (Singer *et al.*, 2006).

Fruhmann-Berger and co-workers (2006) investigated the relationship between horizontal eye and head deviation and spatial neglect. Could it be that the neglect of contralesionally located items is provoked by a tonic deviation of eyes and head towards the ipsilesional side? In a sample of continuously admitted patients with acute left- or right-sided stroke, they measured the spontaneous position of the eyes in the head by electro-oculography, the position of the head on the trunk, as well as the patients' behaviour in clinical neglect tests, such as cancellation and copying tasks. A marked deviation of eyes and head was observed selectively for the group of patients with right hemispheric lesions and spatial neglect.

Measuring stroke patients' eye-in-head position thus might be an additional helpful tool for diagnosing spatial neglect, particularly in the very early period of the stroke in which many patients still are not able to cooperate and perform traditional paper-and-pencil tests. Previous studies used (mostly three-stepped) ordinal rating scales to represent the examiner's clinical (naked eye) observation of patients' eye-in-head position (e.g. De Renzi *et al.*, 1982; Singer *et al.*, 2006). For more precise measurements, techniques such as electro-oculography, magnetic field search coils, infrared reflection procedures or video-oculography are available. However, applications of these latter procedures in a regular clinical setting are demanding and require the collaboration of the subjects. A possible alternative might be neuroimaging. The fact

that cranial MRI or CT scans are routinely performed in stroke patients right after admission could make it an interesting tool to quantify eye-in-head deviation very early after stroke onset. Simon and co-workers (2003) have suggested a method to measure eye deviation reliably on neurological scans. In a total of 107 stroke patients, they showed that the deviation of eyes determined on CT scans allowed a good prediction of the hemisphere affected by the stroke. The present study used this procedure to investigate whether or not the orientation of the eyes in routine clinical brain scans shows a specific relationship to spatial neglect.

Materials and methods

Subjects

We investigated 124 continuously-admitted subjects with unilateral first-ever stroke verified by MRI (*n*=34) and/or Spiral-CT (*n*=90). Right brain damage was diagnosed in 71 patients; the left hemisphere was affected in 53 patients. Patients with diffuse or bilateral brain lesions or with lesions restricted to the brainstem or cerebellum were excluded. A group of control subjects consisted of 17 subjects in whom MRI or Spiral-CT had been conducted due to headache but no pathological findings had been revealed. Clinical and demographic data of all subjects are presented in Table 1. Brain scans were obtained for each subject at admission to the Centre of Neurology at Tübingen University; on average 19.2 h (SD 43.2) after stroke onset. Following the procedure by Simon and co-workers (2003) the patients received no particular instruction regarding eye orientation or eye closure during the scan. The day of image acquisition and clinical assessment (described below) were separated by a maximum of 2 days. All

Table 1 Demographic and clinical data of the subjects with acute unilateral first-ever stroke and the non-brain damaged controls

		Brain damaged stroke patients				NBD controls
		Spatial neglect		No spatial neglect		
Side of lesion		Left	Right	Left	Right	
Number		6	30	47	41	17
Gender		1M/5F	13M/17F	26M/21F	26M/15F	5M/12F
Age	Mean (SD)	68.8 (24.2)	63.0 (14.7)	61.3 (14.4)	61.0 (14.1)	54.4 (10.0)
Time interval O–I (h)	Mean (SD)	12 (19.2)	9.6 (19.2)	28.5 (62.4)	16.8 (26.4)	
Time interval I–C (h)	Mean (SD)	31.2 (12.0)	28.8 (16.8)	31.2 (16.8)	26.4 (14.4)	
Visual field deficit	% present	0	20.0	10.6	19.5	
Aphasia	% present	83.3	10.0	51.1	0	
Neglect						
Letter cancellation (<i>n</i>)						
Left	Mean (SD)	28.5 (2.1)	6.6 (9.1)	28.8 (1.9)	29.1 (2.1)	
Right	Mean (SD)	17.5 (0.7)	20.7 (8.7)	28.5 (2.1)	29.4 (1.9)	
Bells test (<i>n</i>)						
Left	Mean (SD)	10.7 (5.7)	2.8 (4.0)	14.1 (1.22)	14.2 (1)	
Right	Mean (SD)	4.7 (5.0)	9.7 (4.8)	13.7 (1.6)	14.3 (1.3)	
Albert's test (<i>n</i>)						
Left	Mean (SD)	11.3 (5.7)	7.2 (8.1)	18	18	
Right	Mean (SD)	4.5 (9)	14.9 (4.4)	18	18	
Copy task (% omission)	Mean (SD)	50 (37.5)	41.9 (31.3)	2.1 (4.7)	1 (3.4)	

O = stroke-onset; I = imaging; C = clinical assessment; *n* = number of target hits; NBD = non-brain damaged.

subjects or their relatives gave informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Analysis of brain scans

Measurement of eye deviation

To evaluate eye-in-head orientation on the scans we used the technique described by Simon and co-workers (2003). The authors determined the horizontal deviation of eye-in-head position by the angle formed by the intersection of the ocular axis and the 'line of best fit' through the midline structures of the head (Fig. 1). The experimenter who conducted the measurements was blinded with respect to the patients' clinical symptoms. Horizontal deviations towards the ipsilesional side were coded as positive values; deviations to the contralesional side as negative values. For the non-brain damaged control group, rightward deviations were coded as positive values; leftward deviations as negative values. Right and left eye deviation values were averaged for each individual.

Lesion volume and location

We determined the volume and location of brain lesions by using MRIcron software (<http://www.sph.sc.edu/comd/rorden/mricron/>; Rorden *et al.*, 2007). In the subjects who underwent MRI scanning at admission, the boundaries of the lesions were delineated directly on the individual MRI scan. Both the MRI scan and the lesion shape were then mapped into stereotaxic space using the normalization algorithm provided by Statistical Parametric Mapping-5 (<http://fil.ion.ucl.ac.uk/spm/>). For determination of the transformation parameters, cost-function masking was employed (Brett *et al.*, 2001). In those patients with spiral-CT scanning at admission, lesions were drawn directly on the slices of a normalized T₁-weighted template MRI scan from the Montreal Neurological Institute, distributed with the

MRIcron toolset. To evaluate the relationship between lesion location and the degree of deviation of eye-in-head orientation statistically we performed a voxelwise lesion-behaviour mapping (VLBM) analysis by using the nonparametric Brunner and Munzel test as implemented in the MRIcron toolset (<http://www.sph.sc.edu/comd/rorden/mricron/>; Rorden *et al.*, 2007). Permutation thresholding was used to control for the familywise error where 5% permutation thresholds were generated based on 4000 iterations.

Clinical examination

Spatial neglect was diagnosed when patients fulfilled the criterion in at least two of the following traditional paper-and-pencil tests: the Letter cancellation (Weintraub and Mesulam, 1985) task, the Bells test (Gauthier *et al.*, 1989), Albert's test (Albert, 1973) and a copying task (Johannsen and Karnath, 2004). Line bisection was not used as a screening tool (*cf.* Ferber and Karnath, 2001). In the Letter cancellation test, a horizontally oriented 21 cm × 29.7 cm sheet of paper was presented on which 60 target letter 'A's were distributed amid distractors, 30 on the right half of the page and 30 on the left. Patients were asked to cancel all of the targets. They were classified as suffering from spatial neglect when omitting more than four contralateral located targets. The Bells test consists of seven columns each containing five targets (bells) amid 40 distractors. Three of the seven columns are on the left side of a horizontally oriented 21 cm × 29.7 cm sheet of paper, one is in the middle, and three are on the right side. Patients were asked to cancel all of the targets. More than five contralateral located target omissions were taken to indicate neglect. The Albert's test consists of seven columns of 36 black lines. Three of the seven columns are on the left side of a horizontally oriented 21 cm × 29.7 cm sheet of paper, one column is in the middle, and three columns are on the right side. Patients had to cancel all lines. More than one contralateral located target omission was taken to indicate neglect. In the copying task, 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 cm × 29.7 cm sheet of paper. Omission of at least one of the contralateral features of each figure was scored as 1, and omission of each whole figure was scored as 2. One additional point was given when contralateral located figures were drawn on the ipsilesional side of the paper sheet. The maximum score was 8. A score higher than 1 (*i.e.* >12.5% omissions) was taken to indicate neglect.

Visual field defects were examined by the common neurological confrontation technique. Aphasia was assessed conducting a bedside examination that evaluated spontaneous speech, auditory and reading comprehension, picture naming, reading and oral repetition.

Results

In the sample of 71 stroke patients with right-brain damage, 30 patients showed spatial neglect (Table 1). In the sample of 53 patients with left-brain damage, we found six subjects with this disorder (Table 1). Figure 2 illustrates the degree of horizontal eye deviation in the four groups of brain damaged patients as well as the non-brain damaged controls. A 2 × 2 ANOVA with factors subject group (spatial neglect, no spatial neglect) and lesion side (right, left) was conducted. Since spatial neglect occurs more frequently in patients with larger brain lesions (*e.g.* Levine *et al.*, 1986; Karnath *et al.*, 2004), lesion volume was used as a covariate in the ANOVA. It controlled for the possibility that the degree of

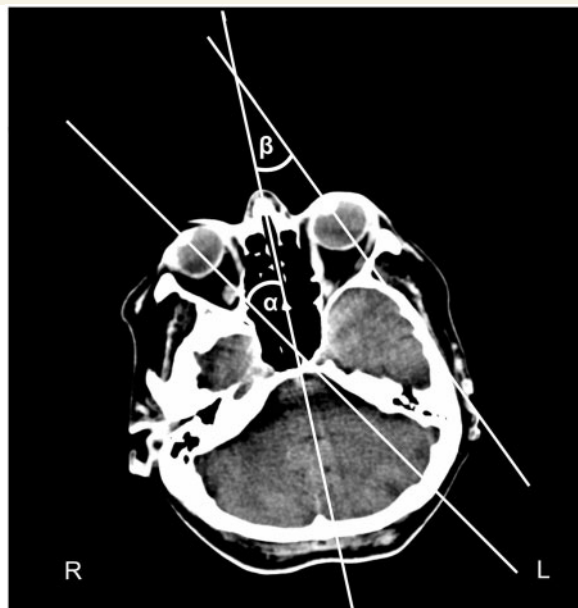


Figure 1 Measurement of horizontal eye-in-head deviation according to Simon and co-workers (2003). The angles formed by the intersection of the ocular axes of the right (α) and left (β) eye and the 'line of best fit' through the midline structures of the head were determined.

eye deviation is related to lesion size rather than spatial neglect. The interaction between the two factors ($F_{1,123}=0.001$, $P=0.970$) as well as the effect of factor lesion side ($F_{1,123}=0.12$; $P=0.734$) did not show significant effects. In contrast, factor subject group

revealed significance ($F_{1,123}=6.76$; $P=0.011$). The degree of eye deviation towards the ipsilesional side was significantly larger in the patients with spatial neglect than the brain damaged subjects without the disorder, even with lesion volume taken into account.

We further compared the degree of eye deviation in the brain damaged patients with the spontaneously occurring eye deviation in control subjects without brain damage. The slightly more pronounced degree of ipsilesional eye deviation in the brain damaged patients without neglect (pooled over lesion side) failed to reach significance compared with controls ($t_{83}=1.85$; $P=0.068$). In contrast, the eye-in-head deviation in the group of patients with spatial neglect (pooled over lesion side) differed significantly from the rightward eye deviation in the group of non-brain damaged controls ($t_{42}=4.18$; $P=0.0001$).

Figure 3 illustrates the results of the statistical VLBM analysis of eye-in-head orientation in the group of 71 patients with right brain damage. The uncorrected statistical map revealed differences in the right superior and middle temporal gyri. No voxels of this map survived the adjustment for multiple comparisons. Nevertheless, despite not reaching statistical significance after correction for the overall alpha-level, the difference in the degree of deviation of eye orientation between patients with versus without damage in this region was considerably larger than the difference in the degree of deviation between these patients in the rest of the brain. In contrast, the VLBM analysis in the group of 53 patients with left brain damage revealed no significant voxels even without correction for multiple comparisons.

Discussion

The present study measured eye-in-head position in the initial MRI or CT scans of acute stroke patients obtained at admission to our

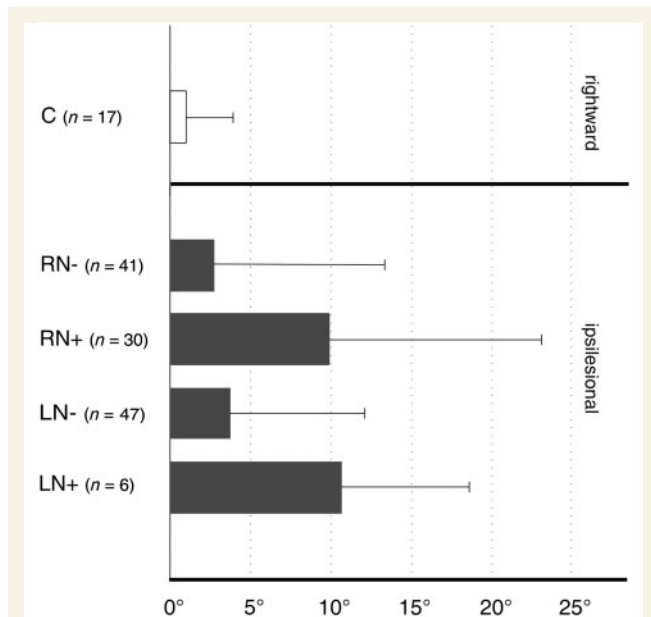


Figure 2 Average horizontal eye-in-head deviation and standard deviation for the group of right hemispheric patients without spatial neglect (RN-), right hemispheric stroke patients with spatial neglect (RN+), left hemispheric stroke patients without spatial neglect (LN-), left hemispheric stroke patients with spatial neglect (LN+), as well as the group of non-brain damaged controls (C).

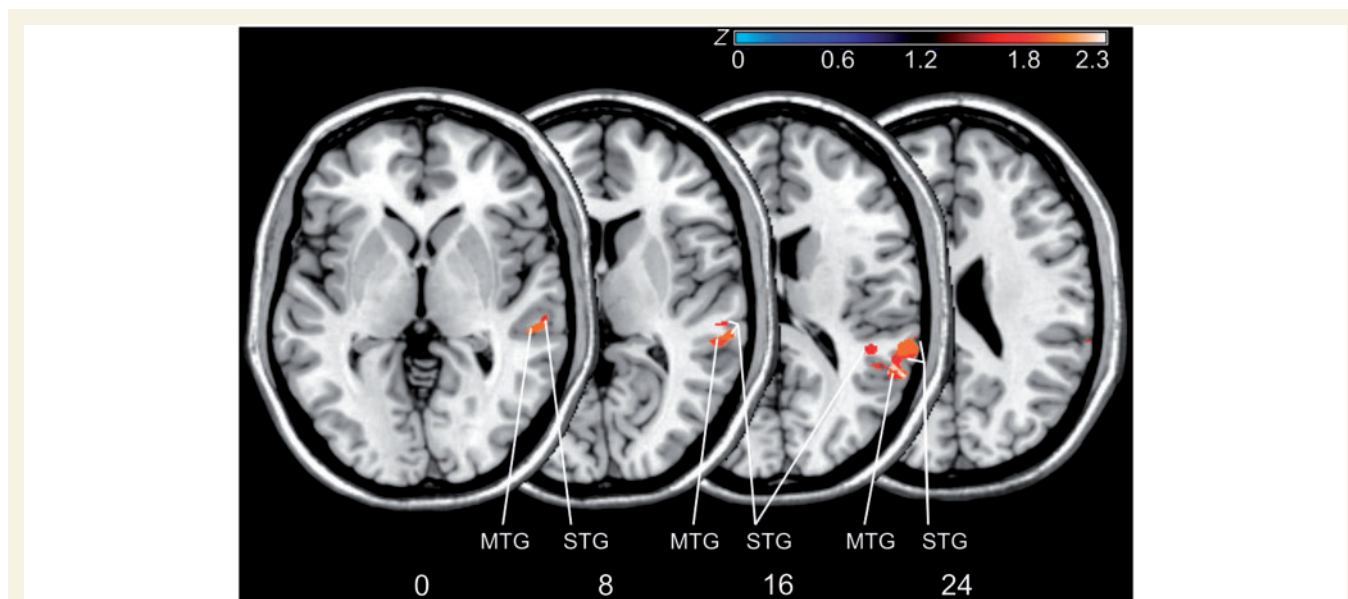


Figure 3 Statistical map resulting from the VLBM analysis of eye-in-head orientation in the group of patients with right brain damage by using the nonparametric Brunner and Munzel test as implemented in the MRICron toolset (Rorden *et al.*, 2007). The data are not adjusted for multiple comparisons (uncorrected data). Colour bar indicates Z-scores. STG = superior temporal gyrus; MTG = middle temporal gyrus.

Centre of Neurology. As in a previous study by Simon *et al.* (2003), we found a relationship between eye deviation on these scans and a stroke lesion. The patients with a right or left hemisphere stroke but no spatial neglect showed a slight although, compared with non-brain damaged controls, non-significant tendency for a more pronounced eye deviation towards the respective ipsilesional side. But our results go beyond this observation. We found that the eye position of patients with spatial neglect were significantly deviated towards the respective ipsilesional side compared with both patients with brain lesions but no neglect and non-brain damaged controls, even with lesion volume taken into account.

Pronounced eye-in-head deviation towards the ipsilesional side on clinical brain scans thus seems to be associated with spatial neglect rather than with brain damage *per se*. This fits with other observations. For example, the cortical regions affected in patients exhibiting spatial neglect (Heilman *et al.*, 1983; Vallar and Perani, 1986; Karnath *et al.*, 2001, 2004; Committeri *et al.*, 2007; Sarri *et al.*, 2009) appear to overlap in part to those observed to be involved with the occurrence of CED (Singer *et al.*, 2006). Singer and co-workers (2006) investigated the anatomy of this sign by using a three-stepped clinical scale (discrete values 0, 1 and 2) for CED as well as a subtraction approach for lesion analysis. In contrast, the methodology used in the present study allowed for continuous quantification of the degree of CED and provided a statistical VLBM analysis to determine the critical lesion location. With respect to the latter, the present analysis did not reveal a significant result after adjustment for multiple comparisons but demonstrated a trend in the uncorrected statistical map for the right superior and middle temporal cortices as critical correlates of CED.

A tight relationship between spatial neglect and the ipsilesional deviation of eyes is also suggested by the recent observation that both signs recover in parallel (Fruhmann-Berger *et al.*, 2008). In that study, analysis of the course of recovery over a period of 10 months post-stroke revealed a parallel decrease in eye position during active visual search and at rest (measured by the magnetic field-search coil technique) that was accompanied by a comparable decline in neglect severity, the latter measured with standard clinical bedside tests of spatial neglect. Observations during the Wada test provide further clues for a tight relationship between spatial neglect and the ipsilesional deviation of eye position. Meador and colleagues (1989) recorded tonic eye deviation in 90 patients during intracarotid sodium amytal injections. They observed a hemispheric asymmetry in that 60% of the patients after right-sided injection presented tonic eye deviation towards the side of injection but only 32% after left-sided injection. Interestingly, patients with left-sided language dominance showed a higher hemispheric asymmetry of eye deviation in contrast to patients with bilateral language dominance, who showed an equal proportion of eye deviation after left and right hemispheric inactivation. Unfortunately, this study did not record the occurrence of spatial neglect in addition to the presence or absence of tonic eye deviation.

Different hypotheses have been put forward to explain the tonic eye-in-head deviation. Some suggested disruption of anatomo-functional circuits by the stroke. Ringman and

co-workers (2005) suggested that CED may result from damage to either sensory attentional or motor intentional networks. Tanaka and collaborators (2002) proposed that CED might result from an imbalance of inputs to the superior colliculus and the premotor reticular formation. According to Derakshan (2005) the unidirectional callosal transfer from the left, language-dominant to the right hemisphere, in combination with disruption of signal transmission to the left eye, might be a possible explanation for the hemispheric asymmetry observed in CED. Karnath and Dieterich (2006) argued that the tonic eye and head deviation may be understood as a pathological adjustment of the stroke subject's normal 'default position' of eye-in-head and head-on-trunk orientation to a new origin on the right side. Their review of the literature revealed that CED is observed in patients with spatial neglect as well as in patients with unilateral vestibular disorders and demonstrated common brain areas involved in (i) the processing of multisensory (vestibular) inputs, as well as (ii) spatial neglect. This correspondence led them to suggest an error in the conversion of multimodal sensory information in higher order spatial representations, leading to a deviation of the body-related spatial reference frames to the ipsilesional side in patients with spatial neglect.

In non-human primates, only few studies reported conjugate deviation of the eyes and the head. After frontal eye field lesions in monkeys, CED towards the ipsilesional side occurred immediately after the animals recovered consciousness and often in combination with circling movements (Kennard and Ectors, 1938; Latto and Cowey, 1971a, b). Latto and Cowey (1971a, b) reported that, despite the tonic ipsilesional deviation, contralateral eye movements were still observed. Different from findings in humans, in monkeys no asymmetry was observed concerning tonic eye deviation after left- versus right hemispheric lesions. The asymmetry in favour of the right hemisphere thus seems to be a feature characterizing humans. Anatomically, in both humans and non-human primates, homologous neural networks appear to exist in the left and right hemispheres, tightly linking cortical regions straddling the sylvian fissure (Karnath, 2009). However, in contrast to non-human primates, in humans these perisylvian networks serve different cognitive functions: a representation for language and praxis in the left hemisphere and a representation for processes involved in spatial orienting in the right (Karnath, 2009). While a lesion of this network in the human right hemisphere may provoke CED (among other disturbances of spatial orienting), a lesion of the same network in the human left hemisphere induces aphasia and/or apraxia. Since this functional specialization of left and right perisylvian networks is still not observed in the non-human primate, one may speculate that the phylogenetic lateralization to the right hemisphere might parallel the emergence of an elaborate representation for language in the left-sided perisylvian network (Karnath, 2009).

To conclude, the present study revealed that pronounced eye-in-head deviation towards the ipsilesional side on brain scans taken at admission is associated with spatial neglect rather than with brain damage *per se*. Routine clinical MRI or CT scans thus may be a helpful additional tool for diagnosing spatial neglect. Measuring eye-in-head position on such scans allows a precise evaluation of this variable and can be determined independently

of the patient's state of alertness, his/her communication abilities, and/or capability to cooperate in clinical tests.

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