Exp Brain Res (2017) 235:83–95
DOI 10.1007/s00221-016-4771-9

RESEARCH ARTICLE

Visual neglect after left-hemispheric lesions: a voxel-based lesion–symptom mapping study in 121 acute stroke patients

Lena-Alexandra Beume[1,2,3] · Markus Martin[1,2,3] · Christoph P. Kaller[1,2,3] · Stefan Klöppel[1,2,3,4] · Charlotte S. M. Schmidt[1,2,3] · Horst Urbach[2,5] · Karl Egger[2,5] · Michel Rijntjes[1,2] · Cornelius Weiller[1,2,3] · Roza M. Umarova[1,2,3]

Received: 26 April 2016 / Accepted: 6 September 2016 / Published online: 16 September 2016

Abstract Visual neglect after left-hemispheric lesion is thought to be less frequent, less severe, and shorter lived than visuospatial attention deficits resulting from right-hemispheric lesions. However, reports exist opposing this assumption, and it is unclear how these findings fit into the current theories of visuospatial processing. Furthermore, only little is known about the exact structure–function relationship between visuospatial attention deficits and left-hemispheric stroke. We investigated neglect in 121 patients with acute left-hemispheric ischemic stroke by following clinical development from within the first 24 h of stroke onset until hospital discharge. Visuospatial attention deficits occurred in 17.4 % ($n = 21$). Voxel-based lesion–symptom mapping associated visual neglect to the right with lesion in the left superior and middle temporal gyrus, temporal pole, frontal operculum, and insula. Neglect severity, captured by the Center of Cancellation Score of the Bells test, was associated with lesion in the left anterior temporal lobe and the left frontal operculum. The left-hemispheric lesion pattern of neglect thus involves areas of the ventral attention system and partly mirrors the critical regions of the right hemisphere known to be associated with neglect. Based on our prospective analysis on a large cohort of patients with left-hemispheric stroke, this study shows that in a remarkable number of patients, the left hemisphere essentially contributes to an intact representation of space and clarifies the impact of the distinct left-hemispheric structures involved in visuospatial processing.

Keywords Visual neglect · Left hemisphere · Hemispheric lateralization · Visuospatial attention system

Introduction

Visuospatial attention deficits such as neglect and extinction are commonly seen as right-hemispheric disorders (Heilman and Watson 2011) but have also been described after left-hemispheric damage (e.g., Becker and Karnath 2007; Beis et al. 2005; Kleinman et al. 2007; Maeshima et al. 1992; Ogden 1985; Ringman et al. 2004). Reports published to date present an incongruent picture of the frequency, severity, and structure–function relationships of visuospatial attention deficits after left-hemispheric damage. These deficits are considered to be less frequent (e.g., Robertson and Marshall 1993) compared to visual neglect after right-hemispheric damage, where a median frequency of 43 % was determined from a meta-analysis (Bowen et al. 1999). Previous studies indicate a wide range for the frequency of visual neglect occurring after left-hemispheric damage, spanning the reported values of 2.4 % (Becker and Karnath 2007), 4 % (Sunderland et al. 1987; Vallar et al. 1991), 10 % (Beis et al. 2005), and 65 % (Mattingley and Bradshaw 1994; Stone et al. 1993), with a large meta-analysis calculating a median frequency of 21 % (Bowen

✉ Lena-Alexandra Beume
lena.beume@uniklinik-freiburg.de

1 Department of Neurology and Neuroscience, University Medical Centre Freiburg, Breisacherstrasse 64, 79106 Freiburg, Germany

2 Freiburg Brain Imaging Centre, University Medical Centre Freiburg, 79106 Freiburg, Germany

3 BrainLinks-BrainTools Cluster of Excellence, University Medical Centre Freiburg, 79106 Freiburg, Germany

4 Department of Psychiatry and Psychotherapy, University Medical Centre Freiburg, 79106 Freiburg, Germany

5 Department of Neuroradiology, University Medical Centre Freiburg, 79106 Freiburg, Germany

et al. 1999). Recently, the incidence of peripersonal neglect in acute stroke was found to range around 23.5 % and was not significantly different between patients with right- and left-hemispheric stroke (Kamtchum Tatuene et al. 2016). It has further been shown that spatial neglect can be uncovered even in chronic left-hemispheric stroke patients when tasks with increased attentional load generated by multitasking are applied (Blini et al. 2016). Visual neglect after left-hemispheric lesions is often regarded as less severe than after right-hemispheric lesions (Ringman et al. 2004; Stone et al. 1991; Ogden 1987; Gainotti 1968), while other studies observed no significant difference in the severity of neglect after left- or right-hemispheric damage (Stone et al. 1993; Suchan et al. 2012; Costa et al. 1969).

These discrepancies in frequency and severity may be partly explained by difficulties in assessing attention deficits in left-hemispheric stroke patients (reviewed in Bowen et al. 1999; Karnath and Rorden 2012; Stone et al. 1991). Aphasia, occurring in approximately 24–38 % of patients after stroke (Pedersen et al. 1995; Laska et al. 2001; Engelter et al. 2006), is an exclusion criterion in some studies, since patients may be unable to participate in certain clinical examinations (Pedersen et al. 1997). Different methods for assessing visuospatial attention deficits that have been used in the different studies will have different detection sensitivities (Halligan et al. 1989). And neuroradiological evidence was not used in all previous studies for lesion localization, which was sometimes derived from the side of hemiplegia. However, only neuroradiological examination can exclude the occurrence of previous silent strokes, which could add to the occurrence of neglect when followed by a contralesional severe stroke (e.g., Taylor et al. 1994). The crucial point, however, might be the variance in frequency according to the timing of assessment. This is highlighted by the fact the given frequencies above are taken from studies that were performed during the acute phase (within 1 week after onset) or subacute phase (within 4 weeks after onset), suggesting a very rapid change in clinical presentation of visuospatial attention deficits after left-hemispheric lesion. This reduction in the frequency of visual neglect with time was found to be more likely after left-hemispheric lesion than after right-hemispheric lesion (Bowen et al. 1999), making early clinical testing and close follow-up during hospitalization necessary to precisely assess incidence and severity.

The exact lesion localization for visual neglect within the left hemisphere has rarely been investigated to date. Two studies, one subgroup analysis of a large multicenter trial of an anticoagulant (TOAST Trial including 394 patients with a left-hemispheric lesion, of which 77 exhibited neglect; Ringman et al. 2004) and one selective report on 20 patients with visual neglect after left-hemispheric stroke (Maeshima et al. 1992), used CT scans to localize the lesioned area and concluded that visual neglect mostly occurs after damage to temporal areas or, in a descending order of occurrence, to parietal, frontal, or occipital regions as well as the basal ganglia or the thalamus. Suchan and Karnath (2011) used voxel-based lesion–symptom mapping in a selected cohort of 11 patients with visual neglect after left-hemispheric stroke, and found the severity of neglect to the right correlated with lesions in the superior and middle temporal areas as well as inferior parietal, inferior frontal areas, and the insular cortex.

The current theory for visuospatial attention assumes an interaction between a bilateral dorsal system, composed of the parietal cortex and frontal eye field, and a right-lateralized ventral system, composed of the right temporoparietal junction and right ventral frontal cortex (Corbetta and Shulman 2002, 2011; Kastner and Ungerleider 2000; Bushman and Miller 2007; Kanwisher and Woicuulik 2000). Not so different, left-hemispheric research on aphasia, apraxia, and acalculia (Kuemmerer et al. 2013; Hoeren et al. 2013, 2014; Martin et al. 2015; Klein et al. 2013) distinguishes parallel dorsal and ventral processing streams, anatomically defined by the course of the long association tracts, either above (dorsal) or below (ventral) the sylvian fissure, connecting pre- and post-rolandic parts of the brain and forming a domain general dual loop (Weiller et al. 2009, 2011; Rijntjes et al. 2013). By integrating this model within the current theory of visuospatial attention processes, the investigation of visual neglect after left-hemispheric stroke may be of additional interest.

For the aforementioned reasons, we used voxel-based lesion–symptom mapping to correlate visuospatial impairment with acute brain lesions and conducted early MRI scans to reduce bias in structure–function relationships in a large, prospectively investigated cohort of 121 consecutive acute stroke patients with left-hemispheric lesions, and followed development of clinical presentation within the very acute phase from emergency admission to hospital discharge. The test battery was carefully adapted for use in aphasic and apraxic patients. Quantitative and qualitative testing was applied to identify the spatial deficit modality and severity.

Materials and methods

Patients

Patients were consecutively recruited between February 2011 and March 2014 from the Stroke Unit of the Department of Neurology at the University Medical Centre of Freiburg, Germany. A total of 475 patients presented with a (thromb-)embolic stroke in the middle cerebral artery territory of the left hemisphere. Patients with (thromb-)

embolic stroke in the right hemisphere or with history of previous stroke were not considered for this study. From the cohort of 475 patients, 347 patients were excluded from further analysis because of (1) contraindication for MRI ($n = 17$); (2) inability to tolerate MRI examination or to perform paper- and pencil-based testing owing to very reduced general health status, coma, or intermittent artificial ventilation ($n = 31$); (3) previous ischemic infarcts that had remained clinically silent but were determined in the current MRI ($n = 86$); (4) structural brain changes, such as severe brain atrophy, moderate to extensive white matter changes, previous traumatic brain injury, previous intracerebral hemorrhage or tumor ($n = 72$); (5) age > 90 years ($n = 8$); (6) native language not German ($n = 8$); (7) major/interfering cognitive impairment ($n = 25$); (8) widespread hemodynamic alterations, such as carotid occlusion with insufficient collateralization ($n = 4$); (9) compliance issues ($n = 38$); or (10) technical or organizational problems ($n = 58$). The remaining 128 patients received clinical and paper- and pencil-based testing for neglect. Extra- and intracranial ultrasound examinations and available MR or CT angiograms were reviewed to ensure sufficient cerebral blood flow at the time of behavioral testing in all cases. From these patients, 89 also participated in a recently published study on pantomime of tool use and imitation of meaningless gestures (Hoeren et al. 2014). Full written consent was obtained from all patients. In cases of severe aphasia, detailed information was given to the patient's relatives or the legal guardian. The study was approved by the local ethics committee.

Behavioral testing

Patients were clinically examined for visual neglect by both a neurologist and a neurologically trained occupational therapist at two time points. The first examination was within 24 h of stroke and the second on the day of discharge to neurological rehabilitation (mean = 9.2 ± 3.9 days after stroke onset).

Visual neglect testing

Visual neglect testing included the formal testing required to generate the National Institutes of Health Stroke Scale (NIHSS) score within the first 24 h after admission, close observation of clinical sings (such as the patient's spontaneous orientation, orientation to an addressee in front or to the left of the patient and/or the ignoring of contralesionally located persons or objects), and additional paper-based testing. All patients performed standardized paper and pencil tests of visuospatial neglect in the peripersonal space in an adapted version of the Behavioral Inattention Test (Wilson et al. 1987). Paper-based neuropsychological neglect testing was conducted as early as possible (mean = 4.9 ± 2.3 days after stroke, range = 1–16 days) in all patients using the Bells test (Gauthier et al. 1989), Ota test (Ota et al. 2001), and line bisection test (Heilman and Valenstein 1979). In the right hemisphere, it has been shown that different neglect tests assess distinct aspects of spatial neglect and that these show different neural correlates (Verdon et al. 2010; Saj et al. 2012; Molenberghs and Sale 2011). We were, however, only able to use three of the well-established neglect tests in our large cohort due to reduced clinical conditions of most of the patients in this early acute stage post-stroke and due to time constrictions in the clinical routine diagnostic and treatment procedures. All tests were presented on a horizontally oriented 21 × 29.7 cm sheet of paper. The Bells test requires identifying 35 Bell symbols distributed within a field of distractor symbols. The Ota test required the patient to mark all circles having a gap on either the circle's left or right side. The main score in the tests was the difference between omissions on the right side relative to the left side of space. Omission of more than three targets in the right hemifield (compared to omissions in the left hemifield) was considered pathological (Marsh and Hillis 2008). Since the Ota test can additionally be used to investigate egocentric versus allocentric (object-based) neglect, we separately evaluated the number of left-outs of circles with a gap on the right side (correlate of right allocentric neglect). The severity of the deficit was determined by calculating the center of cancellation (CoC) score for the Bells and the Ota tests using the procedure and software by Rorden and Karnath (2010). The CoC score expresses the mean horizontal coordinate for items detected in each test, with the center of mass for each test image calculated in terms of pixels. Thus, individuals missing no items or with symmetrically distributed error patterns have a CoC score near zero and individuals detecting only leftmost items (i.e., with severe right-sided neglect) have a score close to −1. Scores below −0.086 were considered pathological (Suchan et al. 2012). In the line bisection task, the patient was asked to mark the midpoint of each of 20 presented horizontal lines differing in length (between 90 and 180 mm) and in distribution on the paper. The deviation to the right or left of the objective center was measured to 1 mm accuracy. Line bisection task scores within 1 standard deviation (SD; score ±1) of the objective center (score 0) were considered normal, scores outside this range were considered pathological. SDs refer to controls' normative scores (Fels and Geissner 1997). Congruent detection in observation of clinical signs of neglect by the neurologist and occupational therapist and performance below cutoff in at least

one of the paper-based neglect tests placed the patient into the group with visual neglect. There were no cases with incongruent judgment.

Visual extinction testing

Visual extinction testing consisted of the standardized bedside test consisting of wiggling fingers for 2 s in one or both visual fields while controlling central gaze fixation, with 10 unilateral trials (five on each side) and five simultaneous bilateral trials. Extinction was diagnosed when a patient failed to report at least two contralesional stimuli during bilateral simultaneous presentation, while accurately detecting unilateral stimuli (Beis et al. 2005). Congruent assessments by the neurologist and occupational therapist constituted diagnosis of visual extinction and placed the patient in the group with visual extinction. There were no cases with incongruent judgment.

Additional clinical testing

To ensure that none of the patients had severe visual field deficit, we assessed the visual fields using standardized neurological bedside examination, similar to previous studies of neglect in acute stroke (e.g., Corbetta et al. 2015; Karnath et al. 2011), since instrumental perimeter examination is not feasible so early following stroke. Aphasia was diagnosed for patients with deficits of at least 7 age-corrected error scores in the Token Test of the Aachen Aphasia Battery (Huber et al. 1984). Apraxia was diagnosed for patients with deficits in either the imitation of meaningless gestures (Goldenberg and Karnath 2006) or the pantomime of tool use (Bartolo et al. 2008; Hoeren et al. 2014) tests. Handedness was assessed by means of the Edinburgh handedness inventory (Oldfield 1971).

Statistical analysis

For statistical analysis of demographical and clinical parameters, the patients groups were compared using the Mann–Whitney *U* test, since the data were not normal distributed according to the Kolmogorov–Smirnov test ($p < 0.001$ for age, handedness, NIHSS admission, NIHSS discharge, mRS discharge, days until discharge, lesion volume, CoC and left-outs Bells test, CoC and left-outs Ota test, line bisection score, Token Test score, error score imitation, error score pantomime). For evaluation of a statistical difference concerning gender as well as incidence of deficits concerning aphasia, imitation, and pantomime between the two groups, the Chi-square test was performed. All statistical analyses on the behavioral data were performed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM).

MRI acquisition

MRI scans were performed on average 2.5 days after symptom onset (SD = 2.9, range = 0–9 days) on either a 3 T Trio scanner or a 1.5 T Avanto scanner (Siemens, Germany). Diffusion-weighted imaging was acquired to delineate lesions in all patients using a standard sequence (23 slices, matrix = 128 × 128 pixel, voxel size = 1.8 × 1.8 × 5 mm, repetition time = 3.1 s, echo time = 79 ms, flip angle = 90, six diffusion-encoding gradient directions with a b-factor of 1000 s/mm^2). Additionally, we acquired fluid-attenuated inversion recovery (FLAIR) images (repetition time = 9000 ms, echo time = 93.0 ms, flip angle = 140°, matrix 200 × 256 pixel, voxel size = 0.94 × 0.94 × 5.00 mm, 23 slices). As a prerequisite for spatial normalization, a high-resolution T1 anatomical scan was obtained (MPRAGE, repetition time = 2200 ms, echo time = 2.15 ms, flip angle = 12°, matrix = 256 × 256 pixel, voxel size = 1 × 1 × 1 mm, 176 slices).

Voxel-based lesion analysis

The diffusion-weighted imaged lesion was delineated using a customized region-of-interest toolbox implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Individual intensity thresholds were applied to find the best match between the binary lesion map and the diffusion-restricted brain tissue. Other available sequences (e.g., FLAIR, apparent diffusion coefficient maps) were consulted to assure the most accurate lesion delineation. Lesion maps were inspected in MRIcron (http://www.cabiatl.com/mrico/mricon/stats.html) and manually adjusted if necessary. No diffusion-weighted image was available for one case, and the lesion was drawn directly onto the FLAIR image. Diffusion-weighted or FLAIR images were coregistered to the anatomical T1 scans to spatially normalize lesion maps. High-resolution T1 scans were segmented using the VBM8 toolbox (r435; http://dbm.neuro.uni-jena.de/vbm/download/). Deformation field parameters for nonlinear normalization into the stereotactic Montreal Neurological Institute (MNI) standard space were then computed using the DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra; Ashburner 2007) approach implemented in VBM8. LB and MM visually controlled the quality of all individual lesion map normalizations. Normalization parameters were obtained from FLAIR ($n = 7$) or apparent diffusion coefficient ($n = 1$) images in cases where the T1 scans had insufficient quality. Nonparametric statistics implemented in MRIcron (Rorden et al. 2006) were used for voxel-based lesion–symptom mapping.

The main purpose of the study was to investigate the frequency and anatomy of spatial attention deficit after left hemisphere stroke on a large sample of patients included

prospectively, as well as to explore the anatomy of neglect severity. Correspondingly, we first used the Liebermeister (1877) test to identify lesioned voxels associated with the presence of visual neglect (binary measure visual neglect yes/no). Voxels affecting <5 % of patients were excluded from whole-cohort analyses. In an additional step, lesion volume was included as a covariate of no interest, using a logistic regression analysis also implemented in MRIcron.

To determine damaged voxels that are related to the severity of neglect, as continuously measured by the CoC score from the Bells and Ota test and the line bisection score, the voxel-based lesion–symptom mapping Brunner–Munzel test (Brunner and Munzel 2000) was performed for all patients separately for each neglect test. Here, only voxels affected in at least 5 % of all subjects (i.e., in at least 6 in the whole cohort) were included in the analyses. Since it is known that the Brunner–Munzel test inflates z-scores when used at voxels affected in only a small patient groups (<10 patients) (Medina et al. 2010), we accounted for it by applying additional permutation analysis (permutation 1000).

Resulting maps display voxels with a significant difference depending on whether the voxel was marked as lesioned or not. Only results below a false discovery rate (FDR)-adjusted threshold of $p < 0.05$ are reported and depicted in the figures. Results are displayed on an in-house average template of 50 nonlinearly normalized T1 scans from a sample of healthy subjects who had participated in various other studies in our laboratory (mean age = 47 ± 20.75 years, range = 22–84 years, 25 male).

Results

Patient characteristics

Altogether, 128 patients underwent careful clinical and paper-based examination, but testing was incomplete in four cases, which were excluded from further analyses. Using clinical and paper-based testing, visual neglect was revealed in 21 and isolated visual extinction in 3 of the remaining 124 patients. Though visual neglect and extinction have to be considered as distinct visuospatial attention deficits (Vallar et al. 1994; Bisiach 1991; Milner 1997; Cocchini et al. 1999; Umarova et al. 2011), the sample size of patient with isolated extinction was too small for reasonable statistical analysis. Therefore, these three extinction patients were excluded from the further analysis. Out of the 21 patients with visual neglect, 7 had recovered from the neglect symptoms until discharge. In 100 patients, no visuospatial attention deficit was present (normal performance in both clinical evaluation at admission and applied paper–pencil tests).

The characteristics of the patients groups with and without neglect are shown in Table 1. The groups did not differ concerning age (Mann–Whitney $U = 909.0$, $p = 0.335$) and handedness ($U = 256.0$, $p = 0.734$). Significant differences were found concerning gender ($\chi^2(2) = 5.707$, $p = 0.017$), NIHSS at admission ($U = 521.0$, $p < 0.001$), NIHSS at discharge ($U = 592.0$, $p = 0.001$), mRS at discharge ($U = 680.0$, $p = 0.009$), time of hospitalization ($U = 573.5$, $p = 0.001$), and lesion volume ($U = 434.0$, $p < 0.001$), where patients with neglect presented with unfavorable characteristics and larger lesions compared to stroke controls.

Results of neuropsychological testing

Table 2 shows the overview of neuropsychological paper-based testing performance in our patient cohort. There was no significant difference concerning test delay between patients with and without visual neglect (Mann–Whitney $U = 790.0$, $p = 0.072$). As expected, patients with visual neglect missed more targets in the right hemifield in the Bells test ($U = 477.0$, $p < 0.001$) and differed correspondingly by higher visuospatial bias captured by the CoC

Table 1 Patients characteristics

Clinical presentation at admission	Gender ($m/f = 75/46$)	Age (years)	Handedness	NIHSS score at admission	NIHSS score at discharge	mRS score at discharge	Days until discharge	Lesion volume (ml)
Visual neglect ($n = 21$)	$m = 18$ $f = 3$*	65.5 ± 12.7	0.7 ± 0.6	11.0 ± 6.8**	4.2 ± 3.5**	2.6 ± 1.2**	12.3 ± 5.2**	51.1 ± 43.8**
No visuosp. attention deficit ($n = 100$)	$m = 57$ $f = 43$*	62.3 ± 14.3	0.9 ± 0.4	5.6 ± 4.5**	2.3 ± 2.5**	1.9 ± 1.3**	8.5 ± 3.1**	16.9 ± 22.0**

Data are presented as mean ± SD

NIHSS National Institutes of Health Stroke Scale, *mRS* modified Ranking Scale

* $p \leq 0.05$; ** $p \leq 0.001$

score ($U = 440.5$, $p = 0.005$) compared to patients without visuospatial deficit. For Ota test and the line bisection test, scores did not significantly differ between the patient groups (missed targets in the right hemifield for the Ota test ($U = 556.5$, $p = 0.103$), CoC Ota test ($U = 784.0$, $p = 0.705$), line bisection score ($U = 781.0$, $p = 212$). As expected, missed targets in the left hemifield did not differ between the groups concerning the Bells test ($U = 861.0$, $p = 0.406$) and the Ota test ($U = 862.5$, $p = 0.887$). None of the patients met the diagnostic criteria of allocentric neglect [only one patient showed one omission of one circle (right hemifield) with a contralesional gap in the Ota test; his CoC score for the Ota test was 0.007, performance over cutoff in Bells and line bisection tests, no further clinical signs of visual neglect or visual extinction]. Also, none of the patients showed visual field deficits. Analyses further revealed significant differences between the two patients groups in the presence of aphasia ($\chi^2(2) = 13.267$, $p < 0.001$) and deficit in pantomime ($\chi^2(2) = 7.814$, $p = 0.005$) and imitation ($\chi^2(2) = 11.430$, $p = 0.001$).

Voxel-based lesion mapping

The lesion overlap of the normalized lesion maps of all 21 patients with visual neglect is displayed in Fig. 1a and the lesion overlap of the remaining 100 patients without visuospatial attention deficit in Fig. 1b. Voxel-based lesion mapping specifically associated visual neglect with lesions to the left superior and middle temporal gyri, anterior temporal lobe, ventral premotor cortex (Brodmann Area, BA6), frontal operculum (BA 44), angular gyrus, and insula (Fig. 2). We further compared patients who retained symptoms of visual neglect at discharge ($n = 14$) with those who had recovered by the time of discharge ($n = 7$). Lesions in patients who retained symptoms of visual neglect clustered around the posterior part of the left superior and middle temporal gyrus (Fig. 3). Additionally, we performed voxel-based logistic regression analysis using severity of neglect expressed in the CoC of the cancellation tests as variable of interest and lesion volume as a covariate of no interest; no significant voxels were found for neglect severity in this analysis. This approach would have allowed identifying regions even after lesion volume is taken into account by covarying it out. The absence of significant voxels associated with severity of symptoms after controlling for lesion size is thus in line with previous lesion–symptom mapping studies (Karnath et al. 2004; Kuemmerer et al. 2013; Martin et al. 2015); it is also known that patients with visuospatial attention deficits have larger lesions compared to patients without visuospatial attention deficits (e.g., Karnath et al. 2004; Smith et al. 2013). A disadvantage of the logistic regression analysis using lesion size as covariate of no interest is that it only has low statistical power when the

Table 2 Results of neuropsychological testing of the patients groups

Clinical presentation on admission	Paper-based testing (days after admission)	CoC score in Bells test	Left-outs in Bells test	CoC score in Ota test	Left-outs in Ota test	Deviation score in line bisection	Aphasia	Apraxia (pantomime)	Apraxia (imitation)
			Left (L): 18 Right (R): 18		Left (L): 20 Right (R): 20				
Visual neglect ($n = 21$)	6.1 ± 3.4	−0.081 ± 0.2*	L: 1.9 ± 3.0 R: 3.5 ± 4.2**	0.001 ± 0.009	L: 0.2 ± 0.6 R: 1.3 ± 4.7	−0.9 ± 2.2	$n = 18$ (85 %)**	$n = 12$ (57 %)*	$n = 12$ (57 %)**
No spatial deficit ($n = 100$)	4.7 ± 1.9	0.003 ± 0.03*	L: 1.2 ± 1.4 R: 1.0 ± 1.3**	0.001 ± 0.01	L: 0.2 ± 0.5 R: 0.2 ± 0.6	−0.1 ± 2.2	$n = 41$ (41 %)**	$n = 26$ (26 %)*	$n = 20$ (20 %)**

Data are presented as mean ± SD

CoC center of cancellation

* $p \leq 0.05$; ** $p \leq 0.001$

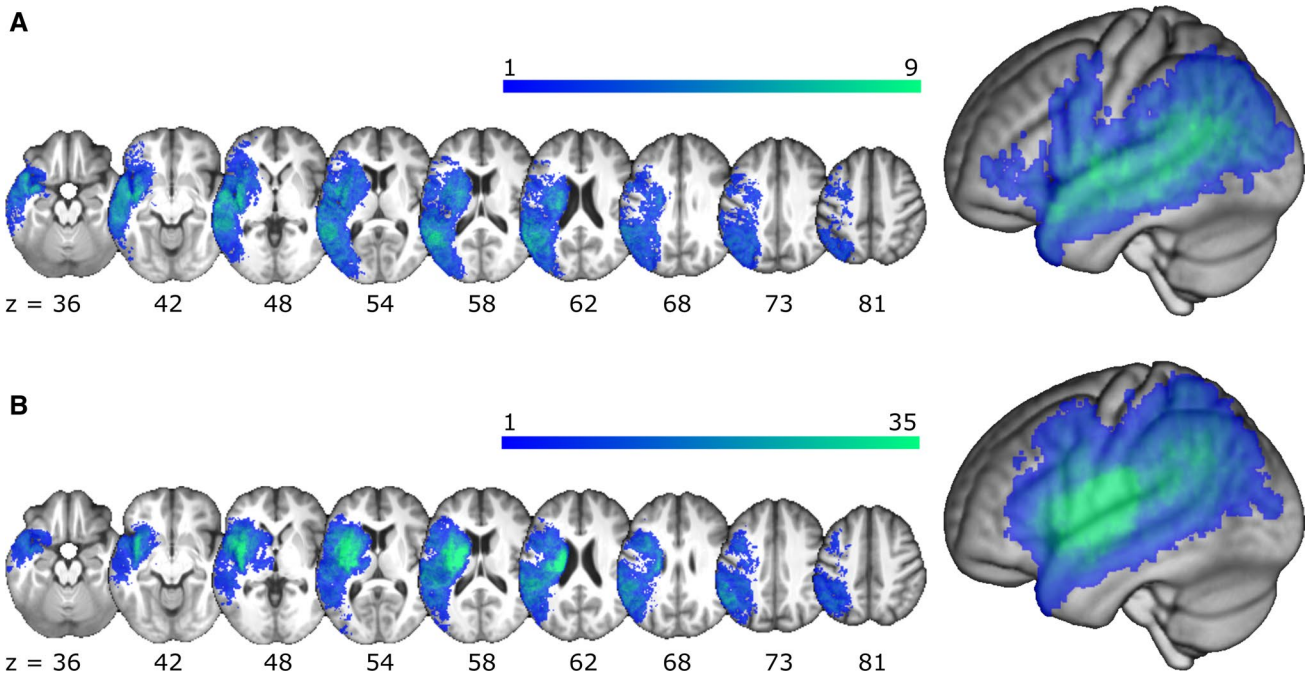

Fig. 1 Overlays of the localization of lesions in 121 stroke patients with stroke occurring in the territory of the left middle cerebral artery. **a** Lesion overlay for patients with visual neglect at admission ($n = 21$). **b** Lesion overlay for patients without any visuospatial attention deficits ($n = 100$). The number of overlapping lesions is illustrated by *different colors* coding increasing frequencies from *blue* ($n = 1$) to *green* ($n =$ max overlap). Z coordinates refer to Montreal Neurological Institute (MNI) space (color figure online)

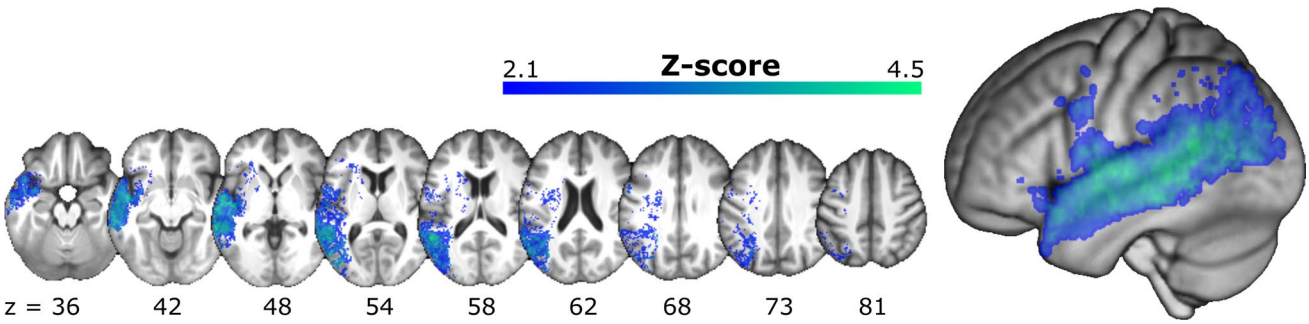

Fig. 2 Voxel-based lesion–symptom mapping in patients with visual neglect or extinction. Voxel-based lesion–symptom map of patients with visual neglect ($n = 21$) compared to stroke patients without visuospatial attention deficit ($n = 100$) shows the left superior and middle temporal lobe, anterior temporal lobe, inferior ventral premotor cortex (BA6), frontal operculum (BA 44), angular gyrus, and insula (Liebermeister test, $p < 0.05$, false discovery rate-controlled)

anatomical structures relevant for spatial neglect correlate with large lesions (due to the anatomy of the middle cerebral artery). The causal relationship between damage to these regions and lesion volume means that logistic regression may not be able to detect a correlation between neglect and damage to these regions after lesion volume has been covaried out (Karnath et al. 2004). We thus present only statistically significant results in which lesion volume is not been accounted for.

In additional analyses, the severity of the visuospatial attention deficit was associated with cerebral lesion using the scores of all applied paper-based tests (Bells test, Ota test, and line bisection test). For the Bells test, the severity of the shift in visual attention to the right was represented by the CoC score from all 121 patients. More omissions of Bells in the right hemifield were associated with lesioned voxels in the left anterior temporal lobe and the left frontal operculum (BA 44) (Fig. 4). Analyses on neglect severity were also performed using CoC score of the Ota test and line bisection score, but did not show any significant results. This is in line with previous studies, which outline the Bells test as the most sensitive paper-based testing

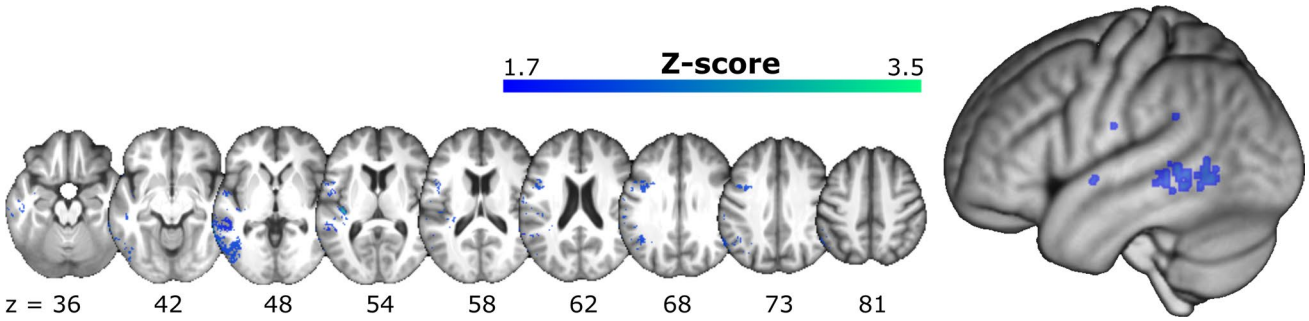

Fig. 3 Lesion sites in patients retaining symptoms of visual neglect until discharge. Voxel-based lesion–symptom mapping analysis was carried out within the group of 21 patients with visual neglect. Patients retaining symptoms of neglect at discharge ($n = 14$) had more often damage to the posterior part of the left middle temporal gyrus compared with those who had recovered before discharge ($n = 7$) (Liebermeister test: $p < 0.05$, false discovery rate-controlled)

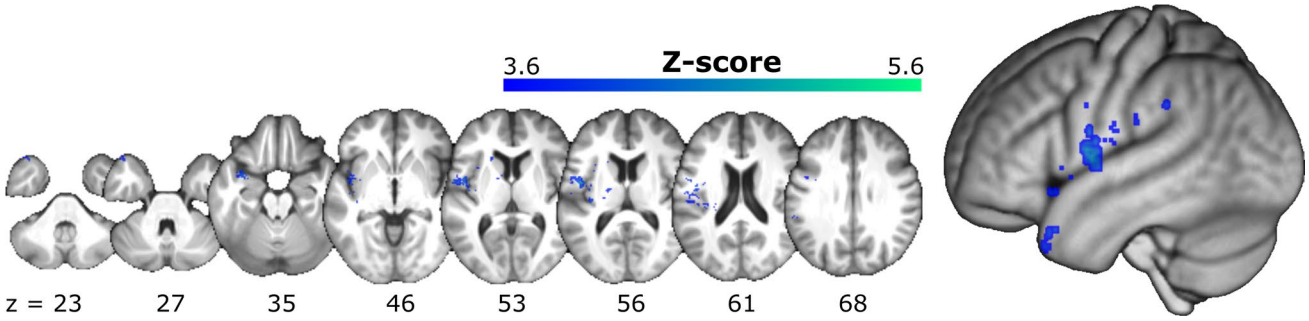

Fig. 4 Correlation of severity of the visuospatial attentional shift with lesioned areas. The Bells test CoC for all 121 patients was correlated with the lesion to the left anterior temporal lobe and the left frontal operculum (Brunner–Munzel test: $p < 0.05$, false discovery rate-controlled)

measure (Azouvi et al. 2002; Beis et al. 2005) by presenting distractors.

Discussion

We present a large prospective study of stroke patients with homogenous stroke etiologies (only first ever embolic ischemic infarcts) with lesions restricted to the left middle cerebral artery territory. In accordance with the assumption of a very rapid recovery from visuospatial attention deficits after ischemia in the left hemisphere, we conducted clinical and paper-based testing as early as possible in combination with close clinical follow-up during hospitalization. Voxel-based lesion–symptom mapping revealed distinct lesion patterns for visual neglect.

Frequency and severity of right-sided visuospatial attention deficits

In our cohort of left-hemispheric stroke patients, 17.4 % (21/121) displayed acute visuospatial attention deficits to the right assessed within the first 24 h upon admission to the hospital. With this, our data roughly confirm the findings of a large meta-analysis, which calculated a median frequency of 21 % (Bowen et al. 1999) for visual neglect after left-hemispheric lesion. However, it must be presumed that the real incidence of neglect after left-hemispheric stroke might be even higher, since we only included patients who understood the study procedure and were stable enough to tolerate clinical examination, to perform paper-based testing and to endure MRI scanning. For example, out of the 31 patients excluded at initial screening due to poor neurological and general health, thus, inability to perform paper-based testing, 27 (87 %) presented clinical symptoms of visual neglect on admission. We hence propose that symptoms of visuospatial attention deficits in the very acute phase following ischemic stroke to the left hemisphere might be more frequent than suggested.

Patients showing symptoms of visuospatial attention deficits required significantly longer hospitalization than stroke patients without attentional deficits in our cohort. We interpret this to be partly due to insufficient recovery from attention deficits, since only 7 of 21 (33 %) patients with visual neglect had spontaneously recovered from these symptoms prior to discharge. No study to date has closely

examined the neuropsychological recovery from visual neglect symptoms within the acute phase after left-hemispheric stroke. Data for spontaneous recovery after right-hemispheric lesion indicate frequencies of 43 and 77 % (Farne et al. 2004; Cassidy et al. 1998). Our data do not confirm that spontaneous recovery from visuospatial attention deficits after left-hemispheric lesion within the acute post-stroke phase is more frequent than after right-hemispheric lesion. As visual neglect is a marker for poor prognostic outcome (Buxbaum et al. 2004, Denes et al. 1982; Fullerton et al. 1986), this emphasizes the need for accurate evaluation of visuospatial attention deficits during early rehabilitation therapy to be able to provide specific treatment also for left-hemispheric stroke patients.

To objectify the severity of the visuospatial attention deficit, CoC scores were calculated for both the Bells and the Ota paper-based tests, which indicate the degree of attentional bias to the contralesional side. Both tests clearly showed the tendency of patients with visual neglect to ignore the right side. However, only the CoC score from the Bells test significantly differed between the three patients groups. This is in line with published data describing the Bells test as more sensitive for diagnosing visual neglect (Azouvi et al. 2002; Beis et al. 2005). A CoC score smaller than −0.086 (Suchan et al. 2012) has been shown to predict neglect. In our cohort of neglect patients, however, mean CoC for the Bells test reached −0.081. In this point, our data confirm studies that found visuospatial attention deficits to be less severe after left-hemispheric brain damage than after right-hemispheric brain damage (Albert 1973; Ogden 1987; Ringman et al. 2004; Stone et al. 1991). None of 124 patients included in the study presented object-based neglect which is in line with the literature, where no differentiation between egocentric and allocentric neglect after left-hemispheric lesion has been reported as of yet.

The line bisection task has often been focus of discussion for neglect in terms of its meaning; dissociation with other neglect tests on a behavioral basis (e.g., Binder et al. 1992) and in terms of lesion location (e.g., Molenberghs and Sale, 2011) has been described. Another opinion is that line bisection test is not specific for neglect representing but rather for dysmetria (Ferber and Karnath 2001). Correspondingly, deviation in the line bisection task must not always be fundamentally related to the severity of spatial neglect. It has therefore been proposed that cancellation tasks are more helpful tools to verify spatial neglect (Sperber and Karnath 2016).

The left hemisphere and spatial processing

Based on our results for visual neglect in the left hemisphere, we suggest that the left hemisphere is also important for an intact representation of space in a striking number of patients. As outlined above, research on visuospatial attention has focused to date primarily on the right side of the brain. This research led to the theory of limited attentional capacity of the left hemisphere. In this theory, attentional functions for both hemispaces are thought to be located in the right, while the left hemisphere provides only (or mainly) visuospatial processing of the contralateral space (Heilman and Van Den Abell 1980; Mesulam 1981). This further developed into the theory of a bilateral dorsal and a right-hemispheric ventral attention system (Corbetta and Shulman 2002). Our findings suggest that the ventral visuospatial attention system might not be as strongly right-lateralized as previously assumed (Mesulam 1981; Corbetta and Shulman 2002), or that it loses its lateralized dominance with aging (Cabeza 2002; Beume et al. 2015). Functional neuroimaging has repeatedly shown a right-hemispheric dominance for visual attention and a left-hemispheric dominance for language, but these studies have also demonstrated—though less prominently—involvement of homologous areas in the respective "nondominant" (i.e., right for language and left for spatial orientation) hemisphere (Himmelbach et al. 2006; Weiller et al. 1995; Vandervliet et al. 2008; Hartwigsen et al. 2010). The prevalence of aphasia after right-hemispheric ischemic lesions ("crossed aphasia" for right handers) is reported to be 0.4–3.5 %, thus appearing much less frequent than visuospatial deficits after left-hemispheric lesion (Alexander and Annett 1996; Carr et al. 1981; Hécaen et al. 1971; Joanette et al. 1982). No matter how strong the lateralization of language might be to the left temporo-frontal cortex, the same strength of lateralization may not be appropriate for attention processes to the right ventral areas.

Within a continuous range of inter-individual differences in the degree of lateralization, both a predominance of the left hemisphere and an equally distributed representation in both hemispheres would result in visuospatial deficits after left-hemispheric lesions. Deducing from results on age-dependent changes in visuospatial attention that show a delateralization of the right-sided attention system (Beume et al. 2015), we suggest that our cohort of elderly stroke patients may be more prone to develop attentional deficits after left-hemispheric lesion. However, no correlation between age and visuospatial deficits was detected in our cohort, so this conclusion may also apply to a broader group of patients regardless of age. Another commonly addressed factor for the degree of hemispheric lateralization on an inter-individual level is handedness, but we also observed no correlation between handedness and visuospatial deficits in our cohort. Remarkably, there is a difference in the distribution between men and women in our cohort, with men presenting significantly more often with visuospatial attention deficits than women. Literature describing possible reasons for the degree of hemispheric lateralization is

vast, and complex explanations range from genetic factors (Alexander and Annett 1996) and hemisphere maturation at birth (Hellige 1990) to developmental right ear or left otolith advantage (Previc 1991). Clearly, these questions have not been the focus in the present investigation, and a simple reason, such as gender, is highly unlikely to be the main explanation for lateralization of visuospatial representation.

From an evolutionary point of view, a function as elementary to survival as visuospatial attention will initially has been represented equally in both hemispheres, as it remains in nonhuman vertebrates (Oleksiak et al. 2011), and only shifted to the right, as language, communication and right-handed motor skills further developed (Chance and Crow 2007). As similarly discussed by Suchan and Karnath, visuospatial attention deficits after left-hemispheric lesions might thus reflect the consequence of a phylogenetic relict in the form of a rather bilaterally represented visuospatial attention system (Suchan and Karnath 2011) and not a left-hemispheric dominance for attention and space ("crossed neglect"). This hypothesis would not contradict our findings that visual neglect and aphasia or apraxia are strongly correlated, meaning that patients with visual neglect more often also presented with aphasia or apraxia compared to patients without any visuospatial attention deficit. It must be added that these patients also had larger lesions, but a mutual mechanism of function might underlie this correlation. Similarly, left-hemispheric temporo-frontal areas, essential to language processing and meaningful planning of higher motor tasks, might also hold a key role in spatial attention (Suchan and Karnath 2011; Ihori et al. 2015).

Anatomical dissociation of visual neglect

Voxel-based lesion–symptom mapping in patients exhibiting visual neglect after left-hemispheric lesions showed damage comprising almost the entire left temporal lobe, including the temporoparietal junction, superior and middle temporal gyri, anterior temporal lobe, inferior frontal cortex (BA 6, BA 44), angular gyrus, and the insula. These findings confirm previous results identifying the left temporal lobe to be most commonly affected in patients with visual neglect to the right (Karnath et al. 2003; Maeshima et al. 1992; Ringman et al. 2004). The importance of temporal areas for the occurrence of neglect symptoms is underlined by our finding that visual neglect persisting at discharge is associated with lesions in the left superior and middle temporal gyri. The homologous areas of the right-hemispheric temporal lobe have often been implicated as crucially involved with neglect to the left (e.g., Karnath et al. 2001, 2004, 2009; Karnath and Rorden 2012; Ringman et al. 2004; Rengachary et al. 2011; Machner et al. 2012; Corbetta et al. 2005; Committeri et al. 2007; Chechlacz et al. 2001) and studies of persistent neglect linked damage to the right superior and middle temporal gyri (Golay et al. 2008; Karnath et al. 2011; Saj et al. 2012). Additionally to the temporal areas, numerous studies in patients exhibiting visual neglect after right-hemispheric lesion have also attributed almost equal importance to parietal (Mesulam 1999; Azouvi et al. 2002; Vallar and Perani 1986; Mort et al. 2003; Hillis et al. 2005) and frontal areas (Heilman and Valenstein 1972; Husain and Kennard 1997; Ringman et al. 2004; Rengachary et al. 2011; Karnath and Rorden 2012; Committeri et al. 2007).

Thus, in the present study, visual neglect followed lesions within the ventral attention system. On the background of the idea of a domain general dual-loop model in the left hemisphere (Weiller et al. 2009, 2011; Rijntjes et al. 2013), the dorsal system stores the capacity to analyze and integrate time- or space-dependent sequences of sensory information, and the ventral system holds a more general, time-independent function of extraction, relation, and implementation of the perceived elements into a set of "a priori" categories, which are thought to be related to semantic memory and meaning (Rijntjes et al. 2013). Transferring this idea to visuospatial attention deficits, one could hypothesize that the ventral attention system might be responsible for integrating direct visual input on the background of a higher-order intrinsic spatial representation (Corbetta and Shulman 2002; Karnath, et al. 2001; Beume et al. 2015) to provide the outline of the internally represented space as a matrix for active spatial exploration (Karnath et al. 2001; Himmelbach et al. 2006).

Acknowledgments We thank G. Lind, S. Hoefer, S. Karn, and H. Mast for assistance in data acquisition and K. Astrahantseff for manuscript editing.

Funding None of the authors has any financial or personal relationships with individuals or organizations that could inappropriately influence this submission. This work was supported by the Brain Links—Brain Tools Cluster of Excellence funded by the German Research Foundation (DFG, Grant #EXC1086).

References

Albert ML (1973) A simple test of visual neglect. Neurology 23:658–664

Alexander MP, Annett M (1996) Crossed aphasia and related anomalies of cerebral organization: case reports and a genetic hypothesis. Brain Lang 55(2):213–239

Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113

Azouvi P, Samuel C, Louis-Dreyfus A, Bernati T, Bartolomeo P, Beis JM et al (2002) Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. J Neurol Neurosurg Psychiatry 73(2):160–166

Bartolo A, Cubelli R, Della Sala S (2008) Cognitive approach to the assessment of limb apraxia. Clin Neuropsychol 21:27–45

Becker E, Karnath HO (2007) Incidence of visual extinction after left versus right hemisphere stroke. Stroke 38(12):3172–3174
Beis JM, Keller C, Morin N, Bartolomeo P, Bernati T, Chokron S et al (2005) Right spatial neglect after left hemisphere stroke: qualitative and quantitative study. Neurology 63:1600–1605
Beume LA, Kaller CP, Hoeren M, Klöppel S, Kuemmerer D, Glauche V et al (2015) Processing of bilateral versus unilateral conditions: evidence for the functional contribution of the ventral attention network. Cortex 66:91–102
Binder J, Marshall R, Lazar R, Benjamin J, Mohr JP (1992) Distinct syndromes of hemineglect. Arch Neurol 49:1187–1194
Bisiach E (1991) Extinction and neglect: same or different? In: Paillard J (ed) Brain and space. Oxford University Press, Oxford, pp 251–257
Blini E, Romeo Z, Spironelli C, Pitteri M, Meneghello F, Bonato M et al (2016) Multi-tasking unconvers right spatial neglect and extinction in chronic left-hemispheric stroke patients. Brain Connect. doi:10.1016/j.neuropsychologia.2016.02.028
Bowen A, McKenna K, Tallis RC (1999) Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. Stroke 30:1196–1202
Brunner E, Munzel U (2000) The nonparametric Behrens-fisher problem: asymptotic theory and a small-sample approximation. Biom J 42(1):17–25
Bushman TJ, Miller EK (2007) Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315:1860
Buxbaum LJ, Ferraro MK, Veramonti T, Farne A, Whyte J, Ladavas E, Frassinetti F, Coslett HB (2004) Hemispatial neglect: subtypes, neuroanatomy and disability. Neurology 62(5):749–756
Cabeza R (2002) Hemispheric asymmetry reduction in old adults: the HAROLD model. Psychol Aging 17:85–100
Carr MS, Jacobson T, Boller F (1981) Crossed aphasia: analysis of four cases. Brain Lang 14:190–202
Cassidy TP, Lewis S, Gray CS (1998) Recovery from visuospatial neglect in stroke patients. J Neurol Neurosurg Psychiatry 64(4):555–557
Chance SA, Crow TJ (2007) Distinctively human: cerebral lateralisation and language in Homo sapiens. J Anthropol Sci 85:83–100
Chechlacz M, Rotshtein P, Bickerton WL, Hansen PC, Deb S, Humphreys GW (2001) Separating neural correlates of allocentric and egocentric neglect: distinct cortical sites and common white matter disconnections. Cogn Neuropsychol 27(3):277–303
Cocchini G, Cubelli R, Della Sala S, Beschin N (1999) Neglect without extinction. Cortex 35:285–313
Committeri G, Pitzalis S, Galati G, Patria F, Pelle G, Sabatini U et al (2007) Neural bases of personal and extrapersonal neglect in humans. Brain 130:431–441
Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3(3):201–215
Corbetta M, Shulman GL (2011) Spatial neglect and attention networks. Annu Rev Neurosci 34:569–599
Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A (2005) Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 8(11):1603–1610
Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS et al (2015) Common behavioral clusters and subcortial anatomy in stroke. Neuron 85(5):927–941
Costa LD, Vaughan HG Jr, Horwitz M, Ritter W (1969) Patterns of behavioral deficit associated with visual spatial neglect. Cortex 5:242–263
Denes G, Semenza C, Stoppa E, Lis A (1982) Unilateral spatial neglect and recovery from hemiplegia. Brain 105:543–552
Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V et al (2006) Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, thrombolysis. Stroke 37(6):1379–1384
Farne A, Buxbaum LJ, Ferraro M, Frassinetti F, Whyte J, Veramonti T et al (2004) Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. J Neurol Neurosurg Psychiatry 75(10):1401–1410
Fels M, Geissner E (1997) Neglect-test (NET) Ein Verfahren zur Erfassung visueller Neglectphänomene. Hogrefe, Göttingen
Ferber S, Karnath HO (2001) How to assess spatial neglect: line bisection or cancellation takss? J Clin Exp Neuropsychol 23(5):599–607
Fullerton KJ, McSherry D, Stout RW (1986) Albert's test: a neglected test of perceptual neglect. Lancet 1(8476):430–432
Gainotti G (1968) Les manifestations de negligence et d'inattention pour l'hemispace. Cortex 4:64–91
Gauthier L, Dehaut F, Joanette Y (1989) The bells test: a quantitative and qualitative test for visual neglect. Int J Clin Neuropsychol 11:49–54
Golay L, Schnider A, Ptak R (2008) Cortical and subcortical anatomy of chronic spatial neglect following vascular damage. Behav Brain Funct 4:43
Goldenberg G, Karnath H (2006) The neural basis of imitation is body part specific. J Neurosci 26:6282–6287
Halligan PW, Marshall JC, Wade DT (1989) Visuospatial neglect: underlying factors and test sensitivity. Lancet 2(8668):908–911
Hartwigsen G, Price CJ, Baumgaertner A, Geiss G, Koehnke M, Ulmer S, Siebner HR (2010) The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. Neuropsychologia 48(10):3155–3163
Hécaen H, Mazars G, Ramier AM, Goldblum MC, Mérienne L (1971) L'aphasie croisée chez un subjet bilingue (vietnamien-francais). Rev Neurol 124:319–323
Heilman KM, Valenstein E (1972) Frontal lobe neglect in man. Neurology 21:660–664
Heilman KM, Valenstein E (1979) Mechanisms underlying hemispatial neglect. Ann Neurol 5:166–170
Heilman KM, Van Den Abell T (1980) Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention. Neurology 30(3):327–330
Heilman KM, Watson RT (2011) Neglect and related disorders. In: Heilman KM, Valenstein E (eds) Clinical neuropsychology. OUP, New York, pp 243–293
Hellige JB (1990) Hemispheric asymmetry. Annu Rev Psychol 41:55–80
Hillis AE, Newhart M, Heidler J, Barker PB, Herskovits E, Degoankar M (2005) Anatomy of spatial attention: insights from perfusion imaging and hemispatial neglect in acute stroke. J Neurosci 25:3161–3167
Himmelbach M, Erb M, Karnath O (2006) Exploring the visual world: the neural substrate of spatial orienting. Neuroimage 32(4):1747–1759
Hoeren M, Kaller CP, Glauche V, Vry MS, Rijntjes M, Hamzei F et al (2013) Action semantics and movement characteristics engage distinct processing streams during the observation of tool use. Exp Brain Res 229(2):243–260
Hoeren M, Kümmerer D, Bormann T, Beume L, Ludwig VM, Vry MS, Mader I, Rijntjes M, Kaller CP, Weiller C (2014) Neural bases of imitation and pantomime in acute stroke patients: distinct streams for praxis. Brain 137(10):2796–2810
Huber W, Poeck K, Willmes K (1984) The Aachen Aphasia Test. Adv Neurol 41:291–303
Husain M, Kennard C (1997) Distractor-dependent frontal neglect. Neuropsychologia 35:829–841
Ihori N, Kashiwagi A, Kashiwagi T (2015) Right unilateral spatial neglect in aphasic patients. Brain Lang 147:21–29

Joanette Y, Puel M, Nespoulous JL, Rascol A, Lecours AR (1982) Aphasie croisée chez les droitiers. Rev Neurol 138:575–586

Kamtchum Tatuene J, Allali G, Saj A, Bernati T, Sztajzel R, Pollak P et al (2016) Incidence, risk factors and anatomy of peripersonal visuospatial neglect in acute stroke. Eur Neurol 75(3–4):157–163

Kanwisher N, Woicuulik E (2000) Visual attention: insights form brain imaging. Nat Rev Neurosci 1:91–100

Karnath HO, Rorden C (2012) The anatomy of spatial neglect. Neuropsychologia 50:1010–1017

Karnath HO, Ferber S, Himmelbach M (2001) Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 411(6840):950–953

Karnath HO, Himmelbach M, Küker W (2003) The cortical substrate of visual extinction. NeuroReport 14(3):437–442

Karnath HO, Fruhmann Berger M, Küker W, Rorden C (2004) The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. Cereb Cortex 14:1164–1172

Karnath HO, Rorden C, Ticini LF (2009) Damage to white matter fiber tracts in acute spatial neglect. Cereb Cortex 19(10):2331–2337

Karnath HO, Rennig J, Johannsen L, Rorden C (2011) The anatomy underlying acute versus chronic spatial neglect: a longitudinal study. Brain 134(Pt 3):903–912

Kastner S, Ungerleider LG (2000) Mechanisms of visual attention in the human cortex. Annu Rev Neurosci 23:315–341

Klein E, Moeller K, Glauche V, Weiller C, Willmes K (2013) Processing pathways in mental arithmetic: evidence from probabilistic fibre tracking. PLoS ONE 8(1):e55455

Kleinman JT, Newhart M, Davis C, Heidler-Gary J, Gottesman RF, Hillis AE (2007) Right hemispatial neglect: frequency and characterization following acute left hemispheric stroke. Brain Cogn 64(1):50–59

Kuemmerer D, Hartwigsen G, Kellmeyer P, Glauche V, Mader I, Klöppel S et al (2013) Damage to ventral and dorsal language pathways in acute aphasia. Brain 136(2):619–629

Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M (2001) Aphasia in acute stroke and relation to outcome. J Intern Med 249(5):413–422

Liebermeister C (1877) Über Wahrscheinlichkeitsrechnung in Anwendung auf therapeutische Statistik. Sammlung Klinischer Vorträge 110:935–962

Machner B, Dorr M, Sprenger A, von der Gablentz J, Heide W, Barth E, Helmchen C (2012) Impact of dynamic bottom-up features and top-down control on the visual exploration of moving real-world scenes in hemispatial neglect. Neuropsychologia 50(10):2415–2425

Maeshima S, Shigeno K, Dohi N, Kajiwara T, Komai N (1992) A study of right unilateral spatial neglect in left hemispheric lesions: the difference between right-handed and non-right-handed post-stroke patients. Acta Neurol Scand 85(6):418–424

Marsh E, Hillis AE (2008) Dissociation between egocentric and allocentric visuospatial and tactile neglect in acute stroke. Cortex 44(9):1215–1250

Martin M, Beume L, Kuemmerer D, Schmidt CS, Bormann T, Dressing A et al (2015) Differential roles of ventral and dorsal streams for conceptual and production-related components of tool use in acute stroke patients. Cereb Cortex 26(9):3754–3771

Mattingley JB, Bradshaw JL (1994) How many neglects? Some considerations based on anatomy and information processing. Neuropsychol Rehabil 4:169–172

Medina J, Kimberg DY, Chatterjee A, Coslett HB (2010) Inappropriate usage of the Brunner–Munzel test in recent voxel-based lesion-symptom mapping studies. Neuropsychologia 48(1):341–343

Mesulam MM (1981) A cortical network for directed attention and unilateral neglect. Ann Neurol 10(4):309–325

Mesulam MM (1999) Spatial attention and neglect: parietal, frontal and cingulated contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc B Biol Sci 354:1325–1346

Milner AD (1997) Neglect, extinction and the cortical streams of visual processing. In: Thier P, Karnath HO (eds) Parietal lobe contributions to orientation in 3D space. Springer, Heidelberg, pp 3–22

Molenberghs P, Sale MV (2011) Testing for spatial neglect with line bisection and target cancellation: are both tasks really unrelated? PLoS ONE 6(7):e23017

Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, Husain M (2003) The anatomy of visual neglect. Brain 126:1986–1997

Ogden JA (1985) Anterior-posterior interhemispheric differences in the loci of lesions producing visual hemineglect. Brain Cogn 4:59–75

Ogden JA (1987) The 'neglected' left hemisphere and its contribution to visuospatial neglect. In: Jeannerod M (ed) Neurophysiological and neuropsychological aspects of spatial neglect. Elsevier Science Publishers, North Holland, pp 215–233

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 8:97–113

Oleksiak A, Postma A, van der Ham IJ, Klink PC, van Wezel RJ (2011) A review of lateralization of spatial functioning in non-human primates. Brain Res Rev 67(1–2):56–72

Ota H, Fuji T, Suzuki K, Fukatsu R, Yamadori A (2001) Dissociation of body-centered and stimulus centered representations in unilateral neglect. Neurology 57:2064–2069

Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS (1995) Aphasia in acute stroke: incidence, determinants, recovery. Ann Neurol 38(4):659–666

Pedersen P, Jorgensen H, Nakayama H, Raaschou H, Olsen T (1997) Hemineglect in acute stroke-incidence and prognostic implications: the Copenhagen Stroke Study. Am J Phys Med Rehabil 76(2):122–127

Previc FH (1991) A general theory concerning the prenatal origins of cerebral lateralization in humans. Psychol Rev 98(3):299–334

Rengachary J, He BJ, Shulman GL, Corbetta M (2011) A behavioral analysis of spatial neglect and its recovery after stroke. Front Hum Neurosci 45:29

Rijntjes M, Weiller C, Bormann T, Musso M (2013) The dual loop model: its relation to language and other modalities. Front Evol Neurosci 4:9

Ringman JM, Saver JL, Woolson RF, Clarke WR, Adams HP (2004) Frequency, risk factors, anatomy, course of unilateral neglect in an acute stroke cohort. Neurology 63(3):468–474

Robertson I, Marshall J (1993) Unilateral neglect. Clinical and experimental studies. Lawrence Erlbaum Associates, Hove

Rorden C, Karnath HO (2010) A simple measure of neglect severity. Neuropsychologia 48(9):2758–2763

Rorden C, Fruhmann Berger M, Karnath HO (2006) Disturbed line bisection is associated with posterior brain lesions. Brain Res 1080(1):17–25

Saj A, Verdon V, Vocat R, Vuilleumier P (2012) 'The anatomy underlying acute versus chronic spatial neglect' also depends on clinical tests. Brain 135(Pt2):e207

Smith DV, Clithero JA, Rorden C, Karnath HO (2013) Decoding the anatomical network of spatial attention. Proc Natl Acad Sci 110(4):1518–1523

Sperber C, Karnath HO (2016) Diagnostic validity of line bisection in the acute phase of stroke. Neuropsychologia 82:200–204

Stone SP, Wilson B, Wroot A, Halligan PW, Lange LS, Marshall JC, Greenwood RJ (1991) The assessment of visuospatial neglect after acute stroke. J Neurol Neurosurg Psychiatry 54:345–350

Stone SP, Halligan PW, Greenwood RJ (1993) The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. Age Ageing 21:48–52

Suchan J, Karnath HO (2011) Spatial orienting by left hemisphere language areas: a relic from the past? Brain 134:3059–3070

Suchan J, Rorden C, Karnath HO (2012) Neglect severity after left and right brain damage. Neuropsychologia 50:1136–1141

Sunderland A, Wade DT, Langton-Hewer R (1987) The natural history of visual neglect after stroke: indications from two methods of assessment. J Int Disabil Stud 8:55–59

Taylor D, Ashburn A, Ward CD (1994) Asymmetrical trunk posture, unilateral neglect and motor performance following stroke. Clin Rehabil 8:48–53

Umarova RM, Saur D, Kaller CP, Vry MS, Glauche V, Mader I et al (2011) Acute visual neglect and extinction: distinct functional state of the visuospatial attention system. Brain 134(11):3310–3325

Vallar G, Perani D (1986) The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. Neuropsychologia 24:609–622

Vallar G, Rusconi ML, Geminiani G, Berti A, Cappa SF (1991) Visual and nonvisual neglect after unilateral brain lesions: modulation by visual input. Int J Neurosci 61(3–4):229–239

Vallar G, Rusconi ML, Bignamini L, Geminiani G, Perani D (1994) Anatomical correlates of visual and tactile extinction in humans: a clinical CT scan study. J Neurol Neurosurg Psychiatry 57(4):464–470

Vandervliet EJ, Verhoeven J, Engelborghs S, De Deyn PP, Parizel PM, Marien P (2008) FMRI findings in an aphasic patient with reversed cerebral dominance for language. Acta Neurol Belg 108(4):161–166

Verdon V, Schwartz S, Loyblad KO, Hauert CA, Vuilleumier P (2010) Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain 133(3):880–894

Weiller C, Isensee C, Rijntjes M, Huber W, Müller S, Bier D, Dutschka K, Woods RP, Noth J, Diener HC (1995) Recovery from Wernicke's aphasia: a positron emission tomographic study. Ann Neurol 37(6):723–732

Weiller C, Musso M, Rijntjes M, Saur D (2009) Please don't underestimate the ventral pathway in language. Trends Cogn Sci 13(9):369–370

Weiller C, Bormann T, Saur D, Musso M, Rijntjes M (2011) How the ventral pathway got lost: and what its recovery might mean. Brain Lang 118(1–2):29–39

Wilson B, Cockburn J, Haligan PW (1987) Behavioural inattention test. Thames Valley Company, Titchfield