Attention-Network Specific Alterations of Structural Connectivity in the Undamaged White Matter in Acute Neglect

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Abstract: Visual neglect results from dysfunction within the spatial attention network. The structural connectivity in undamaged brain tissue in neglect has barely been investigated until now. In the present study, we explored the microstructural white matter characteristics of the contralesional hemisphere in relation to neglect severity and recovery in acute stroke patients. We compared age-matched healthy subjects and three groups of acute stroke patients (9 ± 0.5 days after stroke): (i) patients with nonrecovered neglect ($n = 12$); (ii) patients with rapid recovery from initial neglect (within the first week post-stroke, $n = 7$); (iii) stroke patients without neglect ($n = 17$). We analyzed the differences between groups in grey and white matter density and fractional anisotropy (FA) and used fiber tracking to identify the affected fibers. Patients with nonrecovered neglect differed from those with rapid recovery by FA-reduction in the left inferior parietal lobe. Fibers passing through this region connect the left-hemispheric analogues of the ventral attention system. Compared with healthy subjects, neglect patients with persisting neglect had FA-reduction in the left superior parietal lobe, optic radiation, and left corpus callosum/cingulum. Fibers passing through these regions connect centers of the left dorsal attention system. FA-reduction in the identified regions correlated with neglect severity. The study shows for the first time white matter changes within the spatial attention system remote from the lesion and correlating with the extent and persistence of neglect. The data support the concept of neglect as disintegration within the whole attention system and illustrate the dynamics of structural-functional correlates in acute stroke. *Hum Brain Mapp* 35:4678–4692, 2014. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Neglect is a spatial attention deficit, which manifests with the failure to perceive relevant contralesional stimuli, when these symptoms cannot be attributed to either sensory or motor deficits [Brain, 1941; Critchley, 1949; Heilman et al., 2003]. It occurs more often and persistent in patients with right hemisphere stroke [Cassidy et al., 1998; Stone et al., 1992], thought to be explained by the right hemisphere dominance for spatial processing [Heilman and Van Den Abell, 1980; Mesulam, 1981]. Another model for this spatial deficit builds on the theory of hemispheric rivalry, which considers the functional imbalance between ipsi- and contralesional hemispheres in neglect patients [Kinsbourne, 1970]. Persisting neglect has a negative impact on functional outcome and rehabilitation in the following months and years [Denes et al., 1982; Cassidy et al., 1998; Buxbaum et al., 2004; Jehkonen et al., 2006]. Risk factors for persistence of neglect are: age over 65 [Hier et al., 1983; Gottesman et al., 2008], ischemic lesions (vs. hemorrhagic), lesion size [Hier et al., 1983; Levine et al., 1986], brain atrophy [Gottesman et al., 2008; Levine et al., 1986], initial neglect severity [Levine et al., 1986; Gottesman et al., 2008; Stone et al., 1992], lesion of temporoparietal junction and the superior and middle temporal gyrus [Chechacz et al., 2012; Karnath et al., 2011; Saj et al., 2012] and concomitant anosognosia [Stone et al., 1992]. Most studies on recovery from neglect examined patients not before one week after stroke onset [Farne et al., 2004], though recovery is most rapid in the first 10 days and reaches a plateau after 3 months. Moreover, the severity of chronic visual neglect could be predicted by its severity at day 2 to 3 after stroke [Stone et al., 1992]. This makes the study of neglect and its recovery in acute stroke important, also as the recovery of chronic neglect, which is clinically more relevant, might have the same neurobiological mechanisms. In clinical practice there are frequently patients with complete recovery from neglect within the first week after stroke, a period before major structural brain reorganization sets in. Factors and mechanisms underlying such rapid recovery from neglect are little known.

Reperfusion of attention-relevant cortical areas in the right hemisphere within the first 3 to 5 days after stroke was shown to improve neglect [Khurshid et al., 2012; Vallar et al., 1988; Weiller et al., 1993]. Another mechanism of neglect improvement may be remission of diaschisis. Diaschisis is a (temporary) systematic disturbance of function in the components of a widely distributed function-specific network [Baron et al., 1981; Feeney and Baron, 1986; Von Monakow, 1906]. Reversal of diaschisis would account for

the early and sometimes sudden improvement of the altered function [Von Monakow, 1906]. In both cases, functional but not structural disturbances within the attention network are to be expected. Concerning spatial attention function, there are no data exploring the microstructural characteristics of the undamaged brain tissue in relation to neglect and its recovery. Similarly, the relation of white matter characteristics with the emergence of neglect is rarely investigated. Brain atrophy, also in the left hemisphere, has been suggested to worsen recovery from neglect [Levine et al., 1986]. The same mechanism may explain the negative role of increasing age on neglect in acute stroke [Gottesman et al., 2008]. Lesion of the uncinate fasciculus might also hamper neglect recovery [Karnath et al., 2010]. But is there any remodeling within undamaged white matter, which is related to neglect and its recovery?

If remodeling of the white matter associated with neglect and its recovery exists, then it is expected to occur system-specific: in the white matter adjacent to or connecting the cortical attention centers. Moreover, it should correlate with spatial attention function, since early white matter remodeling is function dependent [Sagi et al., 2012]. If recovery from neglect, especially when occurring rapidly, is influenced by pre-existing white matter alteration due to aging or vascular pathology, then such changes are expected to be present mostly in the subcortical and periventricular regions and to be not specifically related to cortical attention centers [Schmahmann et al., 2008].

The microarchitecture of the white matter and its remodeling is usually investigated in vivo by using brain water diffusion parameters measurable with magnetic-resonance tomography followed by fiber tracking, which aims at reconstructing white matter fascicles [Beaulieu, 2002; Le Bihan et al., 2001; Mori et al., 1999; Pierpaoli et al., 1996]. Both methods provide insight into the white matter anatomy and its reorganisation [Basser, 1997; Li et al., 2009]. The most common parameter used in clinical studies is fractional anisotropy (FA). FA combines the contributions from the different subcompartments of the white matter into a single metric [Jones et al., 2013]. Fiber tracking is less frequently used in patients' studies, partly due to a quantification problem [Jones, 2008]. There are few studies which performed fiber tracking in patients with and without neglect; and those relied on a priori regions of interest, performed tracking through damaged brain tissue and studied patients in the chronic stage of stroke [He et al., 2007; Thiebaut de Schotten et al., 2014; Urbanski et al., 2007, 2011].

The purpose of the present study was therefore, (i) to investigate the microstructural characteristics of the white

matter in the undamaged hemisphere in relation to neglect, its severity and recovery from it in acute right hemispheric stroke; (ii) to identify the thereby affected fiber tracks to assess the hypothesis of a system specific involvement. We focused on the white matter of the left hemisphere because the large infarcts in neglect patients lead to extensive perilesional edema of the undamaged brain tissue and bias the results. Additionally, it ensures that identified changes are indeed the result of white matter remodeling and not the direct effects of ischemia, since neglect patients usually have larger lesions than those without [Karnath et al., 2004; Umarova et al., 2011].

We examined patients with a first ischemic stroke in the territory of the right middle cerebral artery with a neglect test-battery within the first 3 to 5 days after stroke onset and again 1 week later (about 10 days after stroke). Some patients with initial neglect had no signs of the visuospatial attention deficit at the second examination and were classified as patients with rapid recovery from neglect. In total, we had three groups of patients: (i) control stroke patients without neglect; (ii) neglect patients with rapid recovery from it, and (iii) neglect patients without rapid recovery (non-recovered neglect). We compared patients with nonrecovered neglect with the other groups of patients and with age-matched healthy subjects using lesion mapping analysis, voxel-based morphometry (VBM) and voxel-based analysis of fractional anisotropy. Then we used the obtained regions of altered FA as regions of interest for a subsequent fiber tracking analysis. Finally, we performed a correlation analysis between the anatomical and clinical features.

MATERIALS AND METHODS

Subjects

Patients were recruited from the stroke unit of the Department of Neurology, University Medical Centre, Freiburg, Germany. For a period of 47 months (January 2007 to November 2010), we screened all patients with ischemic stroke in the right hemisphere. The inclusion criteria consisted of territorial ischemic first-ever stroke in the right middle cerebral artery territory confirmed by magnetic resonance imaging (MRI). Exclusion criteria were (i) age > 80 years; (ii) hemianopia, to separate effects of the visual and attentional deficits; (iii) inability to maintain alertness, low conscious or arousal level that prevented the neglect testing; (iv) pronounced small vessels disease or additional structural brain lesions; (v) general contraindications for MRI examination; (vi) other neurological or psychiatric conditions that precluded active participation in research and/or altered the interpretation of the behavioral/imaging data (e.g. dementia, schizophrenia); (vii) left-handedness. The functional MRI data of 24 patients included in the present study were published previously [Umarova et al., 2011].

Additionally, we recruited 20 age-matched healthy right-handed subjects (10 males), 67 ± 1 years old (mean $\pm$ SEM)

without any neurological or psychiatric history, which represented a group of healthy controls. They underwent an anamnestic interview and neurological examination to exclude major illnesses. Written informed consent was obtained from each subject in accordance with the Declaration of Helsinki. The Ethics Committee of the University Medical Centre Freiburg approved the study.

Clinical and Behavioral Testing

All patients received a daily basic screening for extinction and neglect. Visual fields were assessed by standardized neurological bedside examination, since standardized perimeter examination was not feasible due to the early inclusion of the patients in the study. Visual neglect was diagnosed based on clinical signs (e.g. when the patient oriented towards the ipsilesional side, when approached from the front or the left side, and/or ignored contralesionally located persons or objects) and the results of the neuropsychological testing. The first detailed neuropsychological testing was performed within the first 3 to 5 days after stroke onset and the second one a week after, at the time of MRI scanning. The fluctuations of alertness in patients with acute right hemispheric lesions influence spatial attention [Robertson et al., 1998], that is why the neglect testing was ensured to be performed in the arousal phase due to the teamwork with therapists and nursing staff. Visual neglect was tested using the same test battery as in the previous study [Umarova et al., 2011].

All patients performed standardized paper-and-pencil tests of visuospatial neglect in the peripersonal space (Manuela Fels, Edgar Geissner Neglect-Test (NET)), which is an adapted version of the "Behavioral Inattention Test" (BIT) [Wilson et al., 1987]. Visual neglect was diagnosed when the patients failed to perform at least two of the following clinical tests: (i) the "line cancellation task," (ii) the "letter cancellation" task, (iii) the "star cancellation task," (iv) text reading, (v) pictures copying task, and (vi) line bisection test. All visual tests were performed with the targets distributed on an A4 sheet of paper, which was centered in front of the patients.

The line cancellation task

This test consists of 40 lines each with a length of 25 mm, which are distributed onto three columns each on the right and left side (each with six lines), and one column in the center (four lines). All lines have to be cancelled. Patients were classified to fail the test in case of (i) omitting at least four left-side targets, or (ii) if right-side targets were also omitted, the difference between omissions on the left and right side was more than 4.

The letter cancellation task

Patients were presented with five rows of different letters, consisting of 34 letters per row. The task was to

cancel the letters “E” and “R,” which are randomly distributed among other irrelevant letters that represented distractors. The interpretation of the results was the same as in the Line Cancellation test.

Star cancellation task

The target stimuli are 56 small stars, which are interspersed between distractors that are represented by the 52 large stars, 13 letters, and 10 short words. The task is to cross out the small stars. The interpretation of the results was the same as in the Line Cancellation test.

Reading

The patient is prompted to read a short text, which is set out in three columns (46, 47, and 46 words in the left, central, and right column). The number of words read is assessed. If one or more sentences were read incompletely on the left but not on the right side, patients were considered to fail.

Copying of the presented pictures

Three pictures are presented to a patient (a four cornered star, a rhomb, and a flower), which are drawn on the left half of the sheet. The task is to copy the figures on the right half of the sheet. Correctness of the general contour (1 score), details (1 score), and their order (1 score) on the copied pictures are assessed. The maximal score for every figure is 3. A sum score less than 6 was defined as deficient.

Line bisection test

Three lines of the 20 cm length are presented, which are in the most left, right, and middle position. The task is to cross the line in the middle. The performance for every line was assessed with 0 (>3 cm from the middle) to 3 (the middle of the line $\pm$ 1 cm). The maximal score for the task 9 (normal performance), the score 6 and lower was defined as deficient.

For subsequent analyses on neglect severity and recovery, the patients were divided into three groups according to the results of neglect testing: (1) patients without clinical signs of neglect or extinction, who represented the group of control patients with normal performance in both neuropsychological examinations; (2) patients with rapid recovery from neglect (recovery within the first days after stroke), who showed visual neglect only in the first neuropsychological examination and not in the second one; (3) patients with nonrecovered neglect, who failed to recover from it within the first week after stroke, and who showed neglect in both neuropsychological examinations.

To quantify neglect severity, we used the Center of Cancellation score (CoC) for line, star and letter cancellation tests and reading [Rorden and Karnath, 2010]. The CoC

score indicates the center of mass for all detected items, such that identifying all the targets would generate a score of 0 (no neglect), whereas identifying of only the rightmost items would provide a score of 1 (very severe neglect). This score is sensitive to both the number and the location of these omissions. CoC scores >0.09 in the Cancellation Tasks was taken to indicate neglect behavior [Karnath et al., 2010; Rorden and Karnath, 2010].

In contrast to the cancellation tasks, the drawing and line bisection tests have a scale from 0 (severe neglect) to 9 (no neglect) and had to be nonlinearly transformed to correspond to the CoC scale of cancellation tests (0: no neglect, 1: severe neglect to the left, 0.09: the threshold score). To this end, the scores of drawing and line bisection tests were transformed with the calculated formula $(9 - \text{score})^{1.6} / 33.63$. Due to the transformation, all tests had a similar scale, therefore it was possible to calculate a general neglect score (NegScore) as a mean of all eight tests (line, star, letter cancellation tests, line bisection, drawing, and reading) for the first and second neuropsychological examinations (NegScore1 and NegScore2 correspondingly).

Patients' clinical data are presented in Table I. We used a one-way ANOVA to compare the clinical characteristics between groups of patients (age, time after stroke onset, stroke severity in terms of NIH Stroke Scale assessed on admission). To detect the differences between all groups in neglect tests, we used the Kruskal-Wallis test as the data were not normally distributed. Both neglect groups with and without rapid recovery were compared with each other using the Mann-Whitney *U* test. Since we expected that rapidly recovered neglect patients would have less severe neglect, we performed the one-tailed test.

MRI Data Acquisition

Structural and diffusion-weighted MRI data were acquired on a 3 T TIM-TRIO MRI System (Siemens, Erlangen, Germany) with a standard head coil.

For routine assessment of stroke lesion, diffusion weighted imaging (DWI) was obtained with a diffusion-weighted Spin-Echo echoplanar imaging (EPI) sequence (repetition time = 3,100 ms, echo time = 80 ms, $b_1 = 0$ s/mm², $b_2 = 1,000$ s/mm², matrix size = 128 $\times$ 128, voxel size 1.9 $\times$ 1.9 $\times$ 5 mm³, three acquisitions, 23 slices) with three diffusion directions.

High-resolution anatomical T1 scans were acquired with a sagittal magnetization-prepared rapid-acquisition gradient echo sequence (MPRAGE, repetition time = 2,200 ms, echo time = 2.15 ms, inversion time = 1,100 ms, flip angle = 12°, matrix = 256 $\times$ 256 pixel, voxel size = 1 $\times$ 1 $\times$ mm³, 176 slices) and were used for coregistration and spatial normalization.

To calculate the structural characteristics of the white matter, high angular resolution diffusion imaging (HARDI) was acquired using a diffusion sensitive single shot spin echo EPI sequence with the following parameters:

TABLE I. Patients clinical characteristics and behavioral tests results (results are reported with median and range unless indicated otherwise)

	Control patients	Patients with rapid recovery	Patients with nonrecovered neglect
No. patients	17	7	12
Age (yrs), mean $\pm$ SEM	64 $\pm$ 3	64 $\pm$ 2	67 $\pm$ 3
Sex (female/male)	8/9	2/5	4/8
Time of the first neglect testing, hours after stroke onset, mean $\pm$ SEM	67 $\pm$ 11	57 $\pm$ 14	74 $\pm$ 10
Time to T1-imaging, hours post stroke, mean $\pm$ SEM	73 $\pm$ 11	97 $\pm$ 29	99 $\pm$ 18
Time to DTI and second neglect testing, days post-stroke, mean $\pm$ SEM	8 $\pm$ 1	9 $\pm$ 0.5	12 $\pm$ 0.6
NIHSS score on admission, mean $\pm$ SEM	8 $\pm$ 1	6 $\pm$ 2	9 $\pm$ 1
Lesion volume (mL), mean $\pm$ SEM ^a	42 $\pm$ 7	64 $\pm$ 12	94 $\pm$ 23
Line bisection, max 9			
Examination 1 ^b	9 [6–9]	7 [0–9]	1 [0–9]
Examination 2 ^b		8 [5–9]	3 [0–9]
Coping of drawings, max 9			
Examination 1 ^b	9 [6–9]	5 [0–9]	2 [0–8]
Examination 2 ^b		9 [7–9]	4 [0–8]
Line cancelation, max 18 (left; right)			
Examination 1 ^b	18 [16–18]; 18 [17–18]	17 [0–18]; 18 [15–18]	2.5 [0–18]; 14.5 [2–18]
Examination 2 ^b		18 [17–18]; 18 [–]	15 [0–18]; 18 [12–18]
Star cancelation, max 27 (left; right)			
Examination 1 ^b	26 [22–27]; 26 [22–27]	10 [0–23]; 25 [19–27]	0 [0–23]; 15 [6–25]
Examination 2 ^b		24 [18–27]; 25 [21–27]	13 [0–23]; 21 [10–25]
Letter cancelation, max 20 (left; right)			
Examination 1 ^b	19 [15–20]; 19 [17–20]	11 [1–19]; 19 [12–20]	0 [0–16]; 10 [2–20]
Examination 2 ^b		19 [15–20]; 18 [14–20]	8 [0–19]; 13 [7–20]
Reading, max 47/46/47 words (left; center; right)			
Examination 1 ^b	47 [45–47]; 46 [45–47]; 47 [–]	0 [0–47]; 46 [0–46]; 47 [42–47]	0 [0–47]; 32.5 [0–46]; 36.5 [6–47]
Examination 2 ^b		47 [–]; 46 [–]; 47 [–]	0 [0–47]; 30 [0–46]; 47 [32–47]
NegScore			
Examination 1 ^b	0.004 [–0.006–0.043]	0.221 [0.083–0.578]	0.629 [0.121–0.975]
Examination 2 ^b		0.006 [–0.01 to 0.07]	0.351 [0.040–0.840]

^aSignificant group effect in a one-way ANOVA;^bsignificant group effect in the Kruskal-Wallis test in Ex. 1 or Mann-Whitney-*U*-test in Ex. 2.

TR = 10,000 ms, TE = 94 ms, voxel size $2 \times 2 \times 2$ mm³, number of slices = 69, no gap; flip angle = 90°. For each of the 61 diffusion encoding directions, b value of 1000 s/mm² was used. In addition, 9 volumes without diffusion weighting (*b* value = 0 s/mm²) equally distributed throughout the scan were acquired. Motion and distortion correction was applied during reconstruction by using a previously acquired reference scan [Zaitsev et al., 2006].

Image Analysis

Preprocessing of imaging data

For computation of FA and b0 map from HARDI data, we used the DTI_tool implemented in SPM8 (<http://sourceforge.net/projects/spmtools/>).

For normalization of the FA and fiber tracking data, we used a Fast Diffeomorphic Registration Algorithm (DARTEL) implemented in SPM8 [Ashburner, 2007]. To this aim, T1 images were classified into grey and white matter and cerebrospinal fluid [Ashburner and Friston, 2005]. Then we created a template using grey and white matter images from all subjects. In the next step the individual images (grey and white matter maps, FA maps) were nonlinearly transformed to the customized template using the subject-specific diffeomorphic estimates from the DARTEL procedure followed by a linear normalization to the standard MNI space. Grey and white matter probability maps were subsequently “modulated” by the Jacobian determinants of the deformations to account for local compression and expansion due to linear and

non-linear transformation and smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum (FWHM). The FA maps were not scaled by the Jacobian determinants (i.e., no “modulation” of parameter values) and smoothed with an isotropic Gaussian kernel of FWHM 10 mm. The global fiber tracking data were transformed from individual to MNI space using the DARTEL normalization parameters as well.

Lesion mapping analysis

DWI is a better imaging method than conventional MRI in detecting early ischemic lesions in stroke patients [Everdingen et al., 1998] that is why it was used for lesion delineation. Routine stroke DWI scans were firstly affine registered to the b0 image of HARDI data. Then the lesions were delineated on the individual DWI images using MRICron Toolbox <http://www.cabiatl.com/mricron/mricron/index.html> [Rorden et al., 2007]. The binary lesion maps were normalized into the standard Montreal Neurological Institute (MNI) space using normalization parameters from the coregistered anatomical T1 scans [Ashburner and Friston, 2005]. The lesion overlap was computed using MRICron.

To clarify if the groups of patients differed in their lesion anatomy, we performed a statistical voxel-wise lesion-behavior mapping. Since the clinical data were binominal (control patients without neglect versus nonrecovered neglect patients, etc.) and the lesion images were binary, the Lieberman test was used, which is implemented in the MRICron Toolbox. The results were controlled for multiple comparisons by using the false discovery rate correction ($P < 0.05$).

Fiber tracking

We used a global tracking algorithm available from http://www.uniklinik-freiburg.de/mr/live/arbeitsgruppen/diffusion/fibertools_en.html, which outperformed related methods in a recent comparison with known ground truth [Fillard et al., 2011]. Global tractography is a class of tractography algorithms that can be seen as greedy algorithms: instead of reconstructing tracts one by one, those algorithms reconstruct all fibers at the same time [Fillard et al., 2009, 2011; Kreher et al., 2008; Reisert et al., 2011]. This algorithm treats each segment of a reconstructed fiber as a parameter to be optimized. Optimization can be imagined as a polymerization process that starts in a very fuzzy state of very short tract-segments, and then each segment tries to associate with neighboring segments to form longer chains of low curvature while modeling the diffusion weighted data at best. Each fiber segment contributes an anisotropic Gaussian component in the signal model, which is eventually optimized to describe experimental data [Fillard et al., 2011; Reisert et al., 2011]. In contrast to the algorithms with the “walker principle,” global tracking is based on the optimization of one global function and,

thereby, is able to overcome small local artifacts and to reduce the number of erroneous connections [Fillard et al., 2011; Kreher et al., 2008; Reisert et al., 2011]. Advantages of the used global tracking algorithm are (i) optimization of all fibers at once with respect to the given HARDI data; (ii) the absence of any boundary conditions, which minimizes the dependence on the operator and keeps the necessary user interaction low; (iii) absence of any a priori assumptions concerning start/stop tracking criteria, seed points or anatomical assumptions; (iv) better reconstruction of crossing and spreading fiber configuration; (v) reproducibility of results across scans; (vi) well-adapted in real and noisy situations [Fillard et al., 2009, 2011; Kreher et al., 2008; Reisert et al., 2011]. As area of reconstruction (mask) we used individual white matter maps containing voxels with an at least 20% probability of containing white matter. The global tracking data were normalized into the standard Montreal Neurological Institute (MNI) as detailed below.

For better anatomical understanding of the identified regions of altered FA, we used voxels with significant FA differences as regions of interest to extract the fibers from the normalized global tracking data. Thus the extracted fiber tracks that passed the regions of altered FA were in MNI space. For illustration purposes we used the averaged fiber tracks of healthy subjects, since the minimal fiber tracks changes occurring 10 days after stroke cannot be captured with fiber tracking.

Statistical analysis of imaging data

First, a VBM analysis was performed to investigate the volumetric characteristics of the white and grey matter and to explore, if the diffusion changes might be a consequence of volumetric differences. In the next step, a voxel-based FA-analysis was performed to assess group differences in structural connectivity. More specifically, we performed a voxel-based analysis of the normalized grey and white matter segments and FA maps using a two-sample *t*-test and contrasting non-recovered neglect patients and those with rapid recovery with each other and against (i) acute stroke patients without neglect, (ii) age-matched healthy subjects. In these statistical tests, only voxels in the left hemisphere at probability value of 20% were included; the whole-brain family-wise error correction for multiple comparisons was applied at $P < 0.05$; voxels threshold > 5 . For purposes of illustration, we display the differences at the statistical level $P < 0.001$ uncorrected. The Anatomy toolbox implemented in SPM8: http://www.fz-juelich.de/ime/spm_anatomy_toolbox was used to obtain the anatomical location of the regional differences [Eickhoff et al., 2005]. To explore further the relationship between identified FA changes and clinical data, we performed a non-parametric correlation analysis (Spearman rank correlation) between FA values, extracted from the peaks of significant clusters, and the clinical parameters. As visual inspection of the relation between FA and NegScore

indicated a non-linear dependency, we performed an additional exploratory analysis with logarithmic transformation of NegScore before fitting a linear regression model. Given that NegScores in acute stroke patients without neglect were close to zero, we performed the correlation analysis only in neglect patients with and without rapid recovery.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software.

RESULTS

A total of 36 patients met the inclusion criteria. The first neuropsychological examination was conducted within the first 3 to 5 days post stroke (mean 67 ± 7 h after stroke onset), the second one a week later (mean 9.1 ± 0.5 days after stroke). The HARDI-examination was performed along with the second neuropsychological examination. Seventeen patients did not have any signs of visuospatial attention deficit and formed the group of control patients. Seven patients presented with visual neglect at admission and in the first neuropsychological examination, but had no spatial attention bias in the second neuropsychological examination (neglect patients with rapid recovery), though some of them still had a deficit of selective attention. Twelve patients had visual neglect at admission, at the first and second neuropsychological examinations (neglect patients with non-recovered neglect). The clinical data are listed in the Table I. The three groups of patients did not differ in age, sex, treatment or the time of the first ($F_{(2,33)} = 0.386$, $P = 0.683$) or the second neuropsychological examinations ($F_{(2,33)} = 0.502$, $P = 0.612$). The interval between stroke and imaging was similar between groups for T1 ($F_{(2,33)} = 0.842$, $P = 0.44$) and DTI acquisition ($F_{(2,33)} = 1.656$, $P = 0.206$). Though neglect patients tended to have a more severe stroke, all groups were similar in stroke severity according to the NIH Stroke Scale score obtained on the admission ($F_{(2,33)} = 1.16$, $P = 0.326$).

Analysis of Neglect Severity and its Recovery

Neglect severity was measured using the NegScore, which represented the mean of CoC indices for all cancellation and reading tests [Rorden and Karnath, 2010] and adapted scores for drawing and line bisection tests (see Methods section). The three groups of patients differed in neglect severity in all neglect tests at examination 1 (Kruskal-Wallis-Test, $P < 0.001$, Table I). Rapid recovered neglect patients had less severe attentional bias than non-recovered ones in line and letter cancellation tests and in reading (Mann-Whitney test, $U = 19.5$, $U = 21.0$, and $U = 20.0$ correspondingly by $P < 0.05$ one-tailed), but the groups were comparable in other tests: star cancellation, line bisection and drawing tests ($U = 25.0$, $U = 24.5$ and $U = 29.5$ correspondingly by $P > 0.05$ one-tailed). Taken together, patients with rapid recovery had less severe initial neglect than non-recovered ones, which was expressed in NegScore 1 ($U = 21.0$, $P = 0.042$ one-tailed).

Figure 1.

Lesion overlap of control patients and neglect patients with and without rapid recovery. Color bar indicates the number of overlapping lesions.

Both neglect groups differed also by NegScore 2 at the second examination ($U = 2.0$, $P = 0.001$). NegScore 2 correlated strongly with NegScore 1 (Spearman correlation, $r = 0.746$, $P < 0.001$). Thus, neglect severity 3 to 5 days after stroke predicted the severity of neglect one week later.

Lesion Mapping Analysis and Voxel-Based Morphometry

The lesion mapping data are shown in Figure 1. Patients groups differed significantly in infarct size ($F_{(2,32)} = 3.63$, $P = 0.038$), as nonrecovered neglect patients had significantly larger infarcts compared with control patients without neglect ($T_{27} = -2.63$, $P = 0.014$). However, rapid recovered and nonrecovered neglect patients did not differ in lesion volumes ($T_{17} = -0.994$, $P = 0.334$). According to the lesion mapping analysis, the three groups of patients did not differ in their lesion anatomy (Liebermeister test, $P > 0.05$, FDR corr.).

The groups of patients and healthy subjects did not differ in the volume of grey ($F_{(2,32)} = 0.369$, $P = 0.694$) or white matter ($F_{(2,32)} = 0.125$, $P = 0.883$) or cerebrospinal fluid ($F_{(2,32)} = 0.474$, $P = 0.765$) (Supporting Information Table I).

TABLE II. The differences of fractional anisotropy between groups (FWE corrected, $P < 0.05$)

Region	Coordinates			T-score	Cluster size (voxels)
	x	y	z		
Healthy subjects > neglect patients without recovery					
Left SPL	-15	-66	43	5.51	70
Left optic radiation	-32	-70	19	5.24	46
Left corpus callosum/cingulum	-14	-48	25	5.05	8
Neglect patients with rapid recovery > neglect patients without recovery					
Left inferior parietal lobule/postcentral gyrus	-54	-21	27	7.42	28

VBM analysis in the left hemisphere showed no differences between groups of patients and healthy subjects in grey and white matter density. To increase sensitivity, we repeated this analysis with a lower statistical threshold ($P < 0.001$, uncorr., Supporting Information Fig. S1).

Voxel-Based Analysis of the White Matter Microstructure and Fiber Tracking

We performed a voxel-based analysis of FA values in the left hemisphere and a correlation analysis with the clinical data to explore the meaning of the white matter differences. Compared with healthy subjects, nonrecovered neglect patients showed FA-reduction in the parietal and occipital lobes and in corpus callosum of the left hemisphere (Table II, Fig. 2, and Supporting Information Fig. S2). The FA values in these regions did not correlate with lesion volume, age, stroke severity and initial neglect severity (NegScore1). However, there was a negative correlation between NegScore2 and FA values in the left parietal and occipital regions (Spearman correlation, $r = -0.56$, $P = 0.012$, and $r = -0.48$, $P = 0.04$, two-tailed). The exploratory regression analysis revealed a logarithmic dependency between FA-values and NegScore 2 ($F_{(1,17)} = 8.524$, $P = 0.010$, $R^2 = 0.334$ and $F_{1,17} = 4.094$, $P = 0.059$, $R^2 = 0.194$). As illustrated in Figure 2, FA-values were negatively correlated with neglect severity in patients with low to moderate neglect (NegScore 2 ≤ 0.3 – 0.4), whereas no association was found for patients with severe neglect consistently showing low FA-values.

Non-recovered neglect patients and control patients without neglect did not differ significantly, but there was a tendency toward FA-reduction in the frontal lobe and optic radiation in the first group (Supporting Information Fig. S3). Compared with patients with rapid recovery, non-recovered patients had FA-reduction in the left supramarginal gyrus (Table II, Fig. 3, and Supporting Information Fig. S2). The FA values in this region did not correlate with lesion volume, age or stroke severity on admission. However, NegScore 1 correlated negatively with FA values in the supramarginal gyrus (Spearman

correlation, $r = -0.53$, $P = 0.021$, two-tailed), but even stronger with NegScore 2 (Spearman correlation, $r = -0.70$, $P < 0.001$, two-tailed). The exploratory regression analysis found that the dependency between FA-values and NegScore 2 could again be well fitted by a logarithmic function ($F_{(1,17)} = 18.603$, $P = 0.001$, $R^2 = 0.523$; Fig. 3) as the negative association between FA-values and neglect severity did account for low to moderate but not severe neglect. Thus, the more severe neglect correlated with the lower FA in the identified region. To ensure that these findings were not biased by the later time of DTI examination in patients with non-recovered neglect (Table I), we performed an additional FA-analysis, in which we compared seven patients with rapid recovery against seven non-recovered ones, matched by interval between stroke and DTI (8.6 ± 0.5 and 9.3 ± 0.2 days post stroke correspondingly). Results remained essentially unchanged as non-recovered neglect patients had FA-reduction in the supramarginal gyrus (Supporting Information Fig. S4).

Patients with rapid recovery did not differ in FA-values of the undamaged hemisphere from healthy subjects and control patients without neglect even at $P < 0.001$ (two-sample t -test).

Next, we aimed to identify fiber streams affected in neglect patients by using the identified regions of changed FA as regions of interest for fiber extraction from the individuals' global tracking data. For fiber tracking analysis, we used the images of healthy subjects to show fibers extending into right hemispheric areas, potentially affected by stroke in the patients groups. Connections, which traveled through the regions with reduced FA in non-recovered neglect patients compared with healthy subjects, could be divided into intra- and interhemispheric tracts (Fig. 4). One bundle traveled from the visual cortex lateral to the inferior horn of the lateral ventricle and to the geniculate body, corresponding to the optic radiation. The second bundle connected superior parietal and superior frontal cortex forming the part I and II of the superior longitudinal fascicle (SLF I/II). The third fascicle, the cingulate bundle, coursed within the white matter of the cingulate gyrus stretching between the ventromedial frontal lobe and the

Figure 2.

Reduction of the fractional anisotropy in patients with non-recovered neglect compared with healthy subjects (two-sample *t*-test, $P < 0.001$ uncorrected) and its logarithmic correlation with neglect severity (MNI coordinates are given).

parahippocampal gyrus. The fourth tract connected parietal cortex with lateral occipital cortex and inferior temporal gyri. The interhemispheric occipital connections traveled through the splenium of corpus callosum to the visual cortex of the right hemisphere.

Fibers, which were altered in nonrecovered neglect patients compared with those with rapid recovery, could also be divided into intra- and interhemispheric connections (Fig. 5). A group of local parietal fibers connected the ventral and dorsal parts of the parietal cortex corresponding to the neighborhood association fibers of the parietal lobe. Other fibers traveled along the upper shoulder of the sylvian fissure connecting the caudal superior temporal gyrus and inferior parietal lobe with the ventral premotor and prefrontal cortex. This tract corresponds to the arcuate fascicle/superior longitudinal fascicle III (SLF III). The interhemispheric connections traveled between the splenium and body of corpus callosum to the contralateral parietal regions.

DISCUSSION

This is the first study exploring the structural connectivity in acute neglect in respect to its severity and persistence using voxel-based whole-brain analysis in combination with global tracking. The microstructural white matter characteristics in non-recovered neglect patients were distinct from those in rapidly recovered patients and age-matched healthy subject. The regions with affected FA were distant from the infarcts and confined to an anatomical network, defined by the exerted function, i.e. visuospatial attention.

Methodological Issues

It was not the main purpose of the present study to explore factors that influence the rapid recovery from neglect, but to investigate the structural connectivity of the contralesional hemisphere in acute neglect and relate the

Figure 3.

Reduction of fractional anisotropy in stroke patients with non-recovered neglect compared with those with rapid recovery (two-sample t-test, $P < 0.001$ uncorrected) and its logarithmic correlation with neglect severity (MNI coordinates are given).

findings to the clinical features. The present data confirm that less severe neglect is favorable for recovery [Gottesman et al., 2008; Levine et al., 1986; Stone et al., 1992], since nonrecovered neglect patients had more severe initial neglect as shown by the positive correlation between NegScore 2 and NegScore 1. The groups were similar in distribution of lesions (Fig. 1), though the absence of statistical differences in lesion anatomy might be also explained by the small group size of those with rapid recovery. There was a tendency towards a later DTI examination in patients without rapid recovery from neglect. This bias could be explained by the later recruitment for the study of neglect patients with large lesions as they had to be able to perform all neuropsychological testing. However, by repeating the findings in an additional comparison between patients with and without rapid recovery from neglect, matched by the interval to DTI-acquisition, we excluded the effect of differences in this parameter on the present results. Though brain atrophy worsens recovery from neglect [Levine et al., 1986], the groups of patients did not differ between each other in brain volume or volumes of the grey and white matter. This might be explained by the strict inclusion criteria, including the absence of known cognitive deficit pre-stroke or pronounced small vessels disease. The present FA-differences cannot be explained by brain atrophy or by volumetric changes in the corresponding regions. A false negative result due to the small group size is unlikely, since there

was not any overlap between FA-analysis and VBM-results with a lower statistical threshold.

The FA-differences between groups are unlikely resulting from the right-hemisphere stroke, as we focused only on the left hemisphere and included a group of stroke patients without neglect. Additionally, FA-changes did not correlate with stroke volume or time after stroke. More to the point, the absence of significant differences in the VBM analysis indicates further that the observed FA-differences are not the result of a global misregistration as this would also affect VBM.

A critical point of the present study is the small number of patients with rapid recovery. However, the study was performed in acute stroke patients within the first days after stroke and with strict inclusion criteria; the complete recovery from neglect was thoroughly controlled clinically and by eight neuropsychological tests. Additionally, all statistical analysis of the neuroimaging data was performed using a correction for the multiple comparisons. Still, given a potential lack of sensitivity, we also report results without correction for the multiple comparisons.

Given the absence of pre-stroke DTI-data, we cannot exclude the possibility that the observed FA-differences were pre-existing. This assumption still does not diminish the present results, which identified white matter locations and related fiber tracks relevant for neglect recovery. However, the pre-existence of FA-differences is unlikely, as FA-values correlated neither with initial neglect or stroke

Figure 4.

Fibers tracks that are altered in neglect patients without rapid recovery compared with healthy subjects. **A.** Fibers are superimposed to the T1-weighted image (MNI coordinates are given). **B.** Three-dimensional illustration of all identified fiber tracks. The color-coding corresponds to the fiber orientation according to the DTI-color map.

severity nor with age, but they did with neglect severity at the time of imaging. Moreover, FA-reduction was localized directly adjacent to the cortical regions relevant for spatial attention [Corbetta and Shulman, 2002]. Pre-existing white matter damage that might influence recovery is expected to be in the deep white matter, where small vessel disease or leukoaraiosis usually is found. We therefore suggest that the identified FA-changes constitute the manifestation of a neglect-induced white matter remodeling, which occurred after stroke. Ideally, additional DTI data should be acquired immediately after (or even before) stroke to demonstrate that the observed changes are not pre-existing, but in the required quality as in the present study it is infeasible.

Functional Correlates of the FA-Changes

A functional-structural correlation was shown previously for acute and chronic motor stroke in the corticospinal

tract [Borich et al., 2011; Schaechter et al., 2009; Thomalla et al., 2004; Werring et al., 2000]. Patients with poorer motor function had reduced FA of ipsi- and contralesional corticospinal tract compared with normal control subjects, whereas patients with better motor skills had elevated FA compared with controls [Schaechter et al., 2009]. Also, animal models of stroke have demonstrated the correlation of motor recovery and white matter structure in the ipsi- and contralesional hemispheres, which was evaluated in vivo using FA-analysis and fiber tracking [Jiang et al., 2006; Liu et al., 2009]. For visuospatial attention, the link between structural connectivity and behavior has been shown only in healthy subjects [Thiebaut de Schotten et al., 2011; Tuch et al., 2005]. The histological correlates of such DTI-findings are less investigated.

Previous works demonstrated the sensitivity of DTI to detect structural “plasticity” already after 90 min learning [Sagi et al., 2012; Zatorre et al., 2012]. Histological correlations for such short-term diffusion changes are astrocyte

Figure 5.

Fibers tracks that are altered in neglect patients without rapid recovery compared with those ones with rapid recovery. **A.** Fibers are superimposed to the T1-weighted image (MNI coordinates are given). **B.** Three-dimensional illustration of all identified fiber tracks. The color-coding corresponds to the fiber orientation according to the DTI-color map.

activation and increase in the number of synaptic vesicles [Sagi et al., 2012]. Animal stroke models show similar data, which usually have been acquired by lesioning of the motor cortex. Such unilateral lesions result in remarkable neuroanatomical changes in the homologue region of the contralesional hemisphere. Specifically, there is evidence of axonal degeneration in the motor cortex opposite to the lesions at 7 to 10 days [Jones, 1999; Jones et al., 2003]. Also around this time, there are reactive changes in a subtype of glial cells and astrocytes as well as increases in the presence of neurotrophic factors and increases in proteins associated with neuronal plasticity [Dahms et al., 1999]. Such changes in the contralesional motor cortex can be modulated by training [Bury and Jones, 2002]; with

other words they are function-dependent. To conclude, the FA-changes found 9 to 10 days after stroke in the contralesional function-relevant areas in the present study are in line with the animal data and may be explained by function-dependent glial reaction.

Structural Connectivity and Recovery From Neglect

Compared with healthy subjects, non-recovered neglect patients showed FA-reduction in the optic radiation, superior parietal cortex and posterior cingulum/corpus callosum of the contralesional hemisphere. The identified

structural changes were system-specific and not related to irrigation territories or patterns of degenerative disease. These regions belong to the trajectories of the left optic radiation, superior longitudinal fascicle I/II (SLF I/II), the parietooccipital connections, the cingulate bundle, and interhemispheric occipito-occipital connections (Fig. 4). The first three bundles connect the lateral occipital complex, superior parietal and superior frontal cortex with each other, which are the centers of the dorsal attention system [Corbetta and Shulman, 2002]. Thus, non-recovered neglect patients showed an alteration of connections wiring the dorsal attention system in the contralesional hemisphere that correlated with the spatial attention deficit. Such structural changes in the undamaged left hemisphere might be related to the hypofunction/hypometabolism of the left attention centers in acute neglect or a consequence of disruption of the functional connectivity between left and right visuo-spatial attention centers [Fiorelli et al., 1991; He et al., 2007; Perani et al., 1993; Umarova et al., 2011; Wilke et al., 2012]. Another affected fiber track, the cingulate bundle is considered to be attention relevant and is crucial for a wide range of motivational and emotional aspects of behavior, as well as for spatial working memory, which are all deficient in neglect [Husain et al., 1997; Malhotra et al., 2005; Mesulam, 1981; Schmahmann et al., 2007]. Similar to the present findings, Bozzali et al. showed widespread changes in diffusion indices in most left hemisphere tracts of neglect patients 1 to 6 months after stroke. They had a predominant involvement of the corpus callosum and its projections on the parietal white matter. A region of association between severity of neglect and brain FA values was found in the posterior part of the corpus callosum [Bozzali et al., 2012]. This study was however made in eight patients with chronic neglect and did not perform fiber tracking to explore the affected networks.

The rapidly recovered patients did not differ in FA-values from healthy subjects or control patients without neglect, but they did differ from those with non-recovered neglect. The latter showed FA-reduction in the left inferior parietal lobule that strongly and negatively correlated with the severity of neglect at the time of imaging. This region of reduced FA belonged to the left arcuate fascicle/superior longitudinal fascicle III, which connects temporo-parietal junction and inferior parietal cortex with the posterior inferior frontal gyrus (Fig. 5), and thus provides the link within the left analogue of the ventral attention system [Bartolomeo et al., 2007; Schmahmann et al., 2007; Umarova et al., 2010]. Since FA-changes are considered to indicate the structural aspects of neuroplasticity [Sagi et al., 2012; Zatorre et al., 2012], the analogue of the ventral attention system in the left hemisphere might play an important role in the early recovery from neglect.

The intriguing question is why patients with non-recovered neglect did not differ significantly from the control patients without neglect, but did from those with rapid recovery. Our previous data showed that the better visuospatial performance in patients with neglect in acute

stroke is associated with the activation of the attention centers in the left hemisphere [Umarova et al., 2011]. As shown in the PET-study, the recovery process in patients with rapid recovery might be also supported by the left attention centers leading to the FA-increase thereafter [Perani et al., 1993]. These FA-changes were significant compared with the nonrecovered neglect but still not strong enough to be differ from the control patients (Supporting Information Fig. S2). The last ones did not have spatial attention deficit, and thus the plasticity processes in the left attention centers might not be presented. This could explain why non-recovered neglect patients differed less from those without neglect and more from those with rapid recovery. However, this hypothesis should be further confirmed by the longitudinal functional studies in acute neglect.

The exploratory regression analysis revealed that the dependency between FA-values and NegScore 2 could be well explained by a logarithmic function. This is to be explained by the almost linear negative dependency between FA and spatial attention function in patients with no or mild to moderate neglect, as described previously in healthy subjects for spatial learning and memory [Sagi et al., 2012]. In contrast, patients with severe neglect had FA-values at a consistently low level and thus showed no further negative association between neglect severity and FA decline.

The present study showed for the first time that neglect is associated with altered structural connectivity distant from the lesion already early after stroke. Although the effects of the structural and functional reorganisation in the ipsilesional right hemisphere should not be underestimated, the present data do demonstrate the structural reorganisation within the distributed attention network in the contralesional hemisphere correlating with the extent and persistence of neglect. It is impossible to separate whether the identified changes causally influence neglect recovery or if they are a consequence of neglect being the direct effect of lesion size, its anatomy, genetic or even demographic factors; but the present data showed connections could be involved in the recovery process. Neglect is thus the result of disintegration of the spatial attention network [Mesulam, 1981]. Here we illustrated the relevance of this disintegration even in the hemisphere unaffected by stroke and demonstrated for the first time the functional-structural correlates in acute neglect.

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