Damage to White Matter Pathways in Subacute and Chronic Spatial Neglect: A Group Study and 2 Single-Case Studies with Complete Virtual "In Vivo" Tractography Dissection

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The exact anatomical localization of right hemisphere lesions that lead to left spatial neglect is still debated. The effect of confounding factors such as acute diaschisis and hypoperfusion, visual field defects, and lesion size may account for conflicting results that have been reported in the literature. Here, we present a comprehensive anatomical investigation of the gray- and white matter lesion correlates of left spatial neglect, which was run in a sample 58 patients with subacute or chronic vascular strokes in the territory of the right middle cerebral artery. Standard voxel-based correlates confirmed the role played by lesions in the posterior parietal cortex (supramarginal gyrus, angular gyrus, and temporal–parietal junction), in the frontal cortex (frontal eye field, middle and inferior frontal gyrus), and in the underlying parietal–frontal white matter. Using a new diffusion tensor imaging-based atlas of the human brain, we were able to run, for the first time, a detailed analysis of the lesion involvement of subcortical white matter pathways. The results of this analysis revealed that, among the different pathways linking parietal with frontal areas, damage to the second branch of the superior longitudinal fasciculus (SLF II) was the best predictor of left spatial neglect. The group study also revealed a subsample of patients with neglect due to focal lesion in the lateral–dorsal portion of the thalamus, which connects the premotor cortex with the inferior parietal lobule. The relevance of fronto-parietal disconnection was further supported by complete in vivo tractography dissection of white matter pathways in 2 patients, one with and the other without signs of neglect. These 2 patients were studied both in the acute phase and 1 year after stroke and were perfectly matched for age, handedness, stroke onset, lesion size, and for cortical lesion involvement. Taken together, the results of the present study support the hypothesis that anatomical disconnections leading to a functional breakdown of parietal–frontal networks are an important pathophysiological factor leading to chronic left spatial neglect. Here, we propose that different loci of SLF disconnection on the rostro-caudal axis can also be associated with disconnection of short-range white matter pathways within the frontal or parietal areas. Such different local disconnection patterns can play a role in the important clinical variability of the neglect syndrome.

Keywords: anatomy, diffusion tensor imaging, human, spatial neglect, stroke

Introduction

In humans, spatial neglect is a debilitating neurological condition that is frequently associated with stroke in the right hemisphere (Gainotti et al. 1972; Oxbury et al. 1974; Weintraub and Mesulam 1987). Patients with neglect have reduced or no attention to events occurring in the contralesional side of extrapersonal (i.e. visual and auditory), personal (i.e. somatosensory), or representational (i.e. imagery space, Mesulam 1981) space and may fail to produce movements toward the unattended space (i.e. motor neglect). The cognitive resources of neglect patients are pathologically biased toward the ipsilesional right side of space, so that events taking place in the contralesional left side of space fail to receive full cognitive processing and to reach patients' awareness. Based on this acquired lack of awareness for one side of space, the study of the anatomical correlates of spatial neglect is considered an important source of evidence for the understanding of the anatomical foundation of consciousness and attention.

Since original seminal case reports (Brain 1941; Paterson and Zangwill 1944; Mcfie et al. 1950), spatial neglect has been classically interpreted as a "parietal sign" (Critchley 1953; Vallar and Perani 1986). However, ensuing investigations pointed out that spatial neglect can also arise from damage to frontal areas (Heilman and Valenstein 1972; Damasio et al. 1980; Mesulam 1981; Stein and Volpe 1983; Husain and Kennard 1996 1997; Husain et al. 2000) to the thalamus (Watson and Heilman 1979; Cambier et al. 1980; Watson et al. 1981; Graff-Radford et al. 1985; Hirose et al. 1985; Bogousslavsky et al. 1986; Motomura et al. 1986; Vallar and Perani 1986; Waxman et al. 1986; Rafal and Posner 1987; Kumral et al. 1995; Chung et al. 1996; Leibovitch et al. 1998; Karussis et al. 2000; Karnath et al. 2002; De Witte et al. 2008) and to subcortical gray matter nuclei. Due to the diffuse connections of subcortical gray matter nuclei with the cortical mantle, in this latter case, spatial neglect has been interpreted as originating from widespread reduction in the functioning of parietal and frontal areas connected with damaged subcortical nuclei. (Hier et al. 1977; Damasio et al. 1980; Healton et al. 1982; Stein and Volpe 1983; Ferro et al. 1987; Perani et al. 1987; Caplan et al. 1990; Weiller et al. 1990; Donnan et al. 1991; Weiller et al. 1993; Kumral et al. 1995; Chung et al. 1996; Leibovitch et al. 1998; Karnath et al. 2002).

More recently, anatomical (Leibovitch et al. 1998; Doricchi and Tomaiuolo 2003; Bartolomeo et al. 2007), neurosurgical (Thiebaut de Schotten et al. 2005; Shinoura et al. 2009) and functional magnetic resonance imaging (fMRI) investigations (He et al. 2007) have provided converging evidence, suggesting that disconnection of long-range white matter

fiber bundles connecting parietal with frontal areas has a relevant role in engendering severe and chronic signs of spatial neglect both in humans and in monkeys (Gaffan and Hornak 1997). These findings provided new vigor to pioneering views by Critchley (1953), Geschwind (1965), and Mesulam (1981), who suggested that enduring lack of awareness for the left side of space can be influenced in a substantial way by damage to white matter connections in the right hemisphere.

One relevant and well-known clinical feature of the spatial neglect syndrome is its reduction in severity and incidence in the chronic when compared with the acute phase of the stroke. Although in the acute phase up to two-thirds of the right brain damaged patients can show spatial neglect signs, the majority of these patients show spontaneous recovery in the post-acute and chronic phase (Stone et al. 1992; Corbetta et al. 2005). In a recent report, using a cytoarchitectonic atlas based on postmortem staining of the myelin of coronal slices of the human brain (Bürgel et al. 2006), Karnath et al. (2009) concluded that damage of gray matter structures is a stronger predictor of acute spatial neglect than associative tract disconnection. However, these authors also commented that, in the acute phase, even small lesions can lead to temporary profound cerebral dysfunctions of large brain areas through mechanisms such as hypometabolism (Yasaka et al. 1998), hypoperfusion (Hillis et al. 2000), or acute diaschisis (Monakow 1914; Kempler et al. 1988; Price et al. 2001; Finger et al. 2004). Thus, the authors concluded that their study cannot decide whether or not spatial neglect should best be interpreted as a "disconnection syndrome" (Geschwind 1965; Watson et al. 1974; Mesulam and Geschwind 1978; Watson et al. 1978; Bartolomeo 2007; Doricchi et al. 2008) and further recommended conducting the same investigation with a large group of patients who have chronic injury.

A few case studies run with direct diffusion tensor imaging (DTI) tracking of white matter pathways have already suggested that fronto-parietal (Shinoura et al. 2009; Ciaraffa et al. 2012) or fronto-occipital disconnection (Urbanski et al. 2008 2011) can be a strong predictor of spatial neglect. However, the role of white matter disconnection in chronic spatial neglect has never been formally tested in large group of patients by using adequate statistical procedures to map the lesion involvement of relevant white matter tracts. The aim of the present study was therefore to evaluate and contrast the respective contributions of gray- and white matter damage to chronic spatial neglect in an adequately large sample of right brain damaged patients.

Studies of the effect of brain lesions on behavior frequently assume that discrete anatomical modules handle specific cognitive functions (Rorden and Karnath 2004). Consequently, analyses to determine the behavioral implications of brain lesions are performed via statistical tests completed independently at each of the intersubjects aligned voxel (voxel-wise or topological statistics), without any attempt to capture correlations across them (Catani 2007; Husain and Nachev 2007). However, 2 voxels should be considered as correlated if they share common anatomical features. While 2 distant voxels cannot share the same neuronal soma, several voxels can pertain to the same axon. Therefore, while the architecture of the cortex and the subcortical nuclei is well suited for voxel-wise statistics, the study of white matter organization requires adapted statistics at the tract level (track-wise or hodological

statistics; Catani and Mesulam 2008; Rudrauf et al. 2008; Thiebaut de Schotten et al. 2008). Track-wise statistics require anatomical knowledge on how voxels in the white matter are associated in common pathways.

Several atlases make this anatomical information now available, but each of them has both advantages and disadvantages. Tracing studies in monkeys provide astonishing details of the white matter organization (Schmahmann and Pandya 2006); however, the precise identification of the homologous structures in human is not straightforward (Thiebaut de Schotten et al. 2012). The human postmortem atlas (Bürgel et al. 2006), used by Karnath et al. (2009), offers high-quality resolution of white matter tracts running parallel to coronal slices used for myelin staining such as the cortico-spinal tract; however, as stressed by Bürgel et al. (2006), this technique strongly underestimates parietal–frontal association pathways that run orthogonally to coronal slices (Bürgel et al. 2006; Thiebaut de Schotten, ffytche, et al. 2011). Importantly, such tracts include some of the crucial pathways whose damage might be important to spatial neglect, such as the superior longitudinal fasciculus (SLF) and the inferior fronto-occipital fasciculus (IFOF). To circumvent these limitations, in the present study, we used an atlas of white matter connections based on DTI dissection of the human brain. Despite some limitation in the resolution of tracts that cross between each other (Jones 2008; Dell'acqua et al. 2010), DTI atlases provide a representative description of the anatomy and variability of the association tracts in the human living brain, giving the opportunity to measure in vivo white matter pathways location, asymmetry and intersubject variability on large populations of patients (Catani et al. 2007; Lawes et al. 2008; Mori et al. 2008; Thiebaut de Schotten, ffytche, et al. 2011).

To investigate the role of gray- and white matter damage in spatial neglect, we used voxel-wise and track-wise regressions. Since it has been suggested that the chronicity and severity of spatial neglect can increase with the size of the brain damage (Levine et al. 1986; Perani et al. 1987), as well as with the presence of an associated visual field defect (Halligan et al. 1990; Doricchi and Angelelli, 1999; Doricchi et al. 2005), we covaried both of these factors out from the analyses.

To summarize, in a first step, we used a classical voxel lesion symptom mapping (VLSM) approach in order to allow a direct comparison with data previously gathered from samples of acute patients (Karnath et al. 2009). In a second step, we employed regression to reveal the location of the brain lesions and the pattern of disconnection that correlate with the occurrence of chronic spatial neglect; right deviation in line bisection and omissions in cancellation tasks covarying out the effect of the lesion size and the presence of an associated visual field defect. Gray matter correlates were studied using a voxel-wise approach that better fits the architecture of the cerebral cortex and the subcortical nuclei. White matter correlates were studied by using a track-wise statistical approach that takes into consideration how different voxels are associated along the same white matter pathway.

During the completion of the group study, we had the rather unique opportunity of performing a complete tractography dissection of white matter fiber tracts in 2 patients who were perfectly matched on all relevant clinical variables (i.e. lesion size, lesion location, stroke onset, sex, age, handedness, educational level), except for the presence or absence of spatial neglect both in the acute and chronic phase. As it will

be shown in the following, direct and complete tractography dissection of these 2 cases added further evidence converging with the main results from the group study.

Materials and Methods

Group Study

Participants

Fifty-eight patients with a vascular stroke in the territory of the middle cerebral artery (MCA) in the right hemisphere participated in this study. Written and informed consent to participate to this research was obtained. The ethics committee of the Santa Lucia Hospital in Rome, Italy approved the study. Chronic visual field defects were assessed by Goldmann perimetry. Seven patients were found to have chronic visual field defects. Left spatial neglect was assessed with the line bisection test (5 trials, line length = 200 mm, cut-off score +6.5 mm; Azouvi et al. 2002) and the letter cancellation task (Diller et al. 1974; cut-off score left minus right omissions = >4; Pizzamiglio et al. 1989). All task stimuli were presented on a horizontally oriented A4 paper sheet. Thirty-eight patients were found to have varying degrees of left unilateral neglect (N+) on both tasks, whereas 20 patients were free from neglect signs (N−). The 2 groups were comparable for age ($t_{(56)}$ = 0.9, P = 0.3) and time of stroke onset ($t_{(56)}$ = 1.8, P = 0.18). As expected, N+ had a larger ipsilesional bias both in line bisection ($t_{(56)}$ = 5.1, P < 0.0001) and letter cancellation ($t_{(56)}$ = 7.6, P < 0.0001) than N−. On average, lesion size was higher in N+ when compared with N− ($t_{(56)}$ = 4, P < 0.001). Clinical and demographic data are reported in Table 1.

Individual Lesion Mapping

Ten of the 38 N+ patients and 5 of the 20 N− patients had CT scan examination. The remaining patients underwent radiological 1.5-T MRI examination, including T1, T2, fluid attenuated inversion recovery, and diffusion images. Radiological examination was run within 10 days from the time of neuropsychological testing. Mapping of lesions was performed using DISPLAY (http://packages.bic.mni.mcgill.ca). For each patient, we rotated the MNI template (Montreal Neurological Institute, MNI) from the MNI space to the orientation of the patients individual clinical MRI or CT slices scan. The lesion was then drawn on the reoriented template by an expert neuroanatomist and subsequently taken back to the MNI space using the inverse rotation (Doricchi and Tomaiuolo 2003).

General Voxel Lesion Symptom Mapping Analysis (Classic Approach)

In a first step, we used a classical VLSM approach in order to allow a direct comparison with data previously gathered from samples of acute patients (Karnath et al. 2009). We used MRIcron (www.sph.sc.edu/comd/rorden/mricron) to compute a Brunner Munzel test between the lesions of the spatial neglect group and the group of patient without spatial neglect for each voxel of the brain (Rorden et al. 2007). The results are corrected for multiple comparisons with a false discovery rate threshold (Genovese et al. 2002) and projected on a high-resolution template (Holmes et al. 1998) in the MNI using MRIcron (www.sph.sc.edu/comd/rorden/mricron).

Voxel-wise "Topological" Lesion-Deficit Analysis

We used MRIcron to compute regressions (Karnath et al. 2004; Rorden and Karnath 2004) in order to identify cortical areas that predicted whether a patient belonged or not to the N+ group (i.e. spatial neglect present or absent on both line bisection and letter cancellation tasks: A binary measure), cortical areas that predicted the degree of ipsilesional-rightward deviation in the line bisection task (a continuous measure of spatial neglect severity), and areas that predicted the number of omissions in the letter cancellation task (a continuous measure of spatial neglect severity). This approach identifies predictive regions by covarying out confounding factors such as, for example, the lesion size or the presence of chronic visual field defect. Time from stroke onset, that was not statistically different between N+ and N−, though numerically longer by 50 days in the N+ group (Table 1), did not need to be considered as a covariate in the analysis. This is because: 1) using stroke onset as a covariate would reveal the anatomical correlates of neglect independently of chronicity, contrary to the aims of our study; 2) differences in stroke onset time cannot account for our results, because it is logical to assume that N− patients, who did not show signs of neglect at an average of 70 days from onset, would not have turned into N+ patients at a longer time interval.

A first logistic regression used 3 independent variables: Lesion volume (a continuous measure), the presence or absence of visual field defects (a binary measure), and whether or not each single voxel ($1 \times 1 \times$ mm) was damaged in each patient (a binary measure). We then calculated whether these 3 variables were able to predict the presence of chronic spatial neglect (the dependent variable and a binary measure).

A second linear regression used 3 independent variables: Lesion volume, the presence or absence of chronic visual field defects and whether or not the target voxel was damaged in each individual. We then calculated whether these 3 variables were able to predict the degree of ipsilesional-rightward deviation in line bisection (a continuous measure).

For the cancellation task, we used the same approach to identify cortical areas that have a predictive value for the number of omissions in the letter cancellation task (a continuous measure).

Track-wise "Hodological" Lesion-Deficit Analysis

We used a recently published DTI atlas (Thiebaut de Schotten, ffytche, et al. 2011) to describe the pattern of disconnection induced by each lesion at the individual level. The atlas provides a probability in the MNI for each voxel belonging to a specific track. When a patient's lesion overlapped on a voxel with a probability superior to 50% to contain a given tract (above chance level), we considered this tract to be disconnected. We used SPSS software (SPSS, Inc., Chicago, IL, United States of America) to compute regressions to identify the tracks whose lesion had a predictive value, after excluding confounding factors such as the presence of chronic visual field defects and the lesion size. Stroke onset was not considered as a covariate.

A first logistic regression used 3 independent variables: Lesion volume (a continuous measure), the presence or absence of chronic visual field defects (a binary measure), and whether or not the target tract was damaged in each patient (a binary measure). We then calculated whether these 3 variables were able to predict the presence of chronic spatial neglect (the dependent variable and a binary measure).

As a control analysis, we performed a second logistic regression by using the presence or absence of spatial neglect, lesion size, and whether or not the target tract was damaged in each individual as independent variables to calculate whether these variables were able to predict the presence of chronic visual field defects.

We then used linear regression to identify the tracks that had a predictive value for right deviation in line bisection and omissions in letter cancellation, after excluding confounding factors such as the presence of chronic visual field defects and the lesion size.

All track-wise hodological lesion-deficit results were subjected to Bonferroni correction for multiple comparisons (α level, P = 0.004).

Table 1

Clinical and demographic data of the groups of patients with (N+) and without (N−) left spatial neglect

	Age (years)	Stroke onset (days)	Line bisection (mm)	Letter cancellation (omissions)	Lesion size (cc)
N+ (n = 38)					
Mean	61.1	120	9.8	55.2	144.1
SD	12.3	113.7	7.1	29.5	116.4
N− (n = 20)					
Mean	57.6	70.4	1.1	3.4	34.8-
SD	13.7	59.3	3.1	3	37.9

SD, standard deviations.

Table 2
Study of the 2 single cases. Demographic and clinical data

	N +		N-	
Sex	M		M	
Age (years)	55		56	
Handedness	R		R	
Educational level (years)	13		13	
Lesion size	130.92		145.48	
Time Testing post-stroke	20 days	13 months	20 days	12 months
Line Cancellation	L 2/11 - R 10/10	L 5/11 - R 10/10	L 11/11 - R 10/10	L 11/11 - R 10/10
Letter Cancellation	L 0/53 - R 40/51	L 0/53 - R 41/51	L 53/53 - R 49/51	L 53/53 - R 49/51

Role of the Different SLF Branches in Spatial Neglect

We took advantage of a recently published atlas of the 3 branches of the SLF I, II, III (Thiebaut de Schotten, Dell'Acqua, et al. 2011) to report the pattern of disconnection induced by each lesion at the individual level by following the same track-wise hodological lesion-deficit described above. Results are presented after Bonferroni correction for multiple comparison (α level, $P = 0.0167$).

Single-Case Study

We had the opportunity to run standard and advanced DTI tractography in 2 patients who were perfectly matched on all clinical relevant variables, except for the presence or absence of spatial neglect signs both in the acute and chronic phase of their cerebrovascular stroke (detailed clinical data are reported in Table 2).

Standard Diffusion Tensor Tractography

We used a 3-T whole-body system (Siemens Allegra) to acquire 60 diffusion-weighted volume directions and height volumes with no diffusion gradient applied covering the whole head of the patient with an isotropic resolution of 2 mm³. At each slice raw diffusion-weighted data were simultaneously registered and corrected for subject motion and geometrical distortions using ExploreDTI (http://www.exploredti.com; Leemans and Jones 2009). The tensor model was fitted to the data using the Levenberg–Marquardt nonlinear regression (Marquardt 1963). The fractional anisotropy (FA) was estimated in each voxel by scaling the water diffusion orientation from zero (random diffusion) to one (one direction only; Basser and Pierpaoli 1996). Whole-brain tractography was performed using an interpolated streamline algorithm that propagates from voxel to voxel following a step length of 0.5 mm and a maximum angle threshold of 35°. Voxel showing an FA value inferior to 0.2 was excluded from the tractography (Jones et al. 2002; Jones 2003, 2004). The whole-brain tractography was imported to "TrackVis" (Wedeen et al. 2008; http://www.trackvis.org) using a home-made software written in Matlab 2009b (http://www.matworks.com). Region of interest (ROIs) were defined on the axial FA images and were used as starting regions for tracking. Unlike other methods that use cortical masks as starting regions, the approach adopted here defines ROIs around the areas of white matter that represent "obligatory passages" along the course of each tract. Hence, the use of obligatory passages as starting seed points for tracking allows to visualize all fibers of a single tract without constraining its cortical projections, which may vary from one subject to the other. Using the ROIs previously described in Catani and Thiebaut de Schotten (2008), we performed single dissections of commissural pathways (anterior commissure and the corpus callosum), projection pathways (cortico-spinal, cortico-ponto-cerebellar, and the fornix) and associative pathways (fronto-temporal, fronto-parietal, and parieto-temporal segments of the arcuate, cingulum, inferior longitudinal fasciculus, inferior occipito-frontal fasciculus, and uncinate fasciculus).

Advanced Spherical Deconvolution Tractography

Standard diffusion tensor tractography does not allow reconstructing the 3 branches of the SLF I, II and III (Thiebaut de Schotten, Dell'Acqua, et al. 2011) because of the crossing of the dorsal association fibers with commissural and projection fibers (Thiebaut de Schotten, Dell'Acqua, et al. 2011). Therefore, spherical deconvolution was chosen to estimate multiple orientations in voxels containing different populations of crossing fibers (Alexander 2006). A modified (damped) version of the Richardson-Lucy algorithm for spherical deconvolutions (Dell'acqua et al. 2010) was employed using the Software StarTrack (http://www.natbrainlab.com). Algorithm parameters were chosen as described before (Dell'Acqua et al. 2012). A fixed fiber response corresponding to a shape factor of $\alpha = 2 \times 10^{-3}$ mm²/s was chosen (Dell'acqua et al. 2012). Fiber orientation estimates were obtained by selecting the orientation corresponding to the peaks (local maxima) of the fiber orientation distribution (FOD) profiles. To exclude spurious local maxima, we applied an absolute and a relative threshold. A first "absolute" threshold was used to exclude small local maxima due to noise or isotropic tissue. This threshold is 3 times the amplitude of a spherical FOD obtained from a gray matter isotropic voxel. A second "relative" threshold of 8% of the maximum amplitude of the FOD was applied to remove the remaining local maxima with values greater than the absolute threshold (Dell'Acqua et al. 2009). Tractography dissection of the SLF I, II and III was performed using a multiple ROIs approach as previously described in Thiebaut de Schotten, Dell'Acqua, et al. (2011).

Results

Group Study

General Voxel Lesion Symptom Mapping analysis

The Brunner Munzel test between the lesions of the spatial neglect group (N+) and the group of patient without signs of spatial neglect (N−) revealed a significant difference ($P < 0.05$) localized mainly in the perisylvian white matter, but also involving other areas such as the posterior part of the middle and the inferior frontal gyri, the pre- and postcentral gyri, the temporo-parietal junction (TPJ; traditionally including supramarginal, angular, and posterior part of the superior temporal gyri), and the white matter just below the frontal eye fields (Fig. 1).

Voxel-wise Topological Lesion-Deficit Analysis

Previous voxel-wise investigations have rarely controlled for the effect of lesion size. A notable exception is the study by Karnath et al. (2004) who, however, showed that when lesion size is used as a regressor in the voxel-wise analysis, results do not survive correction for multiple comparisons. In line with this finding, also in our study, results lost most of their significance when lesion size was used as a covariate and correction for multiple comparisons was applied. To allow comparison with previous studies in the following, we report results not corrected for multiple comparisons. These anatomical findings were projected on a high-resolution template (Holmes et al. 1998) in the MNI by using MRIcron and are showed in Figure 2.

A logistic regression was performed to identify lesion loci crucial to the presence versus absence of spatial neglect (i.e.
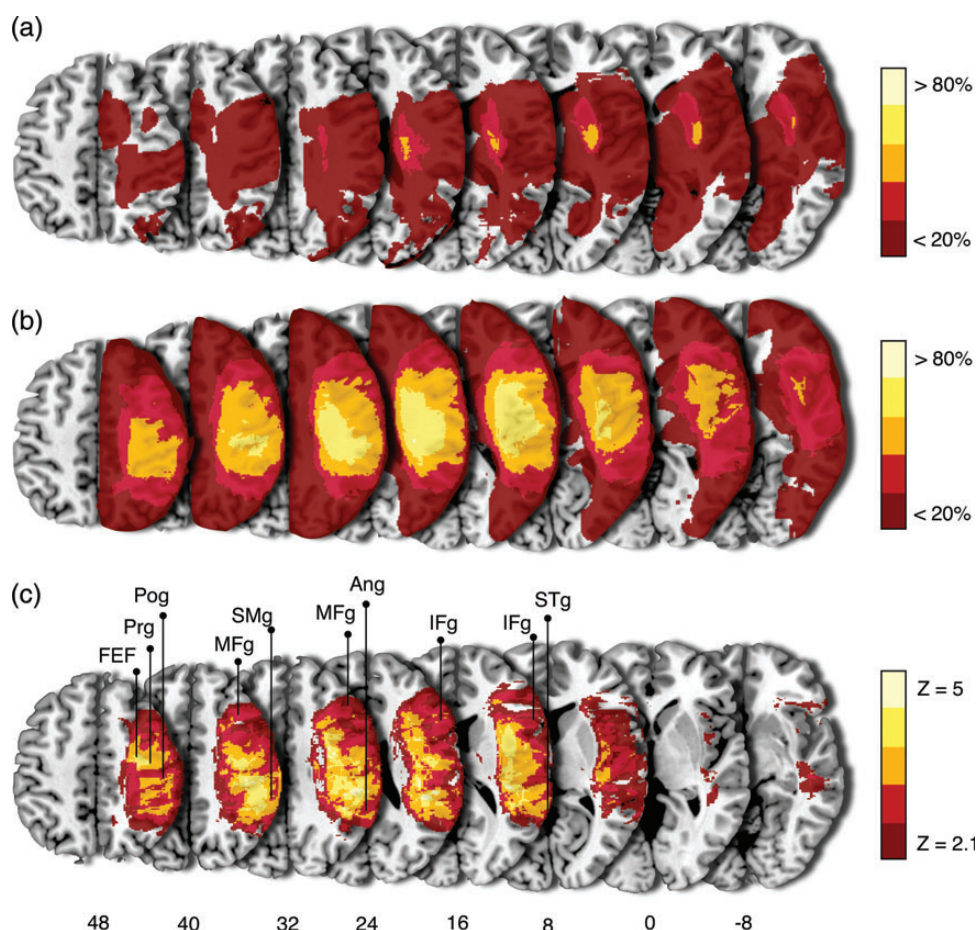
Figure 1. Overlay of lesions in (*a*) patients without left spatial neglect (N−; *n* = 20); (*b*) patients with left spatial spatial neglect (N+; *n* = 38); (*c*) statistical analysis comparing the 2 populations of patients (N+ vs. N−; results are corrected for multiple comparisons, *P* < 0.05 for *Z* > 2.1). Ang = angular gyrus; FEF = frontal eye field; IFg = inferior frontal gyrus; MFg = middle frontal gyrus; Pog = postcentral gyrus; Prg = precentral gyrus; SMg = supramarginal gyrus; STg = superior temporal gyrus.

binary measure) when covarying out the lesion size and the presence of visual field defect. The results (Fig. 2*a*) revealed that especially lesions in the white matter are significant predictors of spatial neglect. However, other areas were also critical (Fig. 2*a*): The supramarginal gyrus and the adjacent most posterior part of the superior temporal gyrus at the temporal–parietal junction [this latter temporal area should not be confounded with the most anterior–central sector of the superior temporal gyrus advocated by Karnath et al. (2001, 2004, 2011)], the intraparietal sulcus adjacent to the angular gyrus, and the superior parietal lobe and a small lesion spot in the frontal eye fields.

In agreement with previous evidence (Binder et al. 1992; Verdon et al. 2010; Aiello et al. 2012), the separate linear regressions performed, respectively, on the continuous measures of rightwards deviations in line bisection and omissions in the letter cancellation task, provided slightly different results. For the line bisection task, there was a significant involvement of several areas in the white matter and cortical areas such as the precentral gyrus ("hand-knob" region), the supramarginal gyrus, the middle and inferior frontal gyri (partes opercularis and triangularis), the temporal–parietal junction, the intraparietal sulcus between the angular gyrus and the superior parietal lobule, and 2 small lesion spots, that is, one in the superior parietal lobule and another in the frontal eye fields (Fig. 2*b*). The linear regressions performed

on the continuous measure of omissions in the letter cancellation task revealed no relevant involvement of parietal areas and a significant implication of the dorsal sectors of the middle frontal gyrus, the white matter just below the frontal eye field, the precentral gyrus (hand-knob region), the adjacent postcentral area, a lesion spot including the posterior portion of middle and inferior temporal gyri (extrastriate cortex), and the underlying white matter.

Track-Wise or Hodological Lesion-Deficit Analysis
Here, except when specifically indicated, we report results that survived the Bonferroni correction for multiple comparisons. A logistic regression was performed to identify tracks crucial to left spatial neglect when covarying out the lesion size and the presence of chronic visual field defect. The analysis revealed that disconnection of the fronto-parietal segment of the arcuate fasciculus (β = 3.782, *P* = 0.002) was a significant predictor of spatial neglect (Fig. 3*a*). The analysis also disclosed an involvement of the fronto-temporal segment of the arcuate fasciculus (β = 2.4, *P* = 0.007), although this result did not survive to Bonferroni correction. As a control, we performed an identical analysis to identify tracks dedicated to chronic visual field defect, after covarying out the lesion size and the presence of spatial neglect. As anticipated, disconnection of the optic radiations resulted to be a significant
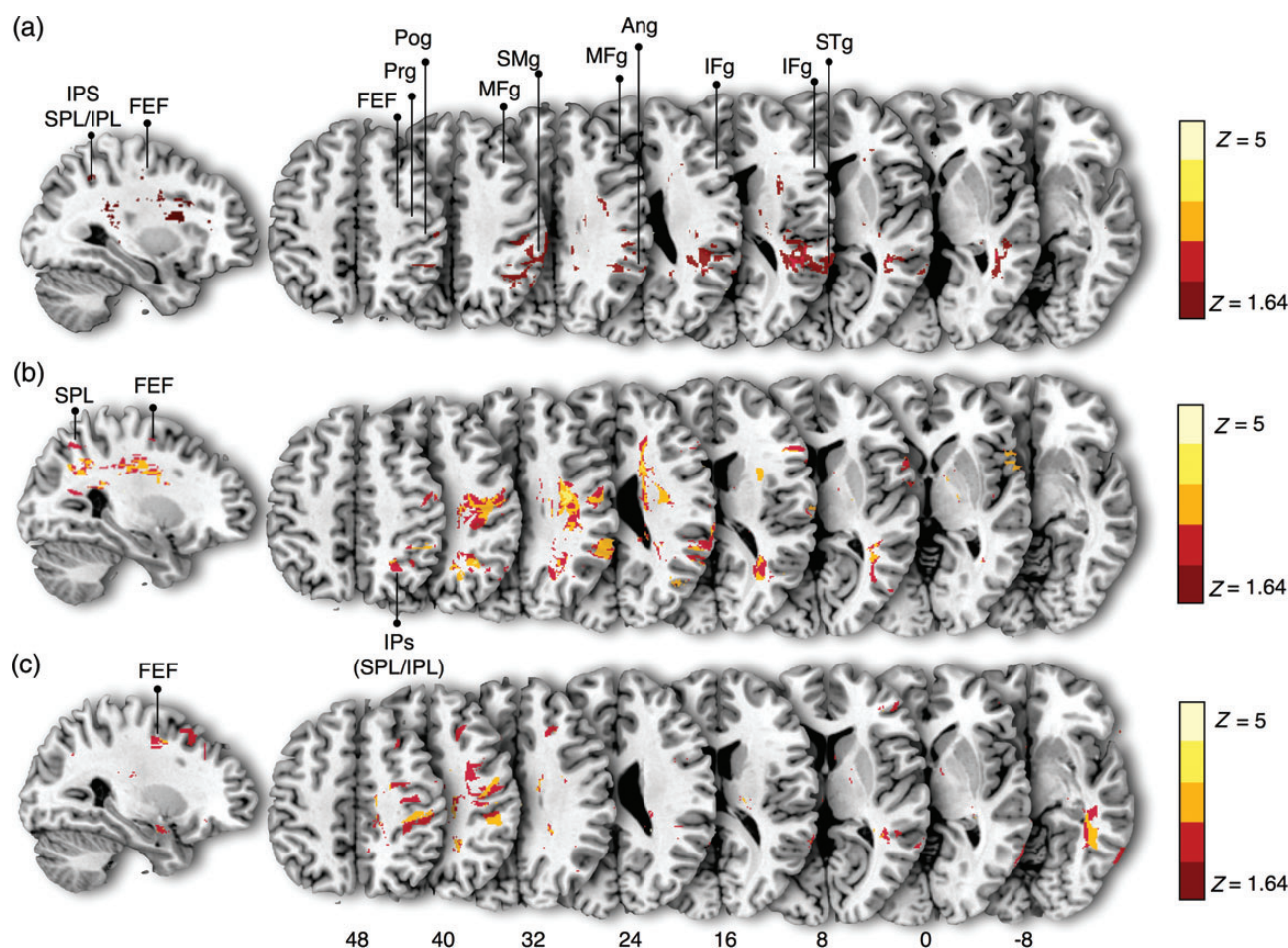
Figure 2. Voxel-wise (topological) lesion-deficit analysis. (*a*) MNI voxels predicting the presence versus absence of left spatial neglect (binary measure) when covarying out the presence of chronic visual field defect and lesion size. (*b*) Damaged MNI voxels predicting the severity of ipsilesiona-rightward deviation in line bisection (continuous measure) when covarying out the presence of chronic visual field defect and lesion size. (*c*) Damaged MNI voxels predicting omissions in the letter cancellation task (continuous measure) when covarying out the presence of chronic visual field defect and lesion size. Results are not corrected for multiple comparisons ($P < 0.05$ for $Z > 1.64$). Ang = angular gyrus; FEF = frontal eye field; IFg = inferior frontal gyrus; IPL = inferior parietal lobule; IPS = intraparietal sulcus; MFg = middle frontal gyrus; Pog = postcentral gyrus; Prg = precentral gyrus; SMg = supra marginal gyrus; SPL = superior parietal lobule.

predictor of chronic visual field defects ($\beta = 3.031$, $P = 0.003$; Fig. 3*b*).

For line bisection, linear regression covarying out the lesion size and the presence of chronic visual field defects revealed that disconnection of the fronto-parietal segment of the arcuate fasciculus ($\beta = 0.576$, $P = 0.00002$) was a significant predictor for rightward deviations on line bisection (Fig. 3*c*).

For the cancellation task, multinomial regression, after covarying out lesion size, revealed that disconnection of the fronto-parietal segment of the arcuate fasciculus ($\beta = 0.403$, $P = 0.001$) was a significant predictor of omissions on the cancellation task (Fig. 3*d*).

The Role of Distinct SLF Branches in Spatial Neglect

A logistic regression analysis was run to investigate the specific involvement of each of the SLF branches (SLF I, II, and III) in spatial neglect (Fig. 4*a*). The initial results from this analysis showed that SLF II disconnection was the most likely lesion to predict chronic spatial neglect ($\beta = 2.334$, $P = 0.004$). SLF III disconnection also significantly resulted ($\beta = 1.621$, $P = 0.023$), but this result did not survive Bonferroni correction for multiple comparisons.

Linear regression analyses were run to investigate the possible specific involvement of each of the 3 SLF branches in the line bisection and letter cancellation tasks. For line bisection, multinomial regression when covarying out the lesion size and the presence of visual field defect, confirmed that disconnection of the SLF II ($\beta = 0.536$, $P = 0.0002$) was a significant predictor for rightwards deviations in line bisection (Fig. 4*b*). SLF III was also significantly reported ($\beta = 0.314$, $P = 0.017$), but this result did not survive Bonferroni correction for multiple comparisons. For the cancellation task, the multinomial regression revealed that disconnection of the SLF II ($\beta = 0.349$, $P = 0.002$) was a significant predictor of omissions, when covarying out the lesion size. SLF I was also significantly involved ($\beta = 0.245$, $P = 0.02$), but this result did not survive Bonferroni correction for multiple comparisons (Fig. 4*c*).

Lesion Localization in Spatial Neglect Patients without Parietal–Frontal Disconnection

Interestingly, 7 of the 38 patients showing chronic spatial neglect did not show neuroimaging signs of fronto-parietal disconnection. These patients had smaller lesions when compared with spatial neglect patients with parietal–frontal
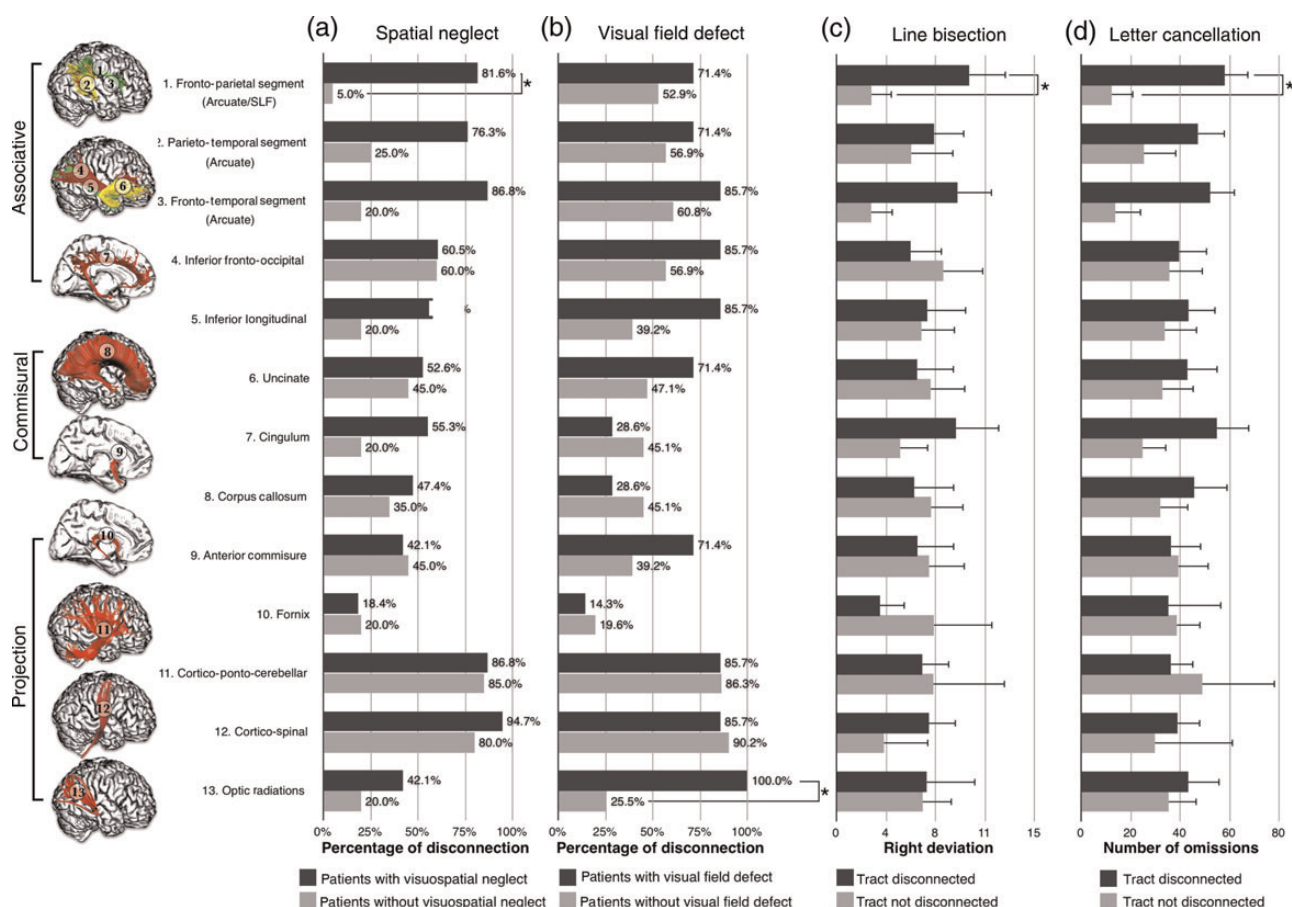
Figure 3. Track-wise (hodotopic) lesion-deficit analysis. (*a*) Percentages of patients with and without left spatial neglect, with disconnection of each of the examined white matter tracts. (*b*) Percentage of hemianopic patients and patients without visual field defects, with disconnection of each of the examined white matter tracts. (*c*) The performance on the line bisection task (mean deviation with 95% confidence intervals) for patients with or without disconnection of each of the examined white matter tracts. (*d*) The performance on the letter cancellation task (mean omissions with 95% confidence intervals) for patients with or without disconnection of each of the examined white matter tracts. *Tracts significantly involved when covarying out the presence of chronic neglect and the lesion size. Only results that survived Bonferroni correction are reported.
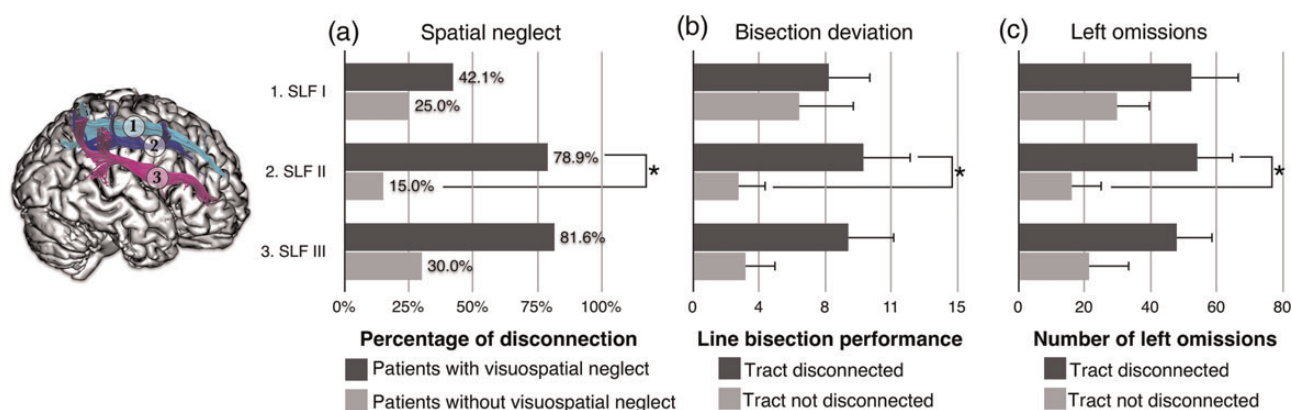

Figure 4. SLF disconnection. (*a*) Percentage of patients with and without left spatial neglect with disconnection of SLF I, II, and III. (*b*) The performance on the line bisection task (mean deviation with 95% confidence intervals) for patients with or without disconnection of each of the 3 different branches of the SLF (I, II, and III). (*c*) The performance in the letter cancellation task (mean omissions with 95% confidence intervals) in patients with or without disconnection of each of the 3 different branches of the SLF (I, II, and III). Asterisks indicate SLF branches showing significant lesion involvement after covarying out the presence of visual field defect and lesion size. Only results that survived Bonferroni correction are presented.

disconnection ($t_{(36)} = 3.421$, $P = 0.001$). Six of these 7 patients had no concomitant visual field defect. There were no significant differences between this subgroup and the fronto-

parietal one in performance on line bisection ($t_{(36)} = 1.205$, $P = 0.235$) and cancellation tasks ($t_{(36)} < 1$). In this small group, we performed a simple overlap of individual lesions
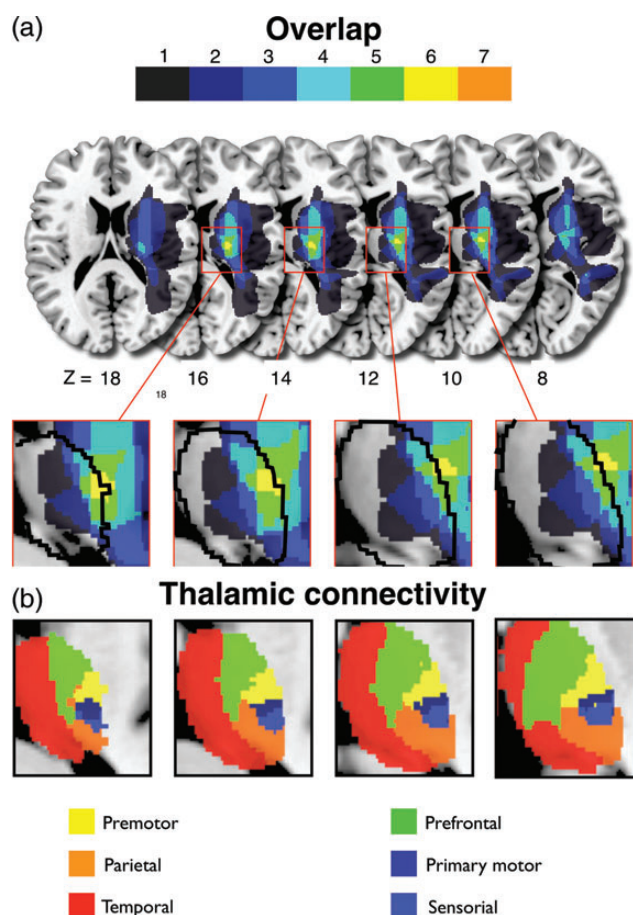
Figure 5. (*a*) Overlay of lesions in neglect patients without fronto-parietal disconnection. (*b*) Tractography atlas of the connectivity-based segmentation of the thalamus (Behrens et al. 2003).

(Bates et al. 2003). Based on a tractography atlas of connectivity-based segmentation of the thalamus (Behrens et al. 2003; FSL 4.1 software package; http://www.fmrib.ox.ac.uk/fsl), we found that individual lesions overlapped within the latero-dorsal portion of the thalamus (Fig. 5). This part of the thalamus has strong connections with the premotor cortex (Behrens et al. 2003).

Single-Case Study

The 2 patients considered in this study showed minor differences in the pattern of cortical damage, with the superior temporal and the inferior frontal gyri being partially preserved in the spatial neglect patient and almost entirely damaged in the non-neglect patient (Fig. 6). Lesion volume was slightly higher in the non-neglect patient (Table 2). Figure 7 shows the reconstruction of the posterior segment, the inferior longitudinal fasciculus, and the cingulum for the 2 patients. Both patients had comparable partial disconnection of the corpus callosum and a complete disconnection of the IFOF and the uncinate fasciculus. The patient with spatial neglect had an additional disconnection of the fronto-parietal segment and the fronto-temporal segment of the arcuate fasciculus and disconnection of the cortico-ponto-cerebellar tract, which were instead normally reconstructed in the non-neglect patient. Advanced spherical tractography of the SLF I, II, and III revealed that both patient had

preserved SLF I and damaged SLF III. SLF II was solely damaged in the spatial neglect patient (Fig. 8).

Discussion

In this study, we used a recently published atlas of human brain connections (Thiebaut de Schotten, ffytche, et al. 2011; Catani and Thiebaut de Schotten 2012) to formally test, in a relatively large sample of the right brain damaged patients, whether lesion of white matter parietal–frontal pathways is a relevant anatomical determinant in the persistence of left spatial neglect in the chronic phase of cerebrovascular stroke. Three main findings emerged from our investigation. First, the most reliable predictor of chronic spatial neglect was the disconnection of one of the branches of the SLF, that is, the SLF II. Additional support to this group study result came by the complete white matter tractography dissection run in 2 clinically matched patients, one with and the other without signs spatial neglect. Although both of these patients had lesions of similar cortical location and size, only the patient with subcortical parietal–frontal disconnection showed signs of spatial neglect both in the acute and in the chronic phase. Secondly, the most reliable predictor of chronic spatial neglect in the gray matter was damage to the middle frontal gyrus and/or the TPJ (i.e. the ventral attentional system) although, in some cases, the lesioned area extended to or was close to areas belonging to the dorsal attentional system, such as the frontal eye field and the superior parietal lobule (Shomstein et al. 2010). Thirdly, in the small subgroup of chronic spatial neglect patients who did not have neuroimaging signs of parietal–frontal disconnection, most lesions affected the latero-dorsal portion of the thalamus.

Spatial Neglect as Both a "Disconnective Breakdown" and a "Disconnective Syndrome"

The role of fronto-parietal white matter disconnection confirms, at an extended group level, evidence gathered from neurosurgical studies in the monkey (Gaffan and Hornak 1997) and from more recent neurosurgical, fMRI, and DTI investigations run in relatively small samples of human patients (Thiebaut de Schotten et al. 2005; He et al. 2007; Urbanski et al. 2008, 2011; Shinoura et al. 2009; Ciaraffa et al. 2012). Altogether, the present evidence supports the conclusions of previous lesion studies that, without beneficiating of the later development of tractography-based track-wise statistics, indicated a role of selective SLF disconnection (Doricchi and Tomaiuolo 2003) in human spatial neglect.

This converging evidence from different studies and methods suggests, rather homogenously, that cerebrovascular damage to long-range white matter parietal–frontal tracts is an important cause of spatial neglect. It is therefore important to discuss the possible pathophysiological mechanisms through which this type of lesion can engender chronic signs of spatial neglect in human patients. A neurological syndrome is usually interpreted as being purely disconnective, when cortical areas that get reciprocally disconnected by brain damage remain functionally and anatomically unaffected whereas any other function depending on their interaction is disrupted (Catani and Mesulam 2008). One might wonder whether this
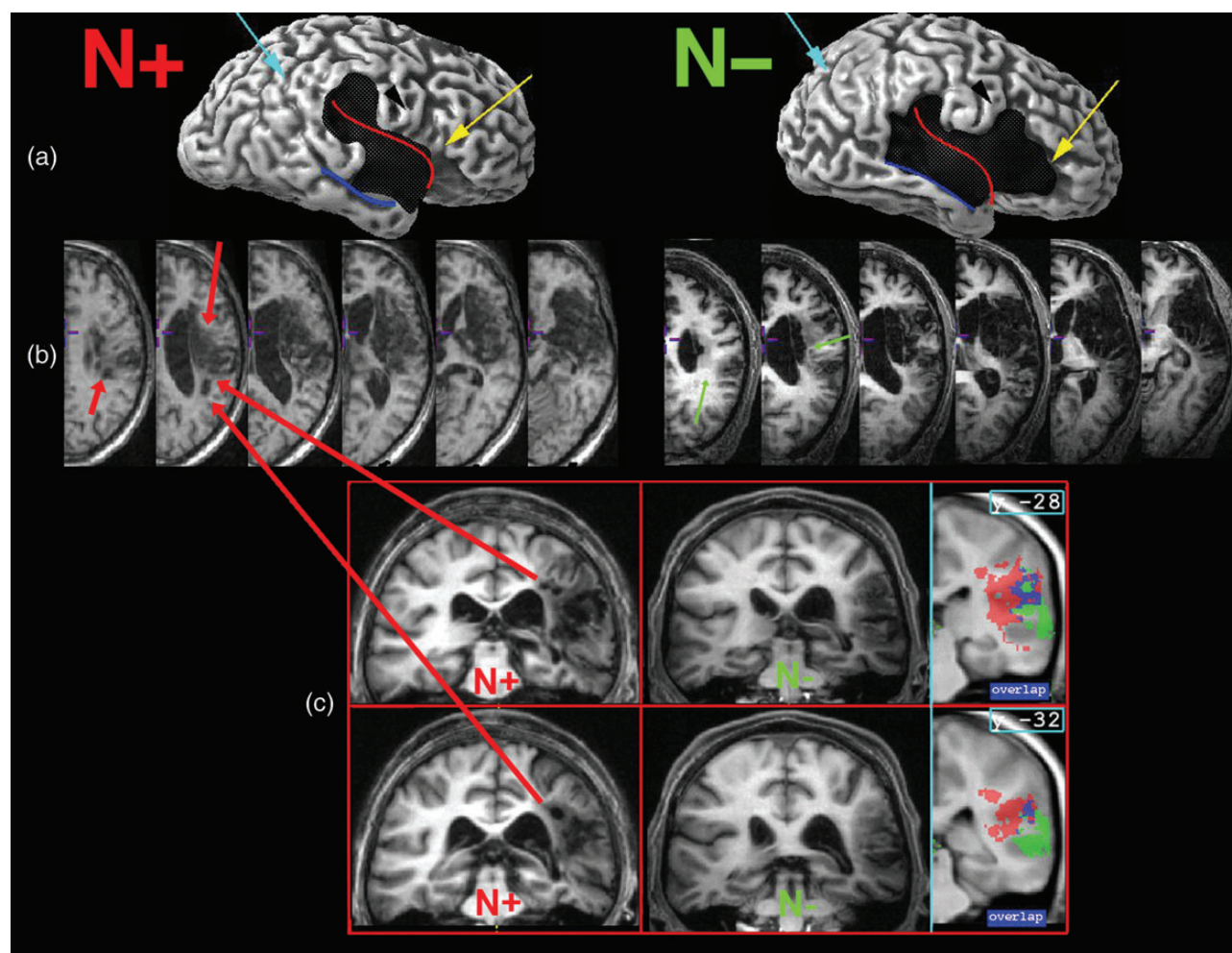
Figure 6. Study of the 2 single cases. (*a*) MRI-based reconstructions of the lesion for the patient with left spatial neglect (N+, top left) and for the patient without signs of neglect (N−, top right). The blue and red lines superimposed on the lateral views of the 3-dimensional reconstructions of the right hemisphere indicate the lateral (sylvian) sulcus and the superior temporal sulcus, respectively. The light blue and yellow arrows indicate the intraparietal sulcus and the vertical ramus of the sylvian fissure, respectively. (*b*) Axial sections showing the localization and extent of brain damage in the 2 patients. Red arrows indicate subcortical areas where the damage produced disconnection of parietal–frontal pathways in N+; green arrows indicate corresponding spared areas in N−. (*c*) Coronal sections passing at Y = −28 and Y = −32 (MNI coordinates) in N+ and N− patients. Red arrows indicate corresponding point of disconnection in coronal and transversal slices in N+ patient. On the rightmost column, the lesion of N+ is drawn in red and that of the N− patient in green. The overlap between the 2 lesions is shown in blue.

is the case for spatial neglect due to damage of parietal–frontal white matter pathways in the MCA territory. It has been suggested (Doricchi and Tomaiuolo 2003; Thiebaut de Schotten et al. 2005; Bartolomeo et al. 2007) that a lesion centered in the tightly packed parietal–frontal white matter fibers can be more disrupting than a cortical lesion of equivalent volume, because it can provoke widespread hypofunctioning of the whole network of interconnected cortical areas. In this sense, MCA spatial neglect could be better interpreted as a disconnective breakdown rather than a purely disconnective syndrome, that is, as resulting from dysfunction of large-scale cortical networks. Further converging evidence supporting this hypothesis comes from recent fMRI studies, demonstrating that the temporal correlation (i.e. functional connectivity) between the blood oxygenation level-dependent (BOLD) signals in ventral parietal (TPJ) and frontal areas (IFG–MFG) is crucially disrupted in spatial neglect patients (He et al. 2007).

It is noteworthy, however, that there are other cases in which neglect can be properly interpreted as a purely disconnective syndrome. Lesions in the right posterior cerebral artery (PCA) territory that cause disconnection of the splenium of the corpus callosum and concomitant damage of the adjacent right striate cortex with accompanying left hemianopia provoke severe left side visual neglect both in humans and in monkeys (Gaffan and Hornak 1997; Bird et al. 2006; Park et al. 2006; Tomaiuolo et al. 2010). Based on a pioneering neurosurgical modeling study run in the monkey, Gaffan and Hornak (1997) have proposed that in this case visual neglect is severe because splenial disconnection confines the visual input arriving from the seeing right visual field in the left hemisphere. Thus, this information cannot reach the anatomically intact attentional parietal–frontal network in the right hemisphere. As a consequence, no exploration of the left unseen hemifield is possible. This pathophysiological mechanism mirrors in the right hemisphere the anatomical–functional impairment that in the left hemisphere produces "pure alexia" without agraphia, a prototypical example of pure disconnective syndrome (Dejerine 1891, 1892; Catani and ffytche 2005), where interruption of callosal fibers conveying visual inputs
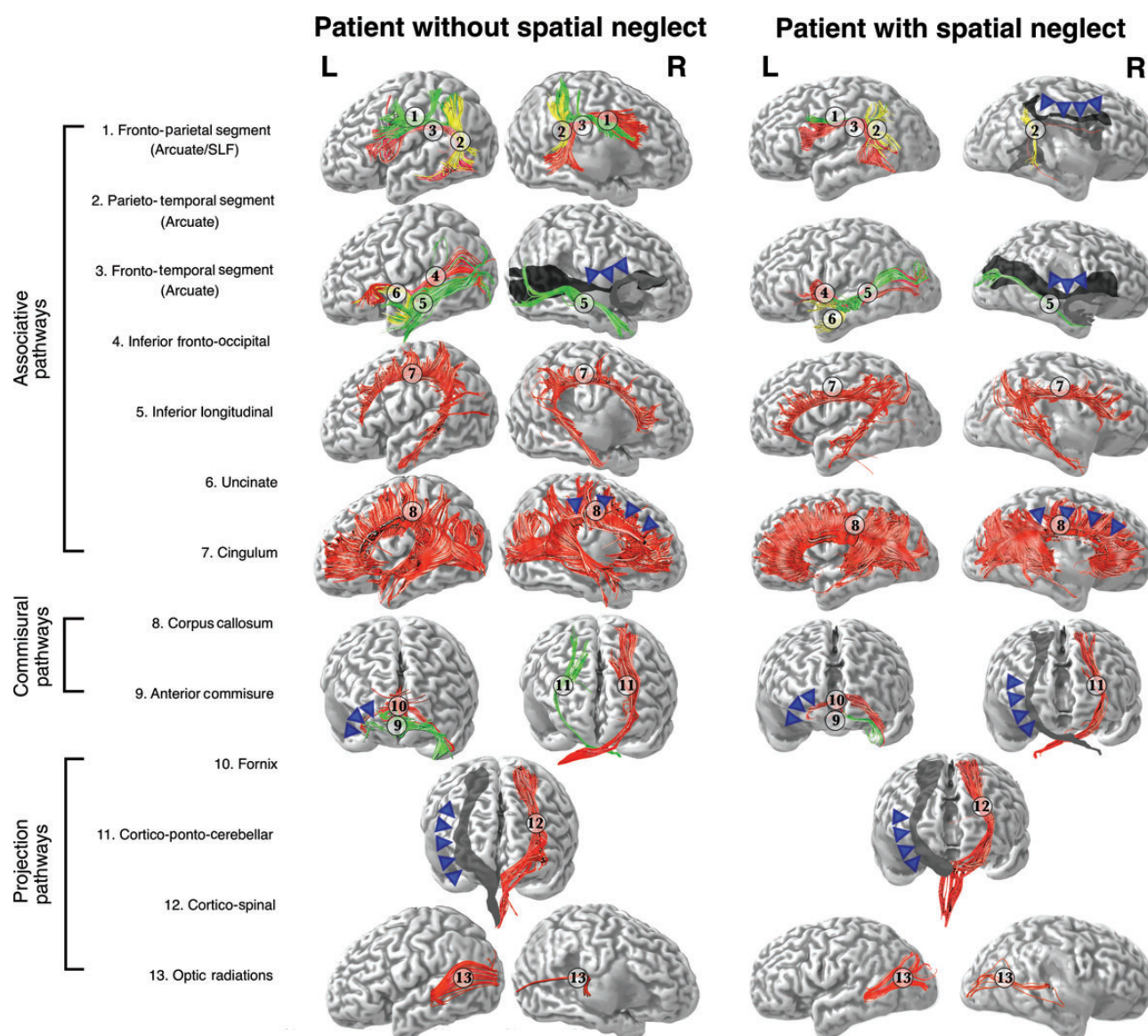
Figure 7. Complete DTI dissection of white matter fiber tracts in the 2 matched cases with (N+) and without (N−) visuospatial neglect. Disconnected tracts were manually drawn in gray.
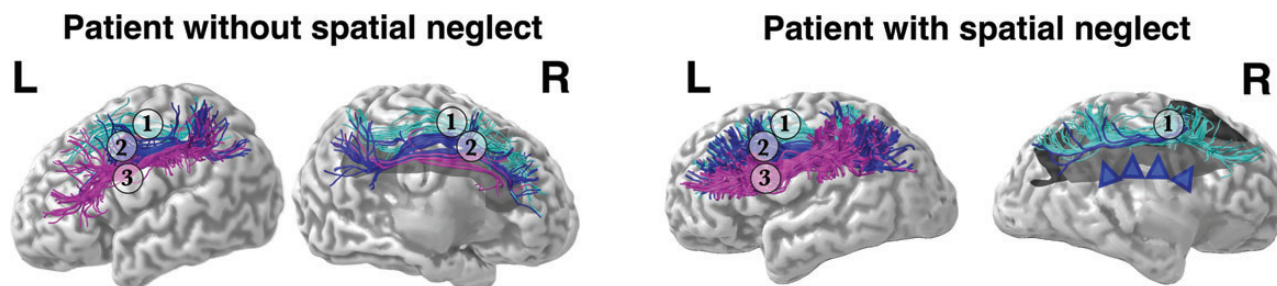

Figure 8. Spherical deconvolution dissection of white matter fiber tracts in the 2 matched cases with (N+) and without (N−) visuospatial neglect. Disconnected tracts were manually drawn in gray.

from the right hemisphere to language centers in the left hemisphere impairs reading with preserved visual and verbal functions. In the case of PCA neglect due to right splenial disconnection, the purely disconnective nature of the syndrome is further confirmed by the finding that in these patients neglect is restricted to the visual domain with no accompanying signs of personal, representational-imagery, or motor neglect (Tomaiuolo et al. 2010).
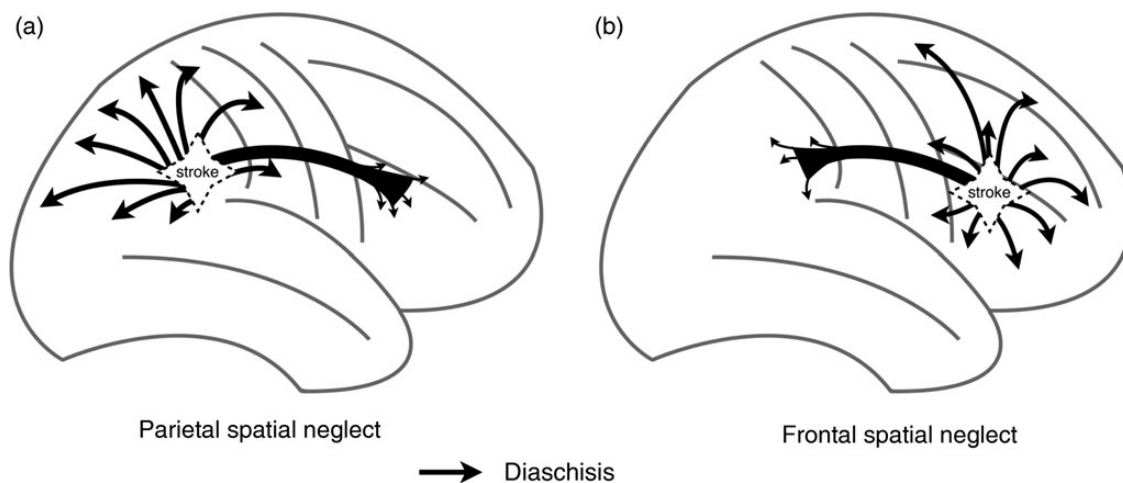
Figure 9. A diaschisis model of the symptomatological dissociation observed between left spatial neglect deriving from parietal or frontal strokes. (*a*) Parietal and (*b*) frontal strokes interrupting long-range parietal–frontal connections, and producing general hypoactivation of the parietal–frontal attentional network, can be associated with interruption of short-range connections causing local dysfunction of the neighboring areas in the parietal or in the frontal lobe.

The Contribution of "Long-Range" and "Short-Range" Disconnections in MCA Spatial Neglect

There is shared agreement that spatial neglect is not a unitary syndrome made up of a homogenous collection of symptoms (Doricchi et al. 2008; Verdon et al. 2010). Spatial neglect cannot only selectively affect different sectors of space (extra-personal vs. personal vs. representational space) or different spatial reference frames (egocentric vs. allocentric), but also different modes of spatial attentional processing as, for example, the simultaneous versus sequential analysis of spatial positions that are entailed by the line bisection and multiple item cancellation tasks, respectively (Binder et al. 1992). Based on this clinical evidence, recent research on the anatomical correlates of spatial neglect has moved from the study of the general anatomical correlates of the syndrome, toward the more focused study of the correlates of the specific clinical features characterizing different forms of the syndrome, or the different types of attentional disturbances associated with the spatial neglect syndrome (i.e. top-down vs. bottom up attention; Shomstein et al. 2010). Expanding on the original findings by Binder et al. (1992), Verdon et al. (2010) used the VLSM technique to demonstrate that different behavioral components of chronic spatial neglect are associated with lesion of different sectors of the right parietal–frontal attentional network. Consistent with original fMRI findings in healthy participants (Fink et al. 2000) and with the results from the present study, Verdon et al. (2010) identified a perceptual visuospatial component revealed by the performance on line bisection, text, and word reading tasks, and associated with lesions of the parietal lobe. By contrast, an exploratory visuomotor component revealed by the performance in sequential multi-item cancellations tasks and was associated with lesion of frontal areas. However, in each of these cases, lesion of the parietal and frontal components of the attentional network was associated with lesion involvement of the underlying white matter. This finding suggests that lesions encroaching upon long white matter connections do not only have diffuse disruptive effects on the entire right hemispheric network and that, depending on their relative posterior or anterior location (Doricchi et al. 2008), they may contribute to the selective functional disruption of more local circuits supported by short-range white matter fibers within the parietal or the frontal lobe (Fig. 9). In keeping with this hypothesis, spatial neglect patients with lesions centered on the supramarginal gyrus show significant changes in task-related BOLD activity in the adjacent visual cortex (Corbetta et al. 2005), whereas those with lesions centered in the inferior frontal gyrus display a breakdown of functional connectivity in more dorsal frontal areas (He et al. 2007). Note, however, that neither lesions limited to the associative visual cortex, nor those restricted to the dorsal frontal regions, typically produce spatial neglect. In summary, spatial neglect patients might demonstrate more perceptual or visuomotor symptoms depending on loss of function induced, by local anatomical diaschisis or functional breakdown, in the cortical areas surrounding the white matter lesion (Fig. 9). This conclusion received support by the recent finding (Aiello et al. 2012) that the severity of spatial neglect in a multiple item letter cancellation task correlates with frontal white matter damage producing both disconnection of the parietal–frontal pathways (i.e. SLF and arcuate fasciculus) and disconnection of a local white matter pathway linking the supplementary motor area and the superior frontal gyrus with the inferior frontal gyrus (Lawes et al. 2008; Oishi et al. 2008; Catani et al. 2012; Thiebaut de Schotten et al. 2012).

It is worth of note that this pathophysiological mechanism can produce chronic effects having the same behavioral selectivity of transitory effects described by Hillis et al. (2000) in acute spatial neglect patients (Khurshid et al. 2012). Using diffusion- and perfusion-weighted MRI, these authors showed that, in the hyperacute phase, neglect limited to specific spatial coordinates (egocentric vs. object-centered neglect) is associated with local hypoperfusion of specific cortical areas, caused by temporary stenosis of blood vessels. Neglect disappeared when pharmacological intervention restored proper blood perfusion.

Gray Matter Components of Spatial Neglect

The voxel-based analyses run in the present study, when taking into account the lesion size as a regressor did not survive correction for multiple comparisons. This result, similarly to

preliminary evidences reported by Karnath et al. (2004), confirm that lesion-deficit analyses focused on the severity spatial neglect are frequently biased by the effect of the lesion size. This result also strongly supports the idea of a distributed cortical origin for spatial neglect underpowering standard voxel-wise topological lesion-deficit analysis. Nevertheless, uncorrected analyses systematically showed that gray matter lesions predicting signs of chronic spatial neglect concern regions reciprocally interconnected through the arcuate fasciculus and SLF, such as the TPJ and the middle frontal gyrus (Catani et al. 2005, 2007; Catani and Thiebaut de Schotten 2008; Thiebaut de Schotten et al. 2008; Tsang et al. 2009). This finding is consistent with earlier observations that were focused on the role of localized gray matter damage in spatial neglect (Vallar and Perani 1986; Husain and Kennard 1996, 1997; Mort et al. 2003; Corbetta et al. 2005; Committeri et al. 2007) and, at the same time, discloses a fine anatomical and functional congruency between the white matter hodological and the gray-matter topological lesional components of spatial neglect, thus reaffirming the crucial role played by the integrated functioning of the right hemispheric parietal–frontal network in spatial orienting and awareness.

The TPJ and the middle frontal gyrus belong to a ventral attentional network that shows an increase in the BOLD when attention is dragged to unexpected visual events (Downar et al. 2000; Corbetta and Shulman 2002; Serences et al. 2005; Asplund et al. 2010). Based on the finding of a selective BOLD activation of the right TPJ and the middle frontal gyrus in response to targets presented at attentionally unattended-invalid spatial locations, Corbetta and Shulman (2002) have proposed that both the attentional disturbances and the higher frequency of spatial neglect after right hemispheric stroke depend on the anatomical and functional disruption of this ventral attentional network. Because of anatomical proximity and reciprocal connectivity, damage of the right ventral network would produce hypoactivation of an adjacent dorsal attentional system composed by the intraparietal sulcus and the frontal eye field areas. Due to reciprocal callosal inhibition, this hypoactivation would release hyperactivation in homologous dorsal areas in the left hemisphere with a pathologically increased rightward attentional bias. This theoretical approach establishes coherence between fMRI and anatomo-clinical findings and opens up new interesting points of discussion and investigation. As an example, one might still argue that since in this model only the role of the right temporo-parietal junction and the middle frontal gyrus is emphasized for attentional disengagement and reorienting, then lesion in the right ventral network should produce a generalized slowing of attentional disengagement. This seems not entirely congruent with the behavior of spatial neglect patients that are well characterized by prevalent defective disengagement from ipsi- to contralesional space rather than from contra- to ipsilesional space. However, residual disengagement abilities in spatial neglect patients could be explained by fMRI findings, showing that also the left TPJ–IFG has an important BOLD response to invalid targets and stimulus driven orienting (Doricchi et al. 2010). This might suggest that in spatial neglect patients slowed reorienting toward invalid targets presented in the left visual field might be due to preferred response of the left ventral network to invalid targets in the right visual space, or to the fact that right brain damage precludes or slows down the processing of invalid

targets presented in the left visual space to the spared reorienting network in the left hemisphere.

It is finally important to stress that different cytoarchitectonic areas form the region that is usually labeled temporal parietal junction: Brodmann area (BA) 40 (corresponding to areas PF, PFt, PFop, PFcm in Economo and Koskinas' atlas; Economo and Koskinas 1925; see also Tomaiuolo and Petrides 2010), BA 39 (corresponding to PG), the caudal of BA 22 (corresponding to TA1), and BA 37 (corresponding to PH, PHP, PHT, PHO). Future studies should clarify whether the different cytoarchitectonic areas forming the temporal parietal junction have different roles in attentional orienting and whether, in case of brain damage, they equally contribute or not to the occurrence of the spatial neglect syndrome.

Subcortical Thalamic Spatial Neglect

A small percentage of spatial neglect patients showed a small lesion sparing the fronto-parietal segment of the arcuate fasciculus and its projections. These patients showed similar clinical signs as the more typical spatial neglect patients with fronto-parietal disconnection. Our analysis revealed that lesions in these patients were centered on the thalamus and its adjacent white matter. Spatial neglect has previously been reported in humans with a lesion in the thalamus (Watson and Heilman 1979; Cambier et al. 1980; Schott et al. 1981; Rafal and Posner 1987; Mesulam 1999) and has been associated with a target engagement deficit in the contralesional hemifield (Rafal and Posner 1987). Nearly all incoming information to the cortex is directed through the thalamus (Behrens et al. 2003). However, in this small percentage, the lesion was found on the latero-dorsal portion of the thalamus, including the posterior and lateral dorsal thalamic nuclei and the anterior part of the pulvinar (Morel et al. 1997; Nieuwenhuys et al. 2008). The lateral posterior nucleus and the pulvinar receive their mains afferent fibers from the superior colliculus and pretectum, known as the visuomotor complex of the midbrain (Trojanowski and Jacobson 1975; Bender 1981; Benevento and Standage 1983; Huerta and Harting 1983; Lysakowski et al. 1986). Apart from the above, the lateral posterior nucleus and the pulvinar also receive input from the motor and premotor cortex (Romansky et al. 1997). Lateral posterior nucleus and pulvinar send efferent fibers toward the superior and inferior parietal lobules (Burton and Jones 1976), while the lateral dorsal nucleus is reciprocally connected with the entire prefrontal cortex including, in particular, the frontal eye field (Tanaka 1976; Huerta and Harting 1983; Schell and Strick 1984; Goldman-Rakic and Porrino 1985; Russchen et al. 1987). The posterior and lateral dorsal thalamic nuclei and the anterior part of the pulvinar can be considered as association nuclei characterized by strong reciprocal connections with the association areas (Nieuwenhuys et al. 2008). It is suggested that these nuclei relay high-order cortico-cortical communication and modulate functions requiring visual–sensory–motor integration (Sherman and Guillery 2002). A disconnection of these nuclei might thus induce an indirect fronto-parietal dysfunction with consequent spatial neglect.

Caveats and Conclusions

Some notes of caution must be considered for the present study. First, the white matter atlas that we have used is based

on anatomical information gathered from a population of normal subjects aged from 18 to 22 years, while the stroke population we studied was much older. A decrease in the size of the pathways reconstructed with tractography in relation to age has been previously reported (Stadlbauer et al. 2008). White matter pathways also show a descending gradient of intersubjects variability going from the stem portion (>90% of the population studied) of the white matter pathways to the most peripheral zones (<50% of the population studied; Thiebaut de Schotten, ffytche, et al. 2011). In our analysis, we chose a probability >50% in order to consider only the almost invariable anatomical core of each single tract and not its periphery (Thiebaut de Schotten, ffytche, et al. 2011).

A second note of caution concerns the possible contribution of interhemispheric callosal disconnection to MCA spatial neglect. At present, DTI tractography poorly reconstructs crossing fibers, with a consequent underestimation of the lateral projections of the cortico-spinal tract and the corpus callosum in the atlas we used. Therefore, the present study does not allow excluding that disconnection of callosal fibers also contributes to spatial neglect following vascular damage in the MCA (Bartolomeo et al. 2007).

In conclusion, this study confirms that lesion of white matter pathways is a relevant determinant of chronic MCA spatial neglect. When the integrated interplay between the right frontal and parietal lobes is interrupted by disconnection (direct anatomical–functional damage) or by thalamic infarction (indirect functional damage), chronic spatial neglect is likely to occur. In addition, we were able to provide advances in the understanding of the role of disconnection in spatial neglect, by pinpointing the role of distinct SLF branches. At variance with the proposals made by Karnath et al. (2001, 2004, 2009, 2011), stressing the importance of purely cortical damage, we conclude that chronicity of left spatial neglect in the post-acute phase of MCA stroke is linked to the anatomical and functional disruption of parietal–frontal white matter connections and not linked to damage of the central sector of the superior temporal gyrus.

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