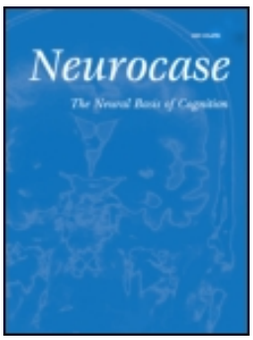

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Visual neglect as a disconnection syndrome? A confirmatory case report

Francesca Ciaraffa[1,2,3,4], Gianmarco Castelli[1], Eugenio Agostino Parati[1], Paolo Bartolomeo[3,4,5], and Alberto Bizzi[1]

[1]Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[2]Department of Neurosciences, Catholic University, Policlinico A. Gemelli, Rome, Italy
[3]Inserm-UPMC UMRS 975, Brain and Spine Institute, Hôpital Salpêtrière, Paris, France
[4]Department of Psychology, Catholic University, Milan, Italy
[5]AP-HP, Pitié-Salpêtrière, Fédération de Neurologie, Paris, France

Visual neglect has classically been associated with right hemisphere injury in parietal, frontal, or temporal cortex, in the basal ganglia or in the thalamus. More recently, visual neglect has been associated with injury extended into fronto-parietal white matter tracts. However, in most published cases white and gray matter injuries were associated. We present the anatomo-clinical study of a patient presenting with severe acute left visual neglect due to ischemic infarct limited to the right cerebral hemisphere white matter. Magnetic resonance diffusion tensor imaging tractography was instrumental to accurately localize the injury to the right arcuate fasciculus that is a component of the large-scale networks controlling visuo-spatial attention. These results add to a growing appreciation that neglect may result from disruption of a distributed attentional network.

Keywords: Visual neglect; Stroke; Diffusion tensor imaging; MR tractography; Arcuate fasciculus.

Patients with visual neglect fail to pay attention to objects presented on the side of space contralateral to a brain lesion. While it is undisputed that lesions in the right hemisphere provoke more severe and durable signs of contralateral neglect than lesions in the left hemisphere, the identification of the anatomic structures that if injured will determine visual neglect has fostered an intense debate in recent years. Classic studies identified the right inferior parietal lobule (IPL) and the adjacent temporoparietal junction (TPJ) (Vallar, 2001) as crucial structures for this syndrome. This finding was subsequently challenged by Karnath, Ferber, and Himmelbach (2001), who suggested that left neglect is not the result of a lesion in the parietal lobe, but of an injury to the middle third of the superior temporal gyrus.

More recent evidence suggested that neglect signs correlate with dysfunction of large-scale networks, whose nodes include the posterior parietal cortex (PPC), the lateral prefrontal cortex (LPFC), the TPJ, and the occipital lobe (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008). These cortical nodes show increased BOLD response during spatial orienting of attention (Bartolomeo, Zieren, Vohn, Dubois, & Sturm, 2008; Corbetta & Shulman, 2002; Nobre, 2001). In particular, functional magnetic resonance imaging (fMRI) studies have shown increased

Paolo Bartolomeo and Alberto Bizzi as senior authors equally contributed to this work.

Address correspondence to Paolo Bartolomeo, INSERM-UPMC UMRS 975, Brain and Spine Institute, Hopital Salpetriere, Paris, France. (E-mail: paolo.bartolomeo@upmc.fr).

BOLD response in a ventral fronto-parietal network lateralized to the right-hemisphere when subjects reorient their attention from an expected location to an unexpected one (Corbetta & Shulman, 2002).

Consistent with the hypothesis of a causal link between neglect signs and impairment of large-scale fronto-parietal networks in the right hemisphere (Bartolomeo, 2006), accumulating evidence has demonstrated an associated injury to white matter pathways connecting these networks in monkey studies (Gaffan & Hornak, 1997) and in human neglect patients (Urbanski et al., 2008, 2011; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). In human patients, however, lesions usually involved both the gray and the white matter. For example, in their review of the literature on neuropsychological consequences of subcortical lesions, Cappa and Vallar (1992) concluded that 'subcortical lesions consistently produce neglect only when the subcortical gray nuclei (the basal ganglia and, most of all, the thalamus) are involved' (p. 21). Subsequently, Vallar (2008) noted that 'while lesions confined to the subcortical white matter are only rarely associated with neglect (Vallar & Perani, 1986), in patients with cortico-subcortical lesions, the white-matter fiber bundles connecting the posterior and anterior regions of the brain are frequently damaged, namely the inferior (Leibovitch et al., 1998) and, particularly, the superior longitudinal fasciculus (SLF), which provides parieto-frontal connections (Doricchi & Tomaiuolo, 2003; Leibovitch et al., 1998)' (p. 309f). However, Hillis et al. (2002) mentioned that 3 out of 7 right brain-damaged patients with pure corona radiata infarction showed spatial neglect (see also Weiller et al., 1993). Nevertheless, in these group studies the anatomical and neuropsychological evidence was necessarily scanty, and white matter damage could not be related to specific anatomo-functional brain networks.

Thus, the available literature lacks detailed clinicoanatomical evidence that injury restricted to white matter may lead to signs of neglect in human patients. Here we describe a case of acute left neglect, assessed by both detailed neuropsychological evaluation and state of the art neuroimaging methods. In this patient, small focal ischemic infarcts were located in specific white matter tracts, which were precisely identified thanks to magnetic resonance (MR) diffusion tensor imaging (DTI) tractography.

METHODS

Clinical data

A 55-year-old right-handed man with 13 years of education came to our observation after the sudden onset of left hemiparesis. Neurological examination showed signs of severe left visual neglect, with tonic deviation of the head towards the right, 'magnetic attraction' of gaze towards right-sided stimuli (Gainotti, D'Erme, & Bartolomeo, 1991), and extinction of left-sided stimuli in both the visual and the somatosensory modalities. At day 2 (60 hours) post-onset, MR diffusion showed few focal areas of signal hyperintensities with decreased diffusivity compatible with acute ischemic infarcts in the white matter of the right cerebral hemisphere. Diffusion weighted images (DWI) and fluid attenuated inversion recovery (FLAIR) images showed no evidence of gray matter infarcts (Figures 1 and 2). Angiography with computerized tomography demonstrated a dissection of the right internal carotid artery.

Neuropsychological tests

Neuropsychological assessment was performed 2 days after onset by using a standardized neglect battery (Azouvi et al., 2002) with additional tests (Bartolomeo & Chokron, 1999), and repeated 12 days after symptom onset. Paper-and-pencil tests included cancellation tests (line, letter and bells cancellation); line bisection, drawing from memory of a clock face, identification of overlapping figures and copy of a linear drawing representing a landscape. The line bisection test consisted of eight lines horizontally disposed in a vertical A4 sheet in a fixed random. There were three 62-mm samples at 38, 81, and 124 mm from the left margin of the sheet, three 100-mm samples at 17, 62, and 90 mm from the margin and two 180-mm samples at 14 mm from the margin. The landscape copy was a linear drawing representing a house and four trees presented on a horizontal A4 sheet. It was scored by assigning 1 point for each tree correctly copied and 2 points for the house (max=6). For the clock test, the patient had to place the 12 hours in the appropriate locations within a circle drawn by the examiner. A three level scale was used: 0, normal performance; 1, omission or rightward displacement of a part of the five left-sided hours; 2,

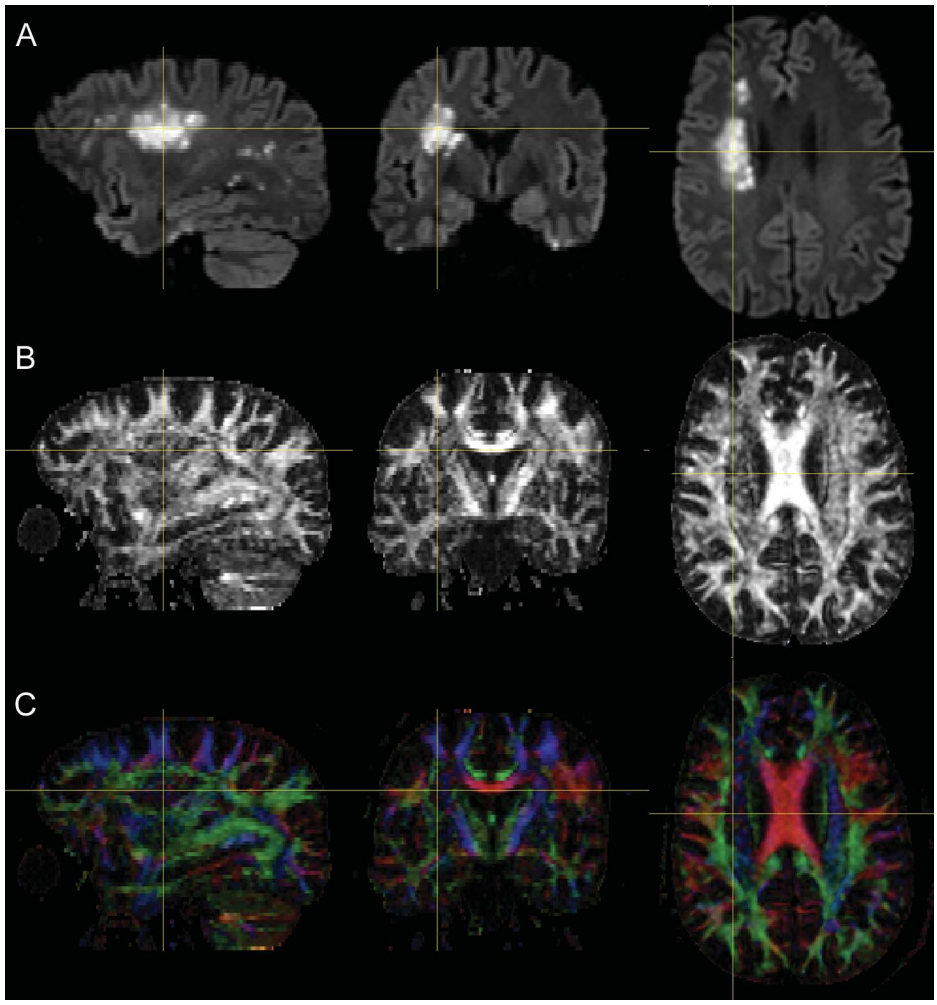

Figure 1. Axial diffusion-weighted MR images (A) in three orthogonal planes showing hyperintense signal abnormalities in the right corona radiata (CR). Fractionary anisotropy maps (B) show decreased anisotropy in the lesion. Orientation color maps (C) confirmed that the lesion is involving a projection tract (colored in blue) in the anterior portion of the CR and an association tract (colored in green) in the anterior portion of the SLF. Note that there was no evidence of cortical ischemic infarcts on DWI at 60 hours after symptoms onset.

omission or rightward displacement of all left-sided hours. There were also tests of reading and writing translated into Italian from the French-language neglect battery (Azouvi et al., 2002).

MR imaging

MR imaging included T1- and T2-weighted images, FLAIR, and DTI, acquired on a 1.5-Tesla Siemens Avanto MR unit (Erlangen, Germany). DTI was acquired with a SE-EPI sequence (TR/TE: 8600/92 ms) using 12 diffusion gradients applied in isotropically distributed orientations (Jones et al., 1999), b value=1000, isotropic resolution ($2\times2\times2$ mm^3), 64 consecutive slices, 8 repetitions. DTI data were corrected for eddy current distortion by means of the software provided with the scanner and were subsequently corrected for head motion by FMRIB Linear Image Registration Tool software (FMRIB, University of Oxford, Oxford, UK) with 12 degrees of freedom. Tractography with DTI (Basser, Mattiello, & LeBihan, 1994) was used to gather additional information about the relationship of the infarcts with the trajectories of main white matter pathways. Fractional anisotropy (FA) and orientation maps were computed offline with the software Diffusion Toolkit (http://trackvis.org).

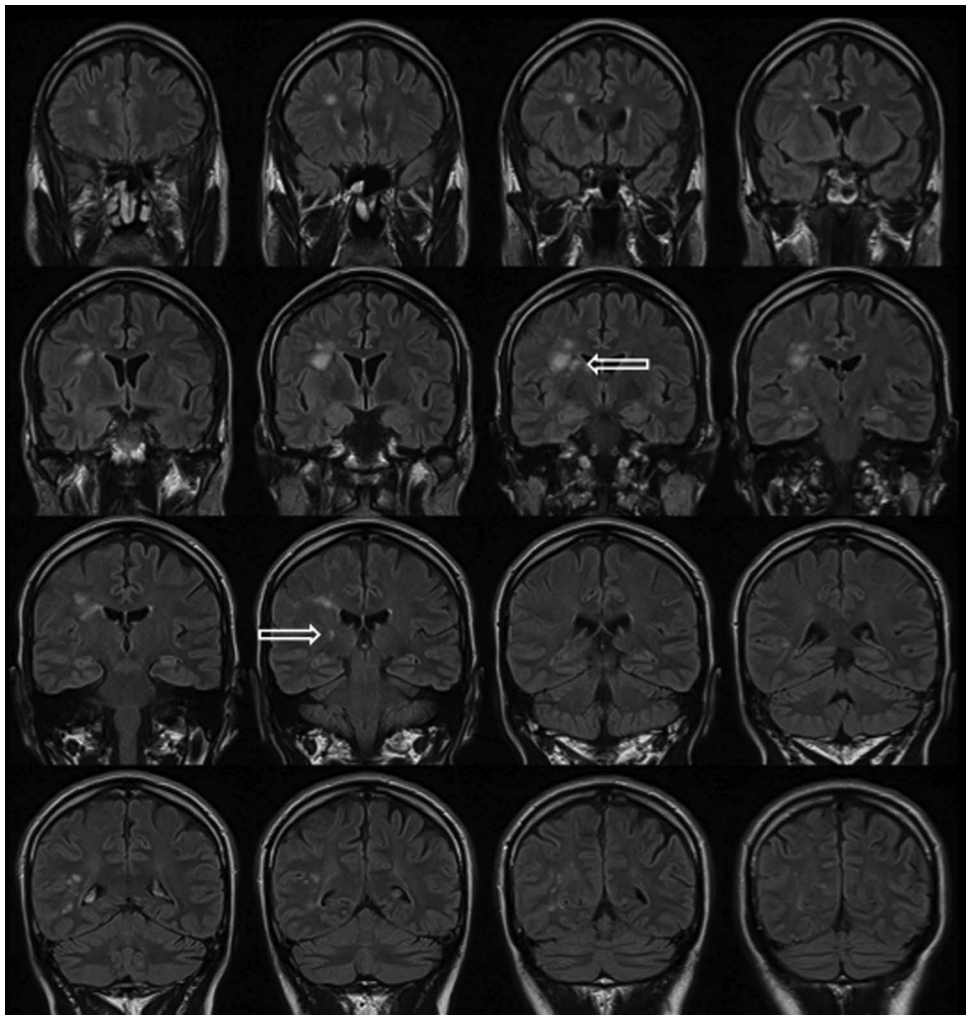

Figure 2. FLAIR images showing no evidence of infarcts in the cortical gray matter, basal ganglia and thalami. Signal hyperintensities are present in the white matter of the right cerebral hemisphere, anterior and posterior limb of the right internal capsule (arrows).

Deterministic tractography was performed with a two regions of interest approach by an expert neuroradiologist (A.B.) using an interpolated streamline algorithm, with FA above a threshold of 0.15 and angle less than 45°. The delineation of the seed regions of interest was based on *a priori* anatomical knowledge (Catani, Jones, & ffytche, 2005; Catani & Thiebaut de Schotten, 2008). The following tracts were reconstructed: the three segments of arcuate fasciculus (AF)–anterior segment (As-AF) connecting the dorsolateral prefrontal cortex (DLPFC) with the inferior parietal lobe (IPL), posterior segment (Ps-AF), connecting IPL with superior temporal gyrus/medial temporal gyrus, long segment (Ls-AF) connecting the inferior and middle frontal gyri and the ventral precentral gyrus; inferior fronto-occipital fasciculus (IFOF) connecting the orbitofrontal cortex with the temporal and occipital lobes; inferior longitudinal fasciculus (ILF) connecting the occipital and temporal lobes, uncinate fasciculus (UF) connecting anterior temporal and orbital frontal lobe.

RESULTS

The results of the patient's performance on the neglect battery are reported in Table 1. At day 2 the patient showed signs of severe left-sided neglect. At day 12 the patient had recovered on several visuo-spatial tasks, but still showed moderate left

TABLE 1
Performance on the neglect battery

Test	*1 (2 days from symptom onset)*	*2 (12 days from symptom onset)*
Line bisection (% rightwards deviation)	29%*	14%*
Line cancellation (left/right hits; max 30/30)	10/29*	30/30
Bells cancellation (left/right hits; max 15/15)	0/4*	7/15*
Letter cancellation (left/right hits; max 30/30)	0/14*	22/30*
Overlapping figures (left/right hits; max 10/10)	1/9*	10/10
Landscape drawing (hits; max 6)	5*	6
Clock drawing (max 2)	1*	0
Reading (max 61/55)	31/41*	50/55*
Writing	8.2 cm*	4 cm

The asterisks indicate pathological performance. For the landscape copy, the patient made one omission on the left side on the first test and no omissions on the second test. For the clock drawing test, the patient omitted two left-sided hours on the first test; he made no omissions on the second test.

neglect on line bisection, bells and letter cancellation, and reading.

MR imaging showed focal ischemic infarcts in the right cerebral white matter without any signal abnormality in the gray matter. Diffusion-weighted images showed two infarcts in the anterior portion of the centrum semiovale (see Figures 1 and 2) and in the subcortical white matter at the TPJ (Figure 3). One additional smaller infarct was located in the deep frontal white matter.

Diffusivity was decreased in all lesions compatible with acute onset infarcts. There was no evidence of chronic ischemic infarcts on FLAIR images. Tractography and orientation color DTI maps were crucial to establishing that the two larger infarcts involved the AF. The anterior infarct involved the As-AF connecting the right DLPFC to the right inferior parietal lobule; the posterior infarct involved the Ls-AF and Ps-AF at the TPJ. The relationship of the two larger infarcts with the three segments of the AF is illustrated in Figure 4. The following mean dti values were measured: 0.456 (right) and 0.429 (left) in the Ds-AF, 0.432 and 0.416 in the As-AF, 0.418 and 0.429 in the Ps-AF. Tractography also demonstrated that the trajectories of the IFOF, UF, and ILF were largely intact and remote from the infarcts.

DISCUSSION

We report a detailed neuropsychological and neuroanatomical study of a patient with an acute stroke secondary to dissecation of the right internal carotid artery. The ischemic infarct was limited to the white matter. In particular, ischemic infarcts affected the right AF at two levels: anteriorly in the As-AF (also known as the third branch of the superior longitudinal fasciculus or SLF III) and posteriorly in the Ls-AF. There was no radiological evidence of other infarcts involving the cortical or subcortical gray matter. An additional smaller infarct was in the anterior frontal lobar white matter.

It has been shown that it is possible to show *in vivo* the trajectories of the main white matter pathways with DTI MR tractography. In particular it is possible to show pathways connecting perisylvian brain areas in the left and right human cerebral hemispheres (Catani et al., 2005). The AF is composed of a direct and an indirect pathway. The direct pathway is connecting the Wernicke territory (including the posterior part of both the superior and middle temporal gyri) with the Broca territory (Brodmann areas 44 and 45, and part of the middle frontal gyrus and inferior precentral gyrus). This long segment presents an asymmetry favoring the left hemisphere, perhaps related to its role in language processes (Catani et al., 2007). The indirect pathway is made of two segments: a posterior segment connecting the Wernicke territory with the IPL, and an anterior segment (As-AF), linking IPL with the posterior part of the middle frontal gyrus. The latter is a fronto-parietal pathway that likely corresponds to the human homologue of the SLF III (Schmahmann & Pandya, 2006; Thiebaut de Schotten et al., 2011). Catani et al. (2007) showed that there are asymmetries of the AF in the normal population. These differences may vary with gender and age. The long segment appears to be present in the right hemisphere only in 40% of the normal population (Catani et al., 2007). Therefore, 60% of people seem to have only the As-AF (connecting IPL and posterior Broca territory) and the Ps-AF

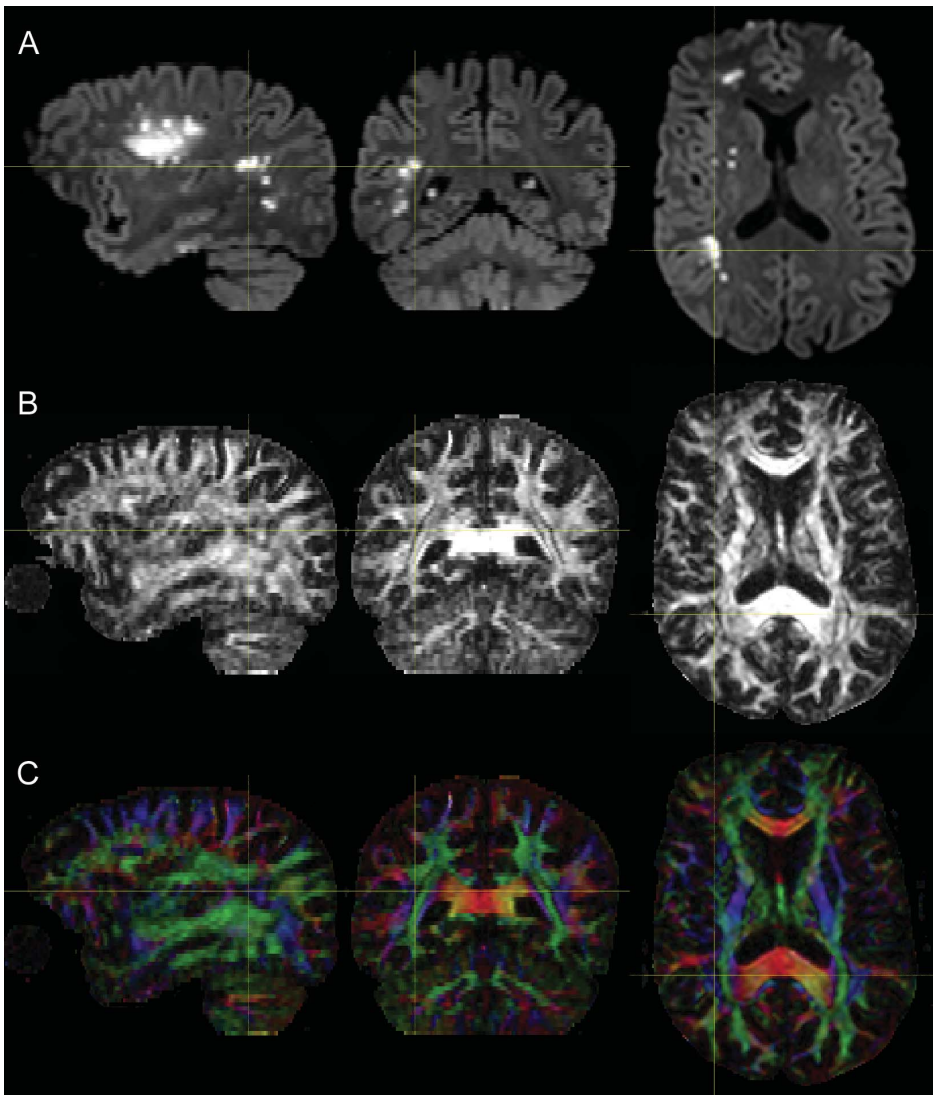

Figure 3. Axial diffusion-weighted MR images (A) in three orthogonal planes showing hyperintense signal abnormalities in the right subcortical white matter at the TPJ. Fractionary anisotropy maps (B) show decreased anisotropy in the lesion (FA=0.496 on the right, FA=0.535 on the contralateral side). Orientation color maps (C) confirmed that the lesion is involving a portion of the tract (colored in blue) along the AF. Note that there was no evidence of cortical ischemic infarcts on DWI at 60 hours after symptoms onset.

(connecting IPL and STg/MTg) in the right hemisphere (Catani et al., 2007).

In the right hemisphere, these association tracts connect cortical regions important for orienting of spatial attention and arousal. The second and third branches of the SLF connect the LPFC and the PPC (Thiebaut de Schotten et al., 2008, 2010, 2011). The right AF might have an important role for praxis and visual attention (Heilman & Watson, 2008). The IFOF links the orbitofrontal cortex with the temporal and occipital lobes; its disconnection in the right hemisphere might be involved in the determinism of neglect (Urbanski et al., 2008).

Evidence is accumulating that signs of neglect in peripersonal space contralateral to the lesion may result from damage to the above white matter pathways, thus supporting network-based models of neglect (Heilman, Watson, & Valenstein, 2003; Mesulam, 1999). Studies in patients with vascular strokes (Urbanski et al., 2008, 2011; Verdon et al., 2010) and in patients with brain tumors (Shinoura et al., 2009; Thiebaut de Schotten et al., 2005) demonstrated that neglect signs can emerge not only from cortical damage, but also from disconnection of caudo-rostral long-range white matter pathways such as the SLF II, the

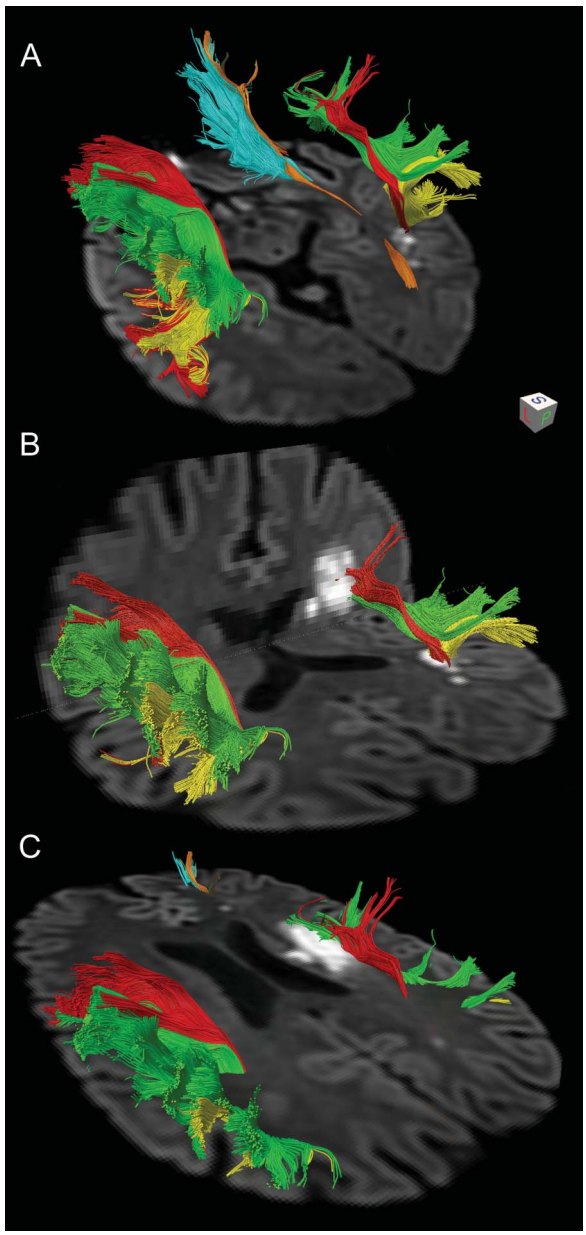

Figure 4. Virtual dissection with DTI MR tractography showing the trajectories of the three segments of the bilateral AF, right IFOF, and right UF projected over axial diffusion-weighted MR images at the level of the midbrain (A), splenium of the corpus callosum (B), and corona radiata (C). Note the relationship of the acute infarcts with the right AF at multiple levels. Ischemic infarcts have involved the long and posterior segments (A, B), the corona radiata and the anterior segment of the AF (C). Virtual dissection of the three segments of the AF shows moderate asymmetry of the direct segments with the left-sided AF being larger than the right-sided one (see Catani et al., 2007; Thiebaut de Schotten et al., 2011). The fasciculi are color-coded: AF segments (long, red; anterior, green; posterior, yellow); IFOF (orange), and UF (cyan). [To view this figure in color, please see the online version of this journal].

As-AF/SLF-III and the IFOF (Doricchi et al., 2008). In addition, a reanalysis (Thiebaut de Schotten et al., 2008) of the results by Doricchi and Tomaiuolo (2003) identified the region of maximal overlap in the SLF at the borders between the human homologue of SLF II and the As/SLF III. The notion of WM damage leading to neglect is consistent with the time-honored notion in neurology that dysfunction in network-based operations may depend not only on lesion to cortical nodes, but also on damage to connections between nodes: the so-called disconnection syndromes (Catani & ffytche, 2005; Geschwind, 1965).

In the present patient, signs of neglect were transient, with recovery within 12th day except for residual moderate deficits on cancellation tasks and line bisection. However, in our opinion this does not undermine the main point of our study, that focal injury limited to right long-range tracts can result in severe left neglect. DTI was helpful to accurately identify the white matter tracts involved by the lesion.

A traditional idea of disconnection necessarily implicates normal functioning of the nodes of the disconnected network. This, however, is not always true even in the most typical examples of disconnection syndrome, such as conduction aphasia or pure alexia, which, in different patients, can result from either disconnection of, or direct cortical damage to, the temporal-parietal junction (Anderson et al., 1999) or the left fusiform gyrus (Epelbaum et al., 2008), respectively. In a similar manner, in the present patient white matter damage could have led to neglect signs by inducing dysfunction in the cortical nodes of the relevant networks (Catani & ffytche, 2005).

It is likely that white matter lesions larger than those observed in the present patient might lead to more durable dysfunction at the network level (Bartolomeo et al., 2007). In the acute phase of a stroke hypoperfusion may be much larger than the core of the ischemic tissue, detected by diffusion-weighted imaging, thus leading to temporary neurological deficits. MR imaging with DWI acquired 60 hours after onset of the acute stroke showed no evidence of infarct (reduced diffusivity) in the cortex. There was no evidence of signal abnormalities in the cortex on FLAIR MR images (see Figure 2). We cannot rule out hypoperfusion in the cortex during the first 24 hours of the acute stroke. However, even if cortical hypoperfusion were present in the

acute stage it did not cause any cortical infarct. At the time neglect was demonstrated (60 hours after symptoms onset) perfusion in the cortex was likely to be normal. It has been shown that severity of impairment reflects severity of hypoperfusion in the cortex within the first 24 hours after stroke (Hillis et al., 2001; Shirani et al., 2009). After 3 hours more than 50% and after 6–8 hours almost the entire penumbra would have disappeared or converted into the irreversibly infarcted core. Some small regions with preserved oxygen consumption but reduced flow may be observed around the lesion at the border zone of the ischemia for up to 24 hours or even a little longer (Heiss, 2011).

There are a few limitations in this case study. One limitation inherent to the method is that MR DTI cannot provide a measurement of the residual functionality of the injured tracts. Unfortunately, perfusion imaging was not acquired during the first 24 hours. Finally, late clinical follow up was not done in this patient, thus complete recovery from neglect signs cannot be excluded.

CONCLUSION

This case report demonstrates that acute isolated injury to fronto-temporal-parietal white matter pathways, and in particular to the right AF, is sufficient to produce signs of visuo-spatial neglect, in agreement with experimental evidence from non-human primates and with neurocognitive models of normal attention in the human brain. Thus, our results add support to the growing appreciation that neglect results from disruption to a distributed attentional network, and not exclusively from focal cortical damage. This study also emphasizes the importance of novel neuroimaging methods such as DTI tractography in precisely establishing the relationship of the lesion with white matter tracts.

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