CORTEX 44 (2008) 983–995

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/cortex

Special issue: Original article

White matter (dis)connections and gray matter (dys)functions in visual neglect: Gaining insights into the brain networks of spatial awareness

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ARTICLE INFO

Article history:
Received 26 June 2007
Reviewed 8 October 2007
Revised 6 March 2008
Accepted 8 March 2008
Published online 23 May 2008

ABSTRACT

Seminal case reports collected during the middle part of the XX century, designated the parietal lobe as the principal area of damage in patients suffering from contralesional spatial neglect (Brain WC. Visual disorientation with special reference to lesions of the right cerebral hemisphere. Brain 1941;64:224–72; Paterson A, Zangwill O. Disorders of visual space perception associated with lesions of the right cerebral hemisphere. Brain 1944;67:331–58; McFie J, Piercy MF, Zangwill O. Visual spatial agnosia associated with lesions of the right hemisphere. Brain 1950;73:167–90). Based on this evidence, textbooks of neurology have traditionally referred to neglect as a "parietal sign". This view found complete accomplishment in the 1986 group study by Vallar and Perani, who confirmed that the inferior parietal lobe was the area most frequently involved in neglect patients with lesions confined to the cerebral cortex and lesions involving subcortical gray matter nuclei. In the same study, it was found that lesions limited to subcortical white matter were rarely associated with neglect. Here, we reconsider recent accumulating evidence, gathered from investigations in animals and human patients, supporting the partially different view that damage involvement of long-range white matter bundles connecting the parietal to the frontal lobe, importantly influence the occurrence and severity of spatial neglect. These findings do not dispute the role of the parietal and frontal cortex in spatial attention and space-related behaviour, but call for a reappraisal of the respective roles of disruption of white matter connections and damage of gray matter cortical modules in the pathophysiology of neglect. Disentangling the connectional and modular anatomical correlates of neglect may be crucial to better understand the pathophysiology of this syndrome, to explain the manifold clinical dissociations often encountered in clinical practice and to increase the impact of behavioural and pharmacological interventions. In this review, we focus

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0010-9452/$ – see front matter
doi:10.1016/j.cortex.2008.03.006

on the role of within-hemisphere white-matter disconnection. The role of interhemispheric disconnection, perhaps the oldest connectionist theory of neglect (Geschwind N. Disconnexion syndromes in animals and man – part II. Brain 1965;88:585–644), was extensively treated elsewhere (Bartolomeo P, Thiebaut de Schotten M, Doricchi F. Left unilateral neglect as a disconnection syndrome, Cerebral Cortex 2007;45:3127–48). We first summarise the structure of long-range white matter connections within the cerebral hemispheres and sketch a brief historical review of the original findings suggesting the role of intrahemispheric disconnection to neglect. We then revisit some of the current functional interpretation of the neglect syndrome in the light of disconnectionist approach and review evidences favouring or disfavouring a purely disconnectionist interpretation of the syndrome. Finally, we address the issue of diagnostic criteria to be used in future anatomo-clinical studies aiming at investigating the role of white matter and gray matter dysfunctions in spatial neglect.

> ''The conception of a purely cortical defect is open to question…Most lesions – if not all – may be looked upon as subcortical or as corticosubcortical.''
> (Critchley, 1953)

1. Long-range white matter connections in the cerebral hemispheres

Within each hemisphere, cortical networks including the dorsolateral prefrontal and the posterior parietal cortex are important for spatial attention and space-related behaviour (Posner and Petersen, 1990; Mesulam, 1981; LaBerge, 2000; Corbetta and Shulman, 2002). Physiological studies in the monkey show that parietal and frontal areas are directly and extensively interconnected (Morecraft et al., 1993; Selemon and Goldman-Rakic, 1988) and demonstrate interdependent neural activity (Chafee and Goldman-Rakic, 2000). In humans, fMRI studies demonstrated almost constant co-activation of parietal and frontal areas during a broad range of visual spatial tasks (Husain and Nachev, 2007). White matter fronto-parietal pathways linking parietal and frontal areas include the superior longitudinal fasciculus (SLF), the arcuate fasciculus (AF) and shorter U-shaped cortico-cortical connections (see also Thiebaut de Schotten et al., 2008, this issue; Catani and Thiebaut de Schotten, 2008, this issue; Catani and Mesulam, 2008a, this issue). In the monkey brain, three distinct branches can be identified within the SLF, on the basis of cortical terminations and course (Petrides and Pandya, 2002; Schmahmann and Pandya, 2006). The SLF I links the superior parietal region and the adjacent medial parietal cortex with the supplementary and premotor areas in the frontal lobe. The SLF II originates in the caudal inferior parietal lobe (corresponding to the human angular gyrus) and the occipito-parietal area and projects to the dorsolateral prefrontal cortex. The SLF III connects the rostral portion of the inferior parietal lobe (homologous to the human supramarginal gyrus) with the ventral premotor area 6, adjacent area 44, the frontal operculum and area 46. The AF links the caudal portion of the temporal lobe with the dorsal portions of the areas 8, 46 and 6 in the frontal lobe (Schmahmann and Pandya, 2006). Recent findings in the monkey brain with Diffusion Spectrum Imaging (DSI'; Schmahmann et al., 2007) suggest that AF projections arriving from the caudal Superior Temporal Gyrus (STG) and running around the end of the sylvian fissure, run beneath and adjacent to the third branch of the SLF. On DSI the rostral course of AF is indistinguishable from those of the most lateral branches of the SLF (i.e., SLF II and SLF III). This is in keeping with original autoradiography studies by Petrides and Pandya (1984, 1988), showing that SLF and AF pathways run in the same general region. Diffusion tensor imaging (DTI), a new technique to map the course of white matter tracts in the living human brain (Pierpaoli et al., 1996), has demonstrated a similar organization of parietal–frontal pathways in humans (Fig. 1) (Catani et al., 2002; Makris et al., 2005; Rushworth et al., 2006; Thiebaut de Schotten et al., 2006; Thiebaut de Schotten et al., 2008, this issue). Unfortunately, the DTI technique currently does not allow to identify the cortical terminations of white matter fibers, or to unequivocally resolve local fiber orientation at the level of the single voxel (see also Jones, 2008, this issue).

More ventral pathways, such as the Inferior Longitudinal Fasciculus (ILF) and the Occipital Frontal Fasciculus (IFOF), also deserve mention here, because several sources of evidence suggest their possible involvement in neglect-related disorders.

The ILF has been implicated in contralesional spatial neglect following strokes in the territory of the posterior cerebral cortex (Leibovitch et al., 1998; Bird et al., 2006). In the monkey, the ILF originates in the ventral–lateral and ventral preoccipital areas and runs in the depth of the temporal lobe to terminate in the superior temporal sulcus, the inferior temporal gyrus, and other temporal areas. It also connects the caudal part of the cingulate gyrus, the IPL, and the STG to the parahippocampal gyrus (Schmahmann and Pandya, 2006). In humans, the ILF originates from extrastriate occipital visual areas, fusiform and lingual gyri and cuneus. It projects to the superior, middle and inferior temporal gyri, to the uncus and parahyppocampal gyrus (Catani et al., 2003).

The IFOF was originally described by Curran in 1909 and subsequently demonstrated by several authors in post-mortem dissections (Ludwig and Klingler, 1956; Crosby et al., 1962; Gluhbegovic and Williams, 1980) and in virtual in vivo

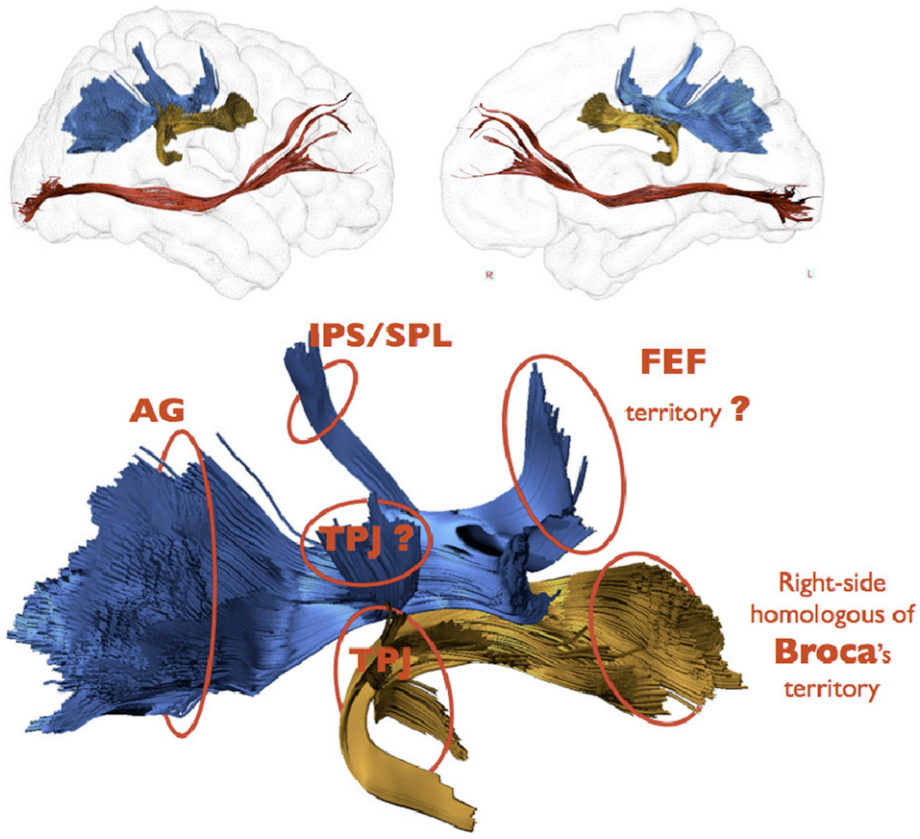

Fig. 1 – Three-dimensional reconstruction of the SLF III (in gold), SLF II (in blue) and IFOF (in red) on an average DTI from 12 subjects with high-resolution DTI acquisition (see this issue, mini-atlas, methods section); (a) lateral and (b) medial view of a glass brain right hemisphere; (c) fronto-parietal connections with their putative cortical projections. AG, angular gyrus; IPS, intra-parietal sulcus; SPL, superior parietal lobule; TPJ, temporo-parietal junction; and FEF, frontal eye field.

DTI-tractography reconstructions (Catani et al., 2002; Jellison et al., 2004; Wakana et al., 2004; Kier et al., 2004). The IFOF connects the lateral and medial orbitofrontal cortex to the occipital lobe, and, at least in humans, it represents the only direct connections between occipital and frontal lobes (Catani et al., 2002, 2003). The function of the IFOF is at present unknown, however, its disconnection in the right hemisphere has been recently documented in two patients with left neglect (Urbanski et al., 2008) (see below).

2. A concise history of the disconnectionist approach to the neglect syndrome

Since the original considerations of Geschwind (1965) on the possible role of interhemispheric disconnection in neglect, the investigation first emphasizing the effects of white matter disruption in spatial neglect was the surgical study in the monkey by Gaffan and Hornak (1997). These authors showed that following unilateral section of long-range communication pathways between the parietal and the frontal lobe in the white matter between the fundus of the intraparietal sulcus and the lateral ventricle, monkeys omitted to respond to targets contralateral to the lesion (see also Gaffan and Wilson, 2008, this issue). Little, if any, contralateral neglect was present after isolated or combined ablations of the frontal cortex anterior to the arcuate sulcus and the posterior parietal cortex comprised between the intraparietal and lunate sulcus. Thus, disconnection really proved crucial to observe neglect in monkeys in this study. Similar results were obtained in rodents (Burcham et al., 1997; Reep et al., 2004).

One year later, analogous findings were reported in human patients in a study using CT scans and SPECT by Leibovitch et al. (1998). These authors investigated the anatomical correlates of neglect in a large sample of right brain-damaged patients not selected for the presence or absence of concomitant visual field defects. The main correlate of chronic neglect was the combined anatomical and functional damage of fibers connecting the parietal and temporal lobes (ILF), as well as those linking the parietal and frontal lobes (SLF) loaded in the white matter beneath the temporal–parietal junction (TPJ).

Six years after the study by Leibovitch et al. (1998), Doricchi and Tomaiuolo (2003) disentangled the contribution of SLF and ILF disconnection to spatial neglect. In their study, lesion overlap was mapped in a sample of chronic neglect patients selected for the absence of concomitant visual field defects. Patients were further divided in two subgroups based on whether the lesion involved or spared the basal ganglia. In both subgroups, areas of maximal lesion overlap were found in the SLF beneath the rostral sector of the supramargynal

gyrus. This finding first showed that, in humans, damage limited to parietal–frontal connections in the SLF is sufficient in contributing to the development of chronic neglect. The authors concluded that disconnection of the fronto-parietal network can render neglect more severe, generalised and persistent in patients who, suffering only partial damage of the functionally heterogeneous parietal-temporal cortex, would otherwise show more selective and perhaps transitory neglect symptoms.

Direct evidence on the role of parietal–frontal disconnection in human neglect came from a study employing intraoperative electrical stimulation in human patients (Thiebaut de Schotten et al., 2005) during brain surgery for resection of low-grade gliomas. This technique allows researchers to map cognitive functions in humans with high spatiotemporal resolution (~5 mm by 4 s). Two patients with gliomas in the right temporo-parietal region were asked to mark the midpoint of 20-cm horizontal lines (a typical neglect task; Azouvi et al., 2002) while being stimulated. Electrical stimulation of the right IPL or of the caudal STG, but not of its more rostral portions, determined mild but significant rightwards deviations on line bisection. Importantly, however, dramatic rightward shifts occurred when one of the patients was stimulated subcortically. Fiber tracking using DTI tractography identified the stimulated site as the likely human homologue of the SLF II, consistent with the postulated role of this pathway in spatial processing (Schmahmann and Pandya, 2006; Rizzolatti and Matelli, 2003). Thus, different spatial tasks (line bisection (Thiebaut de Schotten et al., 2005) or target cancellation (Doricchi and Tomaiuolo, 2003) in humans, target search in monkeys (Gaffan and Hornak, 1997)) led to similar results after fronto-parietal disconnection in humans and in monkeys. These findings strongly suggest a similar organization of spatial processing mechanisms across the two species, and support models of neglect postulating an impairment of large-scale right-hemisphere networks (Mesulam, 1999). More specifically, parietal–frontal disconnection may disrupt the dynamical interactions between bottom–up and top–down processes, which are essential to the functioning of attentional processes (Buschman and Miller, 2007), and which are typically impaired in visual neglect (Bartolomeo, 2006, 2007).

These considerations prompted us (Bartolomeo et al., 2007) to re-examine previous studies comparing vascular lesion overlaps of patients with and without neglect (Corbetta et al., 2005; Doricchi and Tomaiuolo, 2003; Karnath et al., 2004a; Mort et al., 2003). We plotted areas of maximal lesion overlap specifically linked to neglect on a standardized reconstruction of white matter human fibers (Thiebaut de Schotten et al., 2006) (Thiebaut de Schotten et al., 2008, this issue). Despite different normalization algorithms and different target brains were used in these studies, the plots of neglect patients' lesions coordinates (that in all of the reviewed studies were reported in the MNI space) consistently overlapped at or near the subcortical long-range pathways linking the parietal to the frontal lobes. The same meta-analysis revealed the presence of an important lesion overlap in the white matter fronto-parietal connections in the study by Karnath et al. (2004a), who had suggested a possible role of the central sectors of the STG in spatial neglect. This overlap shows striking resemblance with the lesion overlap documented by Doricchi and Tomaiuolo (2003) in the same area, indicating that in the sample of patients studied by Karnath et al. (2004a), lesion overlap in the STG was not selective and that neglect could have been due to parietal–frontal disconnection rather than STG damage.

Most recently, further studies provided additional information on the role of damage to parietal–frontal connections in the pathogenesis of the neglect syndrome in humans. Committeri et al. (2007) focused on the anatomical correlates of neglect for the contralesional half of the patient's own body (personal neglect) and neglect for the contralesional half of the outside-body space (extrapersonal neglect). They proposed that personal neglect is due to lesion involvement of the supramarginal gyrus in the parietal lobe whereas extrapersonal neglect is linked to damage of the central sector of the STG and the inferior frontal gyrus. Although detailed study of damage to specific white matter connections was outside the scope of this study (which only considered the percentage of damaged white matter in the centrum semiovale, the corona radiata and the external and internal capsulae), close scrutiny of the different analyses run by these authors clearly indicates damage of parietal–frontal connections in both the extrapersonal and the personal neglect groups. In a first series of comparisons, Committeri et al. made voxel-by-voxel lesion mapping subtractions between (a) patients with extrapersonal neglect (pure or combined with personal neglect) *vs* patients with pure personal neglect or no neglect at all; (b) patients with personal neglect (pure or combined with extrapersonal neglect) *vs* patients with pure extrapersonal neglect or no neglect. The results of subtractions are reported in Fig. 2 of the Committeri et al. article; here, in the first row of axial slices, an area of overlap is clearly present in the white matter of slice $Z = +28$. On the matching Talairach template, this overlap is perfectly centred on the SLF (Fig. 2), and is only 9 mm caudal and 1 mm superior to the spot of maximum lesion overlap found by Doricchi and Tomaiuolo (2003). A significant lesion overlap on the SLF, also came to light when patients with pure extrapersonal neglect were compared to those without neglect (slice $Z = +28$, third row of Fig. 2 from Committeri et al.). This overlap can be localised on the boundary between the likely human homologues of SLF II and SLF III (see Fig. 1). This finding supports the idea that damage of the SLF underneath the central sulcus (see Doricchi and Tomaiuolo, 2003) plays a part in extrapersonal neglect and cannot be merely attributed to the presence of undetected personal neglect which, according to Committeri et al. would have shifted the lesion overlap dorsally with respect to STG area subserving awareness of extrapersonal space (as proposed by Karnath et al., 2001, 2004a).

In a third analysis, Committeri et al. divided patients into two groups according to whether they did or did not have a lesion affecting each voxel (Voxel-based Lesion-Symptom Mapping, VLSM; see Bates et al., 2003). Scores for extrapersonal and personal neglect were then compared for these two groups, yielding a *t* statistics for each voxel and corresponding *t*-test based statistical maps for the entire voxel based brain volume. Using this method, in the case of extrapersonal neglect, a first lesion overlap was localised underneath the

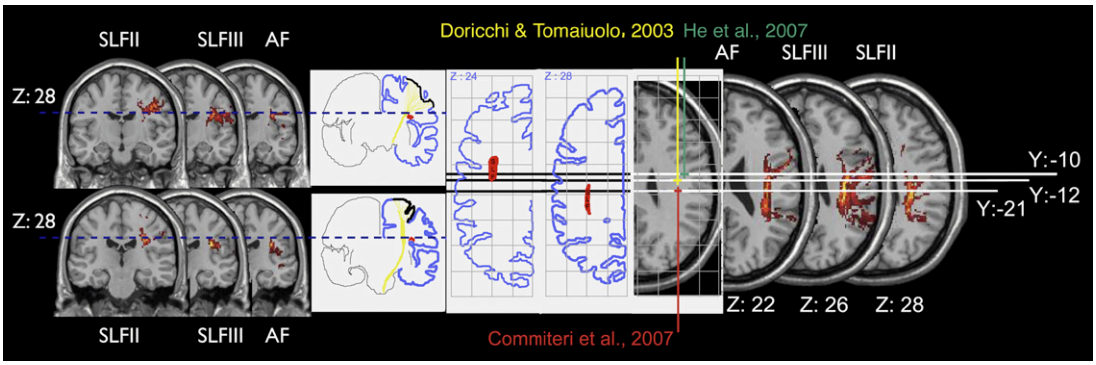

Fig. 2 – Meta-analysis of more recent anatomical studies (for a meta-analysis of previous studies see Fig. 2 in Bartolomeo et al., 2007). Registration of the hotspots described by Committeri et al. (2007) and by He et al. (2007) in patients with extrapersonal neglect, and of the hotspot originally reported by Doricchi and Tomaiuolo (2003) in patients with extrapersonal neglect without hemianopia, with a schematic rendering of the matching Talairach templates (Talairach and Tournoux, 1988) (red, SLF; yellow, pyramidal tract), and the percentage visitation maps for the SLF III and II and for the AF based on DTI of 24 normal subjects (Thiebaut de Schotten et al., 2006). Precise coordinates of the hotspots recently described by Verdon et al. (2006) and Ptak et al. (2007) are not available and thus not reported in the figure.

precentral gyrus at the crossing between the SLF and the pyramidal tract, producing both a parietal–frontal disconnection and a motor disconnection (see first row of their Fig. 4, sagittal slice $x = +36$). In Fig. 4 of Committeri et al.'s article, another area of lesion overlap in the parietal–frontal white matter is clearly visible at the centre of transversal slice $z = +20$ and sagittal slice $x = +36$ (where it is aligned to the end of the white line pointing at the STG; first row, extrapersonal neglect). This spot is centred on the SLF on the matching Talairach template and, according to the colour codes reported in Fig. 4 is very close to the highest level of statistical significance (i.e., Bonferroni correction) in the VLSM analysis.

In the case of personal neglect, two hotspots were present in the white matter and both were centred on the SLF (see second row of Committeri et al.'s Fig. 4, transversal slice $z = +32$ and sagittal slice $z = +36$). VLSM analysis also allows the similarity between *t*-test based statistical maps to be evaluated by calculating the correlations between *t* scores of personal and extrapersonal neglect for each voxel (Bates et al., 2003). A positive correlation in one voxel would suggest that this voxel performs a core function common to both types of neglect (Bates et al., 2003). Committeri et al. obtained a strong positive correlation of 0.84 (reflecting 70% of overlap in the variance[1]) in the inferior frontal gyrus (see Husain and Kennard, 1996), the posterior insular–opercular cortex and in the fronto-parietal white matter underlying the central sulcus (see Doricchi and Tomaiuolo, 2003). The VLSM analysis thus also demonstrated that, independently of the sector of space affected by neglect, parietal–frontal white matter is implicated in a core function for space awareness.

Three other recent studies provided further support to this view. In an fMRI study, He et al. (2007) found that temporal correlation between BOLD signals (i.e., functional connectivity) in the TPJ and the midfrontal gyrus was disrupted in patients with chronic extrapersonal neglect. Anatomical investigation on the neural bases of disrupted connectivity revealed maximal lesion overlap in the AF and in the SLF (involving both the SLF III and the SLF II; see sagittal slices $z = 24$ and $z = 30$ in Fig. 2A from He et al., 2007). This overlap is virtually identical to that originally reported by Doricchi and Tomaiuolo (2003) (see Fig. 2).

In a VLSM study on 80 stroke patients Vuilleumier and coworkers (Verdon et al., 2006), found that damage to fronto-parietal white matter fibers, which the authors identified with the pathway described by Thiebaut de Schotten et al. (2005), correlated with the presence of generalised and severe neglect. These authors, however, importantly noted that deficits of performance on different neglect tasks correlated with damage in different brain areas. For instance, ipsilesional bias in line bisection was associated with posterior occipital–parietal lesions whereas deficits in multiple item cancellation were observed in patients with frontal damage (Binder et al., 1992).

Finally, in a very recent study on the influence of distracters on the initiation of leftward and rightward saccades in patients with left neglect, Ptak et al. (2007) found that in six of their seven neglect patients the area of maximal lesion overlap included the white matter in the centrum semiovale, the white matter underneath the posterior insula and the posterior part of the internal capsula.[2]

The abundant evidence reviewed above, suggests that fronto-parietal disconnection might play a major role in the occurrence and, most of all, in the severity of neglect in unilateral brain damaged patients. There are, however, also patients with signs of left neglect resulting from damage to more

[1] Consider, for the sake of comparison, that Bates et al. concluded for shared processes between verbal fluency and auditory comprehension on the basis of a 0.59 correlation, reflecting 35% of overlap in variance.

[2] The authors commented that this area was "somewhat different than the results of previous anatomical studies". Their finding should sound less surprising after consideration of the wealth of evidence reviewed here on white matter damage in neglect.

ventral regions in the right hemisphere. For example, strokes in the territory of the right posterior cerebral artery can also give rise to signs of left neglect (Mort et al., 2003; Park et al., 2006). Interestingly, also in these patients the maximum lesion overlap seems to be situated in the white matter, in a location compatible with a white matter tract connecting the parahippocampal gyrus with the angular gyrus of the parietal lobe, possibly the ILF (Bird et al., 2006). Urbanski et al. (2008) recently employed DTI tractography to explore the integrity of three major caudo-rostral pathways (ILF, SLF and IFOF) in four patients with strokes in the right hemisphere, two of whom showed signs of left neglect. The pathways were present in both hemispheres in patients without neglect; in neglect patients, however, it was not possible to track the IFOF in the right hemisphere. These results, which are the first obtained with DTI tractography in vascular patients with neglect, need to be confirmed in larger series of patients; they suggest, however, that in some cases a lesion to the direct connections between ventral occipital and frontal regions may contribute to the manifestation of neglect by impairing the top–down modulation of visual areas from frontal cortex or the transmission of visual input to frontal areas important for general arousal.

3. Current models of neglect and intrahemispheric disconnections

3.1. *The role of spatial and non-spatial factors in the pathophysiology of neglect*

In 1982, De Renzi pointed out that "..any attempt at understanding neglect is faced with the question of its greater frequency and severity following right than left brain lesion" (De Renzi, 1982, p. 90). This hallmark of neglect has inspired neurocognitive models of spatial attention in the intact human brain, which, in turn, attempted to provide a functional interpretation of the syndrome.

Several neurocognitive models posit a right hemispheric specialization for spatial and/or non-spatial functions that might be specifically impaired in neglect patients. However, it remains debated whether disruption of spatial or non-spatial functions in the right hemisphere is crucial in the pathogenesis of neglect.

Mesulam (1981, 1999, 2002) proposed that neglect is more frequent after right brain damage because the right hemisphere controls attentional orienting in both the left and right hemispaces, whereas the left hemisphere controls the direction of attention only in the right hemispace (see top panel in Fig. 3; see also Heilman and Van Den Abell, 1980). This organization of spatial functions implies that following right brain damage, attention can only be directed towards the right hemispace by the intact left hemisphere whereas after left damage, orienting of attention towards both hemispaces is maintained by the intact right hemisphere. According to Mesulam (2002), three cortical components subserve spatial attention: the posterior parietal cortex (PPC), the frontal eye field (FEF) and the cingulate cortex. Within the PPC, the cortical surface of the inferior parietal lobule (area 7a in the monkey) provides a saliency map of external space to the lateral intraparietal area (LIP), which, thanks to its connectivity with the FEFs, generates plans for actions. The FEFs, due to their connections with the superior colliculi, cingulate gyrus and other premotor and prefrontal areas, subserve the motor implementation of plans selected in LIP and also exert top–down influence on reflexive motor responses (see also Buschman and Miller, 2007). Because of their intense reciprocal connection, the PPC and FEF constitute an attentional network subserving a level of "sensory-motor integration where the boundaries between action and perception become blurred" (Mesulam, 2002, p. 35). Thus, according to this view, a narrow dichotomy between sensory and motor neglect in relationship to parietal versus frontal brain damage might be unlikely. Finally, the cingulate cortex might be in charge of redirection of attention, performance monitoring and response selection (although, as noted by Mesulam (2002), cingulate lesions rarely engender spatial neglect). In terms of disconnection, damage to the human analogue of SLF II might be crucial to the functional disruption of the parietal–frontal network outlined by Mesulam and consequently produce signs of spatial neglect in humans. Results from the study of Doricchi and Tomaiuolo (2003) and Thiebaut de Schotten et al. (2005) are compatible with this model (see also Thiebaut de Schotten et al., 2008, this issue). Mesulam (2002) also pointed out that lesions within the fronto-parietal-cingulate network "are likely to cause multimodal neglect, whereas lesions that disconnect it from specific sensory or motor areas could yield modality-specific neglect symptoms". This proposal envisages complex anatomical–functional scenarios consistent with the heterogeneity of the neglect syndrome (see Bartolomeo et al., 2007) and with the idea that multiple sensory-to-motor mapping systems subserve space representation (Rizzolatti et al., 1997). In this perspective, we propose that functional disruption of different networks could be associated with different neglect signs. This could depend on selective lesion of different white matter fasciculi, on the localisation of disconnection at different points along the same fasciculus and on the combination of these pathophysiological factors with damage of different cortical modules or efferents from these modules.

A different point of view on the pathophysiological foundations of neglect was recently advanced by Corbetta and Shulman (2002). Based on fMRI evidence in normal subjects, these authors proposed that voluntary orienting of spatial attention is not lateralized in the right hemisphere and that it is subserved by a dorsal, bilateral and symmetrical attentional network (DAN) which includes parts of the intraparietal sulcus and the superior frontal cortex (FEF). The functioning of this bilateral network is modulated by a Ventral Attentional Network (VAN), which is strongly lateralized in the right hemisphere and composed of the temporal–parietal junction (TPJ) and the ventral–lateral frontal areas (middle and inferior frontal gyrus; see bottom panel in Fig. 3). According to the same authors, the ventral network subserves non-spatial functions that are identified in the detection and reorienting of attention towards unexpected sensory events, spatial and temporal capacity, working memory and vigilance (see also He et al., 2007). Thus, the ventral network is able to interrupt the current focusing of attention maintained by the dorsal system and trigger the spatial re-orienting of attention to a novel

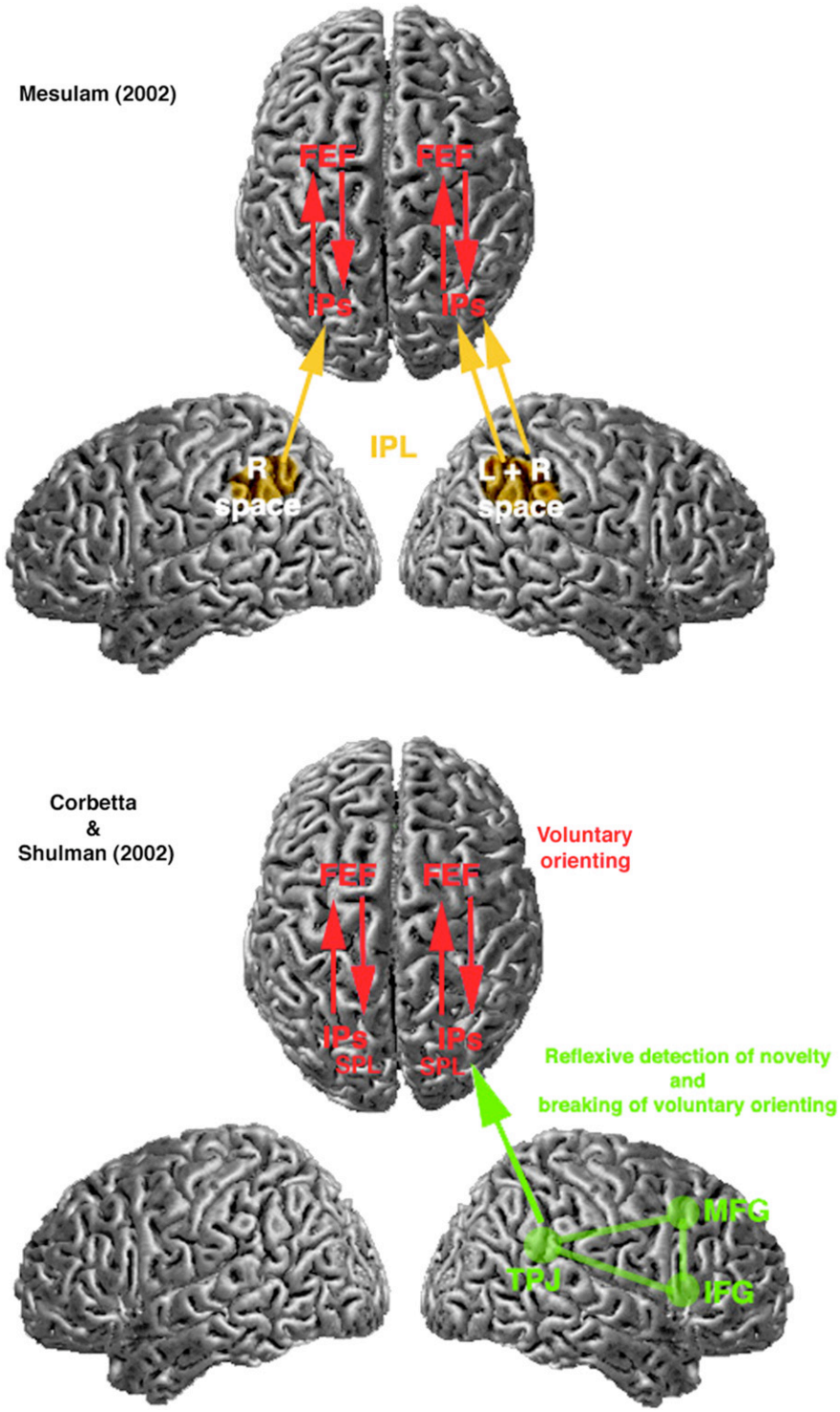

Fig. 3 – Hemispheric specialization of attentional functions according to the models proposed by Mesulam (2002) and Corbetta and Shulman (2002). FEF, frontal eye fields; IPL, inferior parietal lobule; IPs, intra parietal sulcus; SPL, superior parietal lobule; TPJ, temporal parietal junction; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; L, left; and R, right.

salient event. These authors have proposed the original view that ''neglect reflects primarily a lateralization of nonspatial functions rather than spatial functions, which when disrupted also produce asymmetrical deficits in spatial functions'' (He et al., 2007). Therefore, neglect is consequent to direct anatomical damage of the ventral system, provoking a functional imbalance of the dorsal system. With reference to white matter pathways it is conceivable that disruption of the ventral network depends on damage of the human homologous of the most ventral branch of the SLF (i.e., the human

homologous of SLF III) and the AF. Anatomical data reported in the studies by Doricchi and Tomaiuolo (2003), Thiebaut de Schotten et al. (2005) (see also Thiebaut de Schotten et al., 2008, this issue) and He et al. (2007) converge on the involvement of the human homologues of SLF II and III. Data reported by He et al. (2007) also suggest the involvement of the AF.

In our opinion, the original point made by Corbetta and Shulman (2002) (He et al., 2007) is consistent with the frequent association of impairments of vigilance and spatial working memory with spatial neglect (Husain and Rorden, 2003), an association deserving consideration in future investigations. However, at the same time, the proposal by Corbetta and Shulman might suffer some explanatory limitation due to the manifold behavioural dissociations that clinicians so often encounter in the examination of neglect patients. Performance dissociations observed in these patients (Bartolomeo and Chokron, 2001) most commonly pertain to the sector of space selectively affected by neglect (as for example when neglect is limited to the extrapersonal, peripersonal, personal-body or imagery space), to the specific spatial reference frame affected by neglect (egocentric, allocentric or object-centred) or even to tasks requiring different attentional processing modes (parallel *vs* serial) for the analysis of the same sector of space (e.g., line bisection *vs* multiple item cancellation tasks in the peripersonal space; Binder et al., 1992). For instance, neglect along the horizontal mental number line used for the spatial representation of numbers (Dehaene et al., 2004; Zorzi et al., 2002) is doubly dissociated, functionally and anatomically, from neglect along physical horizontal lines (Doricchi et al., 2005). Is the variety of these dissociations reconcilable with the idea that disruption of a heterogeneous ensemble of non-spatial functions in the VAN is the primary cause of contralesional spatial neglect? Following this hypothesis, indeed, the existence of several different VANs, each relative to the sector of space or the spatial attentional function selectively or predominantly affected by neglect, should be postulated to explain clinical dissociations. Alternatively, the possibility might be advanced that different and non-hemispherically lateralized networks underpinning the representation of different sectors of space can be selectively disconnected from the VAN.

In conclusion, disentangling the prevalent role of right hemisphere lateralized spatial and non-spatial factors in the pathogenesis of neglect seems to be one of the important issues to be addressed in future studies. Studying whether in the normal human interhemispheric asymmetries of white matter are present in dorsal, ventral or both dorsal and ventral fronto-parietal bundles might help resolve the debate between spatial and non-spatial interpretations of neglect. Here, it is also important to remind that an intermediate position between spatial and non-spatial interpretations was originally advanced by Husain and Rorden (2003), who emphasized the clinical relevance of the association of non-spatial vigilance impairments to spatial neglect (see the pioneering observations by Husain et al., 1997; and Robertson et al., 1998).

3.2. *The Superior Temporal Gyrus and visual neglect*

The traditional views pointing at the role of damage to the right inferior parietal region as main lesional correlate of spatial neglect in humans were radically challenged by the proposal that neglect would rather derive from damage to the central portion of the right STG (Karnath et al., 2001, 2004a). This provocative proposal had the merit of prompting a lively debate and of renewing interest on the anatomical correlates of neglect. In our opinion, however, perusal of clinico-anatomical studies reveals that in all of the studies pointing at the role of the lesion of the central sector of the STG in spatial neglect, the brain damage was never restricted to STG and always associated to damage of the parietal–frontal connections in the white matter (this was localised in the SLF in the meta-analysis reported in Fig. 2 in Bartolomeo et al., 2007). For instance, the coupling between these two lesions is clearly present in data gathered from a sample of 140 patients by Karnath et al. (2004a).[3] Parietal–frontal white matter damage, whether involving the AF or the SLF, would disconnect large portions of the parietal, parietal–temporal and temporal cortex from frontal areas, thus casting doubts on the proposed role of damage to the central sector of STG in the pathogenesis of neglect. Note, however, that commenting on the uncertain role of STG damage in spatial neglect [see, for example, the debate between Karnath et al. (2004b) and Mort et al. (2004)] requires careful consideration of important differences in the methods and results of various studies. For example: (a) some studies (Karnath et al., 2001; Doricchi and Tomaiuolo, 2003), but not others (Karnath et al., 2004a; Mort et al., 2003; Corbetta et al., 2005; Committeri et al., 2007), separated patients according to the presence or absence of lesion involvement of the basal ganglia or the thalamus, which can influence spatial neglect; (b) some studies separated patients according to the vascular territory affected by stroke [middle *vs* posterior cerebral artery; (Mort et al., 2004; Corbetta et al., 2005)], whereas others did not (Karnath et al., 2001, 2004a; Committeri et al., 2007; Doricchi and Tomaiuolo, 2003); (c) some studies (Karnath et al., 2001; Doricchi and Tomaiuolo, 2003; Corbetta et al., 2005), but not others (Karnath et al., 2004a; Mort et al., 2004; Committeri et al., 2007), selected patients according to the presence/absence of visual field defects. Notwithstanding these differences, investigations run with various methodologies (Vallar and Perani, 1986; Mort et al., 2003; Ellison et al., 2004; Thiebaut de Schotten et al., 2005; Corbetta et al., 2005; He et al., 2007) concur in suggesting a role of the junction between the caudal portion of the STG and the inferior parietal lobule in the awareness of contralesional space.

However, the attribution of a similar role to the central sectors of the STG (Karnath et al., 2001, 2004a) seems far more controversial. Temporary inactivation of the middle and rostral portions of the STG by TMS (Ellison et al., 2004) produced no lateralized deficits both on a visual search task involving difficult discrimination between targets and distracters (upright uppercase L among rotated Ls) and on an easier task requiring the detection of a short line segment among similar but differently oriented segments (i.e., very similar to

[3] See the identical white matter lesion overlap, in slice $Z = +24$ from Figs. 1B, 2 and 3 in Karnath et al. (2004a). The authors locate the overlap in Figs. 1B and 2 on the white matter and the overlap in Fig. 3 on the caudate nucleus; see also the meta-analysis reported by Bartolomeo et al. (2007).

the classic line cancellation task used for the screening of neglect; Albert, 1973). In the same study, TMS stimulation of the central sectors of the STG caused no lateralized effect on judgments of the length of horizontal lines (Landmark task) whereas inactivation of the posterior parietal cortex provoked lateralized effects in the same direction as that shown by patients with neglect tested on the same task (Milner et al., 1993). More importantly, Karnath and co-workers recently showed that direct electrical inactivation of the central sector of the STG during brain surgery produced no lateralized impairment in visual search (Gharabaghi et al., 2006), confirming the previous TMS findings by Ellison et al. (2004). Finally, using electrocortical stimulation mapping before epilepsy surgery, Kleinman et al. (2007) found that stimulation of the central sector of the right STG produced auditory perceptual changes without producing effects on neglect tests (line bisection, detection of gaps on the left side of circles).

3.3. *Problems with purely disconnective accounts of neglect*

Despite the abundant evidence reviewed above, an apparent challenge to the role of subcortical disconnection in the pathogenesis of neglect comes from a number of investigations on the correlation between levels of cortical perfusion and presence of neglect in the acute, or hyperacute, post-stroke phase. Using perfusion weighting imaging, based on estimates of arrival and clearance of a bolus of contrast indicating the level of functional activity in otherwise structurally spared cortical areas, Hillis et al. (2002) investigated the functional correlates of neglect and aphasia due to hyperacute (within 48 h from stroke) subcortical infarction. They found that, independent of the lesion localisation (corona radiata or caudate/capsular structures), neglect was only present in patients who had associated cortical hypoperfusion, and absent in those having no cortical hypoperfusion. This study suggests that a lesion in the white matter does not necessarily cause neglect. Unfortunately, no tracking of white fibers touched by the lesions was made, thus leaving unexplored the relationship between the location and extent of white matter damage, cortical hypoperfusion and neglect. Notwithstanding this limitation, the findings by Hillis et al. are relevant in that they confirm that a subcortical disruption of parietal–frontal connections might cause neglect by reducing functional activity in the entire cortical–subcortical parietal frontal network connected by these pathways.

A second note of caution on the study of the anatomical correlates of neglect in the white and gray matter, concerns data gathered from lesion overlap studies. Husain and Nachev (2007) noted that the reliability of the lesion overlap approach might be weakened by the fact that the structure of the vascular tree introduces a marked inhomogeneity in the shape and distribution of stroke lesions. This caveat suggests that inferences on the anatomy of neglect gathered from lesion overlap studies should be carefully tested by comparing patients with and without neglect suffering lesions of comparable volume (see also Catani and Mesulam, 2008a, this issue). Studies on the effects of surgical selective inactivation of restricted portions of the white and gray matter, like the one by Thiebaut de Schotten et al. (2005), allow circumventing this caveat. Findings from these studies (see also Gharabaghi et al., 2006) seem already being tempering the idea that lesion volume "per se" might be a relevant cause of neglect.

4. Some points for future research

4.1. *Methods of testing spatial neglect and anatomical–functional correlations*

An important issue when trying to establish anatomical–functional correlations, or to compare the anatomical results reported by different authors, is a careful consideration of the behavioural tasks used to assess spatial neglect. In the most recent literature, this issue has proven to be a relevant source of confounding and disagreement among authors (see Karnath et al., 2004b; Mort et al., 2004) that should be avoided in future studies. For instance, Committeri et al. (2007, p. 433) argued that the line bisection test "is a very good test for research purposes but not for diagnostic purposes", because ipsilesional deviation up to the 3% of line length can be found even in elderly normal subjects (Halligan et al., 1990), and because performance in line bisection does not correlate with the neglect observed in everyday life (Ferber and Karnath, 2001). If accepted, this conclusion might crucially reduce the relevance and reliability of anatomo/clinical studies based on the use of the line bisection task (see for example Mort et al., 2003; Thiebaut de Schotten et al., 2005). It is worth noting, however, that in the study by Halligan et al. (1990) quoted by Committeri and co-workers, the average rightward group deviation with line of conventional length (203 mm) was equivalent to the 0.1% (0.22 mm) of total line length. In the same group only two outliers were present: one had 4% leftward deviation (8.5 mm, case 2, Table 2, see Halligan et al., 1990), the other 3% rightward deviation (6.2 mm, case 5, Table 2, see Halligan et al., 1990). Therefore, the average rightward group deviation observed by Halligan et al. (1990) seems far below those observed with lines of equivalent length in the studies by Doricchi and Tomaiuolo (2003), which amounted to 10.4 mm (these patients had also significant contralesional impairments in cancellations tasks) and by Thiebaut de Schotten et al. (2005) (surgical inactivation of the SLF: range 26–40 mm; SMG: 6.25 mm; caudal STG: range 6.5–8.8 mm). It also seems much smaller than the cut off for 200-mm lines (i.e., 6.5 mm rightward) based on the performance of 204 right brain damaged patients (Azouvi et al., 2002). Ferber and Karnath (2001) have also explicitly called into question the sensitivity of the line bisection task to spatial neglect. Based on the study of a sample of 35 right brain damaged patients with clinical signs of neglect, Ferber and Karnath argued that cancellation tasks provide a more sensitive measure of neglect compared to line bisection because significant ipsilesional deviation in bisection occurred in only 60% of patients whereas 94% of them showed a significant rate of contralesional omissions in multiple item cancellation. The point made by Ferber and Karnath is importantly weakened by the fact that in their study the lines to be bisected were positioned on the right side of the page. It is well known that positioning lines in the ipsilesional space significantly reduces the pathological rightward bias shown by neglect

patients when lines to be bisected are placed with their centre aligned to the head–body midsagittal plane (Schenkenberg et al., 1980). The evidence collected by Azouvi et al. (2002) in a larger sample of 204 right brain-damaged patients also runs contrary to the conclusions by Ferber and Karnath. Azouvi et al. (2002) found that the sensitivity of the conventional bisection task with 200 mm lines presented centrally, was only 3.6% lower than that of multiple item cancellation tasks. A factorial analysis from the same study also demonstrated that line bisection and multiple item cancellation tasks belonged to two different factors. Ipsilesional deviation in line bisection was specifically associated with lesions of retroro-landic parietal, occipital and temporal areas. In the light of this converging evidence, we propose that it would be more advisable to view line bisection and multiple item cancellation tasks as providing different measures of neglect, i.e., that they test lateralized impairments of different spatial abilities.

The behavioural and anatomical dissociations indicated by the study of Azouvi and co-workers also corroborate the idea that it is unwise to consider neglect as a homogenous collection of symptoms. In our opinion, this view should be extended further and applied to more subtle clinical features and dissociations observed in neglect patients. For instance, relevant dissociations are also found with different tasks used to assess similar features of the neglect syndrome. Binder et al. (1992) first demonstrated that extrapersonal deficits in line bisection can be dissociated from extrapersonal deficit on multiple item cancellation tasks (see also Halligan and Marshall, 1992); impairments in bisection correlated to damage of posterior occipital–parietal areas, whereas impairments in cancellation occurred after damage of the frontal cortex and basal ganglia. These findings were replicated by Doricchi and Angelelli (1999) and Azouvi et al. (2002), by Verdon et al. (2006) using the VLSM approach, and are supported by neuroimaging data (Fink et al., 2000). In our view, this very type of dissociation is a clear example of the symptomatological richness of the neglect syndrome, suggesting that only the combined use of different diagnostic tools can give a complete picture of the specific spatial impairments suffered by each neglect patient.

4.2. *Hodological and topological factors*

As noted by Mesulam (2002), between-patients variability in the symptomological composition of the syndrome is often the rule rather than the exception in clinical practice. Thus, one of the major challenges for future anatomical studies is the need of dealing with and explaining the heterogeneity of the neglect syndrome. In the present review, we advance the very general idea that functional disruption of different white matter/gray matter networks could be associated with different neglect signs. It is, however, more difficult to define whether dissociations of performance result from selective damage to different white matter bundles, from damage to different points along the same bundle or from the combination of disconnection and damage to different grey matter modules. Following the theoretical framework recently proposed by Catani and ffytche (2005), this problem refers to the role of topological factors, related to dysfunction of cortical specialized areas, and hodological factors, related to dysfunction of connecting pathways among the same areas. Disconnection might produce, indeed, more of a deficit than cortical damage/dysfunction alone through several, not mutually exclusive, mechanisms. (1) Damage to the tightly packed fibers of the white matter may result quantitatively more disrupting than damage to equivalent cortical volumes, by impairing the functioning of larger cortical areas (Bartolomeo et al., 2007). (2) Brain networks are composed of cortical modules interacting with each other. Disturbed communication between modules might thus produce not only cortical hypo-functioning, but also hyper- or inadequate functioning of several cortical areas, resulting in a more severe disintegration of complex functions than the deficit resulting from lesion to isolated modules (Catani and ffytche, 2005) (3) Cortical lesions may leave the possibility for other cortical areas to functionally compensate for the deficit (see, e.g., Duffau, 2005); on the other hand, white matter damage, which provokes the dysfunction of a whole network of connected areas, might render compensation more difficult to obtain (see also Catani and Mesulam, 2008b, this issue). The combined use of morphometric, DTI, functional and perfusion techniques could offer promising ways of exploring the respective roles of hodological and topological factors in spatial neglect.

In conclusion, the study of the anatomical correlates of unilateral spatial neglect seems to be entering a new exciting phase, where contrasting views on the localisation of selective cortical lesions causing neglect can be reassessed in the light of the idea, pioneered by Critchley (1953), Geschwind (1965) and Mesulam (1981), that enduring and generalised disruption of cortical–subcortical networks subserving awareness for one side of space is importantly influenced by damage to white matter connections allowing the integrated functioning of these networks. New technical developments in neuroanatomy and comprehensive diagnostic neuropsychological testing are already reinvigorating the study of several long-standing clinical and anatomical issues related to disturbances of spatial cognition and attention in humans.

Acknowledgements

The authors wish to thank the guest editors of this issue and three anonymous reviewers for their suggestions. F.T. wishes to thank the ''Cassa di Risparmio di Volterra'' for providing technical equipment and Dr. G.Mariani (General Manager) and G. Brunale (President) for their support in setting up the ''Laboratory of Neuroanatomy'' at the ''Auxilium Vitae'' Volterra (Pisa). This study was supported by grants from the Fondazione Santa Lucia and the ''Universita' agli Studi di Roma'' ''La Sapienza'' to F.D. and by grants from Assistance Publique – Hôpitaux de Paris (Interface Program) and Université Pierre et Marie Curie – Paris6 (Bonus Qualité Recherche) to P.B.

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