

A Parietofrontal Network for Spatial Awareness in the Right Hemisphere of the Human Brain

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Patients with lesions of the right hemisphere often show signs of left-sided unilateral neglect. Left-sided neglect may impair the ability of patients to live independently and entails a poor functional outcome. When exploring a visual scene, patients with left-sided neglect fail to pay attention to left-sided objects. They do not eat from the left part of their dish, they bump their wheelchair into obstacles situated on their left, and they have a tendency to look to right-sided details as soon as a visual scene unfolds, as if their attention were “magnetically” attracted by these details.¹ On visuospatial testing, they fail to cancel or describe left-sided targets in search tasks, deviate rightward when bisecting horizontal lines, and fail to copy the left part of drawings^{1,2} (**Figure 1**).

The study of left-sided neglect is important for neuroscientists to understand the brain mechanisms underlying spatial awareness. From the clinical point of view, research on neglect can ameliorate the diagnosis by devising appropriate visuospatial tests, clarify the prognostic factors for individual patients with particular patterns of impairment, and allow the development of rational strategies of rehabilitation. Despite decades of research, however, the lesional bases of neglect within the right hemisphere still remain controversial.

The usual strategy to identify the lesional correlates of neglect has been to use the lesion overlapping method. The magnetic resonance or computed tomographic images of the lesions of a number of patients who had experienced a stroke, with or without neglect, are superimposed, and the zone of overlap of patients with neglect is considered to be the crucial lesional basis of this condition. These studies^{3,4} have usually indicated the inferior parietal lobule (IPL) as the site of maximal lesion overlapping. Recent evidence, however, pointed rather to a crucial role of

lesions of the middle and rostral parts of the superior temporal gyrus and tended to exclude a role for lesions of the temporoparietal junction.⁵ The underlying subcortical association circuits have received less attention,⁶ despite evidence from animal studies⁷⁻⁹ suggesting an important role for parietofrontal disconnection.

However, the lesion overlap method used for human studies has several problems.¹⁰ First, an obvious limitation is the lack of spatial resolution, resulting from the coarse boundaries of vascular lesions, aggravated by the fact that lesions are usually plotted, or “normalized,” on a standard brain, which can only approximate the spatial arrangement of real individual brains. Second, vascular lesions may well reflect differences in vascular territories rather than true functional organization of the brain. Third, in case of multiple lesions (by no means a rare occurrence in neglect), the region of overlap may be identified as the crucial region, whereas the deficit may in fact result from the co-occurrence of distinct lesions. Finally, and more generally, the lesion overlapping approach tends to rely on a “phrenological” view of anatomical-functional relationships, according to which each brain region is dedicated to, and crucial for, a particular function. Much

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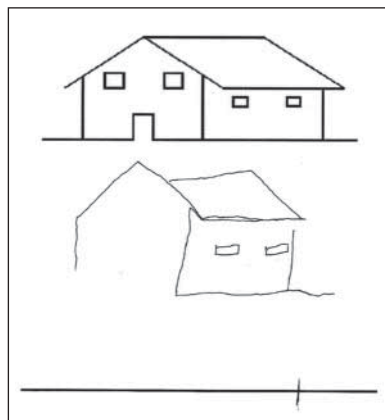


Figure 1. Copy of a drawing and bisection of a line by a patient with left-sided neglect.

evidence from cognitive neuroscience suggests, instead, that the brain is a mosaic of functionally distributed and highly interactive regions. As a consequence, the function of a given brain region may only emerge through the interaction with other regions, in a functional network organization.

METHODS

In a recent study,¹¹ a different approach was used to explore the neural bases of human spatial processing. When removing a brain tumor, the surgeon tries to perform a resection that is as radical as possible, without leaving the patient with a neurological deficit. To accomplish this, the patient is awakened during the intervention, and small brain regions (approximately 5 mm) are temporarily inactivated with electrical stimuli while the patient performs functional tasks. If the patient produces incorrect responses, the surgeon leaves the region intact, to preserve the patient's functional abilities. In the present study, the visuospatial functions during brain surgery were assessed by asking 2 patients to bisect 20-cm horizontal lines.² Patients deviated rightward on inactivation of the supramarginal gyrus (the rostral subdivision of the IPL) and of the caudal part of the superior temporal gyrus, but performed accurately when more rostral portions of the superior temporal gyrus or the frontal eye field were inactivated. More important, however, the strongest deviations occurred in one pa-

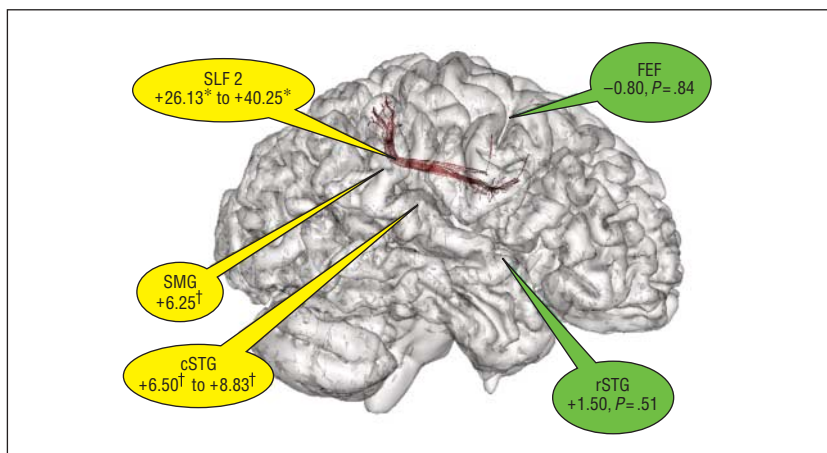


Figure 2. Three-dimensional reconstruction of the brain of a healthy individual showing the second branch of the superior longitudinal fasciculus (SLF 2) (in red), as tracked by diffusion tensor imaging. There is schematic localization of the sites whose temporary inactivation did yield (yellow) or did not yield (green) significant rightward deviation on line bisection in 2 neurosurgical patients (the study by Thiebaut de Schotten et al¹¹ provides more details). cSTG indicates the caudal portion of the superior temporal gyrus; FEF, frontal eye field; rSTG, rostral portion of the superior temporal gyrus; SMG, supramarginal gyrus; positive values, rightward deviations; and negative value, leftward deviation. * $P < .01$ (2-tailed) compared with control subjects' performance. † $P < .05$ (2-tailed) compared with controls' performance. Values are expressed in millimeters.

tient on inactivation of a white matter region in the depth of the IPL, after most of the tumor had been removed. To map the course of long association fibers in the white matter of this particular patient, post-operative magnetic resonance images were obtained and a new technique (called diffusion tensor magnetic resonance tractography) capable of tracking the white matter fibers was used. The tract in which inactivation had brought about the maximal rightward deviation likely corresponds to the human homologous of the second branch of the superior longitudinal fasciculus¹² (**Figure 2**).

Thus, in this study, functional parietofrontal disconnection dramatically disrupted the symmetrical processing of the visual scene, consistent with previous findings obtained in rodents,⁷ nonhuman primates,⁸ and human patients who had experienced a stroke.⁶ Visuospatial testing during brain surgery was also clinically important. The neurosurgeon was careful not to remove the regions in which inactivation had provoked rightward shifts of the subjective line center. As a consequence, patients had no signs of neglect a few days after surgery.

As with all techniques of brain-behavior analysis, direct brain stimulation has limitations. The sites and

the number of stimulations are dictated by clinical needs, and are often disarmingly limited for the researcher. Phenomena of cortical plasticity, frequent with low-grade gliomas,¹³ can complicate the interpretation of the mapping data. Most important, however, these limitations are not the same as with other methods, such as the lesion studies in rodents, nonhuman primates, and humans. In the case of neglect, evidence from all of these approaches converges in underlining an important role of parietofrontal disconnection.

RELEVANCE TO THE PRACTICE OF NEUROLOGY

It is important to stress the necessity of visuospatial testing for brain-damaged patients. Signs of unilateral neglect may easily pass undetected if appropriate paper-and-pencil tests are not given. As a consequence, patients may remain undiagnosed and receive no rehabilitation. Testing for neglect is easy; it requires a few tasks that can be administered at the bedside. Line bisection, target cancellation, and the copy of a drawing are sufficient to make a diagnosis of neglect in most cases. Standardized versions of these tests are available,² which allow the examiner to compare the patient's per-

formance with that of age-matched groups of individuals without neurological impairment.

The findings of Thieaut de Schotten et al¹¹ also underline the importance of visuospatial testing during brain surgery. Intraoperative functional mapping is important to minimize postoperative morbidity while increasing the quality of the resection and, thereby, to improve patient survival. Until now, intraoperative mapping has essentially been dedicated to sensorimotor and cognitive functions, such as language, memory, or calculation, whereas visuospatial functions have been largely ignored. When the surgery involves the temporoparietal region or the dorsolateral frontal cortex, visuospatial functions should be assessed systematically, by asking patients to bisect 20-cm horizontal lines. If the patient shifts the subjective center in the direction of the operated on hemisphere by more than approximately 6.5 mm (further described by Azouvi et al²), then the neurosurgeon should not resect the tested area. Such a simple, safe, well-tolerated, and cost-effective procedure can prevent postoperative neglect and, consequently, allow patients to resume the tasks of a normal socioprofessional life, such as driving a car.

RELEVANCE TO THE STUDY OF NEUROSCIENCE

The stimulation study by Thieaut de Schotten et al¹¹ directly demonstrates that structures at the junction between the parietal and the temporal lobes, and long-range parietofrontal connections, are critical to the symmetrical processing of the visual scene in humans. These data confirm and specify some of the previous results based on lesion overlapping, which indicated damage to the temporoparietal junction⁴ and, perhaps more important, to the underlying white matter⁶ as crucial antecedents of left-sided neglect. The finding of maximal neglect on inactivation of parietofrontal pathways is reminiscent of results obtained in monkeys.⁸ In that study,⁸ neglect occurred after unilateral sectioning of the white matter between the fundus of the intraparietal sulcus and the lateral ventricle,

which sectioned long-range parietofrontal pathways; little or no neglect occurred after lesions, either isolated or combined, of the frontal and/or the parietal cortex.

The task used in the study by Gaffan and Hornak⁸ involved searching a target among several horizontally arranged distractors. Monkeys with neglect often failed to respond to targets contralateral to the lesion, choosing instead an ipsilesional distractor. Thus, there is a remarkable consistency between results obtained in humans and in monkeys, with different behavioral tests (line bisection in humans¹¹ and target search in monkeys⁸). This strongly suggests a similar organization of space-processing mechanisms across the 2 species. Also consistent with these findings, rats with unilateral sectioning of the connections between the medial agranular cortex (the rodent analogue of the frontal eye field) and the posterior parietal cortex showed impaired orienting toward contralateral stimuli in the visual, auditory, or tactile modality.⁷ These results support models of neglect postulating an impairment of large-scale right hemisphere networks,^{14,15} including prefrontal, parietal, and cingulate components. The parietal component could be especially important for the perceptual salience of extrapersonal objects, whereas the frontal component might be implicated in the production of an appropriate response to behaviorally relevant stimuli, in the online retention of spatial information, or in the focusing of attention on salient items through reciprocal connections to more posterior regions. In line bisection, parietal inactivation might, thus, modulate the relative salience of the 2 line segments. The subjective center of the line would then be displaced toward the side of the (subjectively) more salient segment, because this segment would then appear to be longer than it is.

The relative saliency of the line segments might also be influenced by spatial attention. It is tempting, although speculative, to explore the possible links between shifts in line bisection and biased orienting of attention in patients with neglect. Attention can be directed to an object in space either in a relatively stimu-

lus-driven way (ie, exogenously) or more voluntarily, or endogenously (Bartolomeo and Chokron¹⁶ provide a review).

Patients with left-sided neglect often demonstrate a rightward exogenous orienting bias, an impaired leftward exogenous orienting, or both, with relative sparing of endogenous orienting.¹⁶ In line bisection, the required perceptual comparison between the 2 segments is implicit, thus typically recruiting exogenous processes.¹⁷ The attentional imbalance in patients with neglect might, thus, increase the relative salience of the right-sided segment and, consequently, displace the subjective center toward the right-sided end point. Neuroimaging studies¹⁸ have identified a right hemisphere network especially concerned with orienting to unexpected stimuli, a typical function of exogenous attention. This network includes the IPL and the caudal part of the superior temporal gyrus, as well as the inferior and middle frontal gyri and the frontal operculum. More dorsal and bilateral networks, including the superior parietal lobule and the frontal eye field, are instead implicated in endogenous attention. Interestingly, the cortical lesions more often associated with left-sided neglect largely overlap with the exogenous attentional network, consistent with the prevalent exogenous impairment in these patients.¹⁶ Corbetta et al¹⁸ found that patients with neglect who had lesions in the white matter beneath the IPL demonstrated abnormal functional magnetic resonance imaging activation of structurally intact areas of the dorsal network, with the left-sided components of the network being relatively overactive compared with their counterparts in the right hemisphere. These findings represent additional evidence consistent with the hypothesis that impairments of spatial awareness do not result from damage of a single brain area but are the expression of the dysfunction of large hemispheric networks. The identification of the component parts of these networks, of their precise functional roles, and of their connections constitutes a fascinating challenge for future research.⁸

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REFERENCES

1. Bartolomeo P, Chokron S. Levels of impairment in unilateral neglect. In: Boller F, Grafman J, eds. *Handbook of Neuropsychology*. Vol 4. 2nd ed. Amsterdam, the Netherlands: Elsevier Science Publishers; 2001:67-98.
2. Azouvi P, Samuel C, Louis-Dreyfus A, et al; French Collaborative Study Group on Assessment of Unilateral Neglect (GEREN/GRECO). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry*. 2002;73:160-166.
3. Vallar G. Extrapersonal visual unilateral spatial neglect and its neuroanatomy. *Neuroimage*. 2001;14(pt 2):S52-S58.
4. Mort DJ, Malhotra P, Mannan SK, et al. The anatomy of visual neglect. *Brain*. 2003;126:1986-1997.
5. Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*. 2001;411:950-963.
6. Doricchi F, Tomaiuolo F. The anatomy of neglect without hemianopia: a key role for parietal-frontal disconnection? *Neuroreport*. 2003;14:2239-2243.
7. Burcham KJ, Corwin JV, Stoll ML, Reep RL. Disconnection of medial agranular and posterior parietal cortex produces multimodal neglect in rats. *Behav Brain Res*. 1997;86:41-47.
8. Gaffan D, Hornak J. Visual neglect in the monkey: representation and disconnection. *Brain*. 1997;120:1647-1657.
9. Reep RL, Corwin JV, Cheatwood JL, Van Vleet TM, Heilman KM, Watson RT. A rodent model for investigating the neurobiology of contralateral neglect. *Cogn Behav Neurol*. 2004;17:191-194.
10. Godefroy O, Duhamel A, Leclerc X, Saint Michel T, Henon H, Leys D. Brain-behaviour relationships: some models and related statistical procedures for the study of brain-damaged patients. *Brain*. 1998;121:1545-1556.
11. Thiebaut de Schotten M, Urbanski M, Duffau H, et al. Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science*. 2005;309:2226-2228.
12. Schmahmann JD, Pandya DN. *Fiber Pathways of the Brain*. New York, NY: Oxford University Press; 2005.
13. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol*. 2005;4:476-486.
14. Mesulam MM. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events [published correction appears in *Philos Trans R Soc Lond B Biol Sci*. 1999;354:2083]. *Philos Trans R Soc Lond B Biol Sci*. 1999;354:1325-1346.
15. Heilman KM, Watson RT, Valenstein E. Neglect and related disorders. In: Heilman KM, Valenstein E, eds. *Clinical Neuropsychology*. 3rd ed. New York, NY: Oxford University Press Inc; 1993:279-336.
16. Bartolomeo P, Chokron S. Orienting of attention in left unilateral neglect. *Neurosci Biobehav Rev*. 2002;26:217-234.
17. Fink GR, Marshall JC, Weiss PH, Toni I, Zilles K. Task instructions influence the cognitive strategies involved in line bisection judgements: evidence from modulated neural mechanisms revealed by fMRI. *Neuropsychologia*. 2002;40:119-130.
18. Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat Neurosci*. 2005;8:1603-1610.

Correction

Errors in Byline. In the article titled "A Comparative Study of Primary and Secondary Hemifacial Spasm," published in the March issue of the ARCHIVES (2006;63:441-444) on page 441 the first names of Drs Avanzino and Marinelli were switched. The byline should have read as follows: "Carlo Colosimo, MD, Matteo Bologna, MD; Simona Lamberti, MD; Laura Avanzino, MD; Lucio Marinelli, MD; Giovanni Fabbrini, MD; Giovanni Abbruzzese, MD; Giovanni Defazio, MD; Alfredo Berardelli, MD."