Visual neglect.

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Purpose of review

Left visual neglect is a frequent and dramatic consequence of right hemisphere lesions. Diagnosis is important because behavioural and pharmacological treatments are available. Furthermore, neglect raises important issues concerning the brain mechanisms of consciousness, perception and attention.

Recent findings

Recent behavioural findings and new techniques, such as transcranial magnetic stimulation, direct cortical and subcortical stimulation during brain surgery, and diffusion tensor imaging tractography, have provided evidence relevant to the debate concerning the functional mechanisms and the anatomical bases of neglect.

Summary

Several component deficits appear to interact in producing different forms of neglect. Rather than lesions at single cortical levels, dysfunction of large-scale brain networks, often induced by white matter disconnection, may constitute the crucial antecedent of neglect signs.

Keywords

Spatial cognition, Perception, Attention, Mental imagery, White matter fiber pathways

Abbreviations

BA	Brodmann area
CT	computerised tomography
DT	diffusion tensor
FEF	frontal eye field
IPL	inferior parietal lobule
MRI	magnetic resonance imaging
REMs	rapid eye movements
SLF	superior longitudinal fasciculus
STG	superior temporal gyrus
TMS	transcranial magnetic stimulation

Introduction

In a neurological ward, it is frequent to come upon patients who look at objects on their right side with intense interest, while paying no attention to what happens on their left. Visual neglect is a dramatic but often overlooked consequence of right hemisphere damage, usually of vascular origin. Patients do not eat from the left part of their dish, they bump their wheelchair into obstacles situated on their left, and have a tendency to look to right-sided details as soon as a visual scene deploys, as if their attention were 'magnetically' attracted by these details [1]. They are usually unaware of their deficits (anosognosia), and often obstinately deny being hemiplegic [2]. Patients with left brain damage may also show signs of contralesional, right-sided neglect, albeit more rarely and usually in a less severe form [3]. Diagnosis is important, because neglect predicts poor functional outcome in stroke [4]. Moreover, effective rehabilitation strategies are available [5], and there are promising possibilities for pharmacological treatments [6].

Bedside testing

A few paper-and-pencil tests, which can be administered at bedside, can confirm diagnosis [7]. Neglect patients omit to cancel left targets in search tasks, deviate rightward when bisecting horizontal lines, fail to copy the left part of drawings [8].

Patients' asymmetries of performance in cancellation tasks scan vary from a few left-sided omissions, to cancellation of only the rightmost items. Some patients will cancel again and again the same right-sided items, thus showing a pathological "revisiting behaviour" for objects presented in the supposedly "normal" sector of space [9]. Patients who can compensate for their deficit to some extent, either as a result of spontaneous recovery or after rehabilitation, may cancel out all the elements, but keep starting from the right extremity of the sheet, at variance with normal participants, who most often start from the left part of the sheet [10], perhaps as a consequence of the left-to-right reading habits typical of Western cultures (see

[11]).

Line bisection is also a useful tool to discriminate between neglect and visual field defects, such as left homonymous hemianopia, which was once thought to cause neglect. Contrary to this hypothesis, there are patients with left hemianopia but no neglect, who deviate *left*ward on line bisection [12,13,14]. The association of left neglect and hemianopia, however, produces the largest rightward deviations on line bisection [12,13,15]. When given relatively short lines to bisect (e.g., 5 cm or less), patients may paradoxically shift the bisection point leftwards (so-called crossover effect) [16]. The co-presence of visual field defects may be a necessary condition for this [17] and other neglect-related behaviours [15] to occur.

When copying a drawing, neglect patients often omit left-sided details (more rarely, patients may *increase* the number and spatial extension of left-sided details [18*]).When drawing well-known objects from memory, patients may demonstrate similar omissions of left-sided details. Surprisingly, however, some of these patients make more symmetrical drawings when blindfolded than in free vision (Fig. 1) [19]. Thus, even in drawing from memory, patients' attention may be "magnetically" drawn to the right-sided details they just drew, rendering difficult the completion of the drawing on the left, neglected side. Perhaps sensory deprivation might be used in neglect rehabilitation to offset the attention-capturing power of right-sided visual details.

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Fig. 1 about here

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Imaginal neglect

Despite these demonstrations of the importance of right-sided visual stimuli in eliciting left neglect, neglect can manifest itself in the absence of visual stimuli. When describing known places from memory, patients

may omit details situated in the left part of the (mental) scene [20]. However, only a minority of patients with visual neglect also show imaginal neglect, perhaps because imagined details have less attention-capturing power than real ones [10,21]. Imaginal neglect can also occur in the absence of signs of perceptual neglect, either at onset [22] or, perhaps more commonly, as a result of selective compensation for the perceptual aspects of the syndrome [10]. Patients often learn with time (and possibly the help of people around them) to explore more thoroughly their visual environment. However, compensation may be more difficult to obtain in the more abstract imaginal domain, which is rarely the object of rehabilitation or of more informal reminders to "look to your left".

Neglect patients may also deviate rightwards on the mental bisection of number intervals; for example, when asked which is the median number between 11 and 19, they may answer "17" [23*]. In this domain as well, visual and imaginal performance may dissociate. Biased performance with mental number lines might be related to concomitant prefrontal damage and spatial working memory impairment [24]. It would indeed be surprising to find that all neglect patients demonstrate such a mental bias, given that people do not always imagine numbers in spatial arrangements, and even when they do, their mental diagrams are not necessarily oriented along the horizontal direction [25].

When a patient was asked to use a black touch screen to represent the night sky, and to touch the locations occupied by (imaginary) stars [26*], he put significantly more stars to the right of the screen midline, but especially when the stars remained illuminated after the touch. If the screen remained black, the asymmetry was less evident. This again suggests an attention-capturing influence of real right-sided visual stimuli on patients' neglect [19,27]. But perceptual influences on spatial imagery seem less relevant for casual, task-unrelated stimuli. When patients were asked to imagine and describe the map of France with eyes open or blindfolded, performance was similar regardless of the condition [28*]. During sleep, neglect patients may show suppression of leftward-directed REMs. A recent case report described a patient with left visual neglect and frequent nystagmoid REMs with alternating leftward slow/rightward fast phases,

corresponding to dreams with consistent visual events, such as a train running leftward, but virtually no nystagmoid REMs in the opposite direction [29**]. The complex relationships between perception and imagery in general [30], and concerning neglect in particular, are difficult to predict from the available theoretical models.

Functional mechanisms

It should be clear even from this brief description that left neglect cannot be considered as a unitary, homogeneous entity. Several dissociations of performance have been described between the outcomes of neuropsychological tasks, whether clinical [31] or experimental [32*]. It has proven difficult to find a clear correspondence between behavioural dissociations and different lesion localizations, perhaps because clinical, low-definition images are often used, and the focus has mainly been on grey matter lesions (see below). As mentioned before, a possible source of (spurious) dissociations may result from patients learning to use compensatory strategies in a domain but not in another. This occurrence may be difficult or impossible to ascertain; functional dissociations with corresponding lesional differences (e.g., [24,31]) seem the best suited to substantiate claims for different underlying causes.

The possible mechanisms leading to neglect have fostered considerable debate during the last decades. Several independent deficits, probably interacting with each other, may contribute to neglect signs. These may include deficits in orienting of spatial attention [33], in building or maintaining spatial representations [34], or in programming left-directed hand movements [35*]. It is also possible, however, than some deficits have more weight than others in shaping patients' behaviour. For example, deficits of spatial attention, such as an engagement of attention towards right-sided, non-neglected items as soon as the visual scene unfolds [1,32*,36,37*], followed by impaired disengagement from these same items [38], have often been considered key component deficits of neglect. Importantly, these deficits seem mainly to concern exogenous, or stimulus-related, orienting of attention, with relative sparing of endogenous, or voluntary,

orienting [32*,39]. Thus, the simple presence of right-sided distractors can disrupt patients' performance [27,40**]. Also non-lateralized deficits can contribute, perhaps crucially [41,42], to clinical neglect. For example, also processing of items presented in central [43] or right-sided locations [44,45] can be impaired in left neglect. However, attentional deficits can occur after right brain damage even in the absence of clinical neglect [38,46,47*], consistent with the idea that several deficits must combine to produce overt neglect behaviour [1,35*].

Lesional correlates

In keeping with the multifarious nature of their symptoms, patients with neglect often have relatively large lesions of the right hemisphere, which are likely to disrupt several functional modules. However, the precise localization of these lesions still remains controversial. Neglect patients' lesions, as detected by CT or MRI, often overlap on the inferior parietal lobule (IPL), at the junction with the temporal lobe [48]. Conflicting evidence, however, also indicates lesions of the middle and rostral parts of superior temporal gyrus (STG) [49*,50], and tends to exclude a role for lesions of the temporo-parietal junction [51]. Recent proposals have suggested that parietal or STG dysfunction may lead to different forms of neglect (respectively, personal/extrapersonal [49*], or viewer-centred/stimulus centred [52]). However, the lesion overlap method obviously lacks spatial resolution, may reflect differences in vascular territories rather than true functional architecture, and does not satisfactorily deal with multiple lesions [53,54]. Thus, other neuroimaging techniques have recently been applied to the study of the neural bases of neglect.

Transcranial magnetic stimulation (TMS) transiently disrupts the integrated activity of cortical networks in a relatively non-invasive fashion. TMS over the left hemisphere decreased left extinction and neglect in right brain-damaged patients [55]. Temporary inactivation of the middle/rostral portions of the STG produced non-lateralized impairments in visual search tasks [56]. In the same study, TMS stimulation of the central sectors of the STG did not modify judgments of the length of horizontal lines (Landmark task), in

contrast to inactivation of the posterior parietal cortex, which provoked lateralized effects similar to that shown by patients with neglect on the same task.

Functional MRI has been employed to explore the neural correlates of sub-acute and recovered neglect [57]. Four weeks after a stroke, when performing a response time task to lateralized stimuli, neglect patients had decreased activation of structurally intact fronto-parietal regions in the right hemisphere (especially the intraparietal sulcus, the superior parietal lobule and the dorsolateral prefrontal cortex), coupled with robust activation of the homologous regions in the left hemisphere. Thirty-nine weeks after lesion onset, recovery of neglect signs was paralleled by the disappearance of the imbalance between the two superior parietal lobules. Thus, lesions of the right temporo-parietal junction may determine a functional imbalance of the superior parietal lobules, which are structures important to attentional orienting, with consequent biased orienting towards right-sided objects. A promising implication of these results is the possibility to ameliorate left neglect by functionally inhibiting the left parietal lobe using TMS [55].

Temporary electrical inactivation of small brain regions (~5mm) stimuli can be performed during brain surgery to prevent post-operative deficits. Thiebaut de Schotten et al [58] described the performance of two patients who bisected horizontal lines while being submitted to the surgical resection of low-grade gliomas. Patients deviated rightward upon inactivation of the supra-marginal gyrus (the rostral subdivision of IPL) and of the caudal part of the STG; however, bisection performance was accurate when more rostral portions of the STG or the frontal eye field (FEF) were inactivated. These findings run counter to a strong version of the STG hypothesis [51], at least as far as line bisection is concerned. Importantly, however, the strongest deviations occurred in one patient upon inactivation of a white-matter region in the depth of the IPL after most of the tumour had been removed. The course of long association fibres in the white matter of this particular patient was mapped in post-operative MRI scans using diffusion tensor MRI tractography (DT-MRI), a new technique capable of tracking white matter fibres [59*]. The tract whose inactivation had brought about the maximal rightward deviation corresponded to the likely human homologous of the second

branch of the superior longitudinal fasciculus [60**]. This pathway connects the inferior and the superior parietal lobules, particularly the angular gyrus (BA 39), including the intraparietal sulcus (IPS), to the middle and superior frontal gyri (BA 9, 8, 46 and 6) [61]. The observation that functional fronto-parietal disconnection dramatically disrupted the symmetrical processing of the visual scene is consistent with many findings obtained in rodents, in non-human primates and in human stroke patients (see [54,62**], for review). A more recent intraoperative stimulation study [63] confirmed the TMS findings reviewed above [56], by showing that electrical inactivation of the central STG during brain surgery produced non-lateralised impairments in visual search. These results [56,63] thus seem consistent with the possibility that regions of the right temporal lobe are important for visual recognition and memory [64], but their relevance to neglect remains unclear.

DT-MRI tractography can be used to track the long-range white matter pathways (Fig. 2) and then explore, in a standardized brain space, their relationships with the lesions found in stroke patients with standard, anatomical MRI. Thus, for the first time white matter pathways can be explored in detail in the living human brain, and the focus can shift from impairment of cortical modules to dysfunction of cortical networks [59*]. A recent meta-analysis [62**] of previous lesion overlapping studies demonstrated that the subcortical lesions of neglect patients invariably overlapped at or near the human homologues of SLF II and III. Disconnection between cortical modules might thus be a general mechanism of neglect [54]. This possibility is also consistent with the results of computer simulations of attention [65*].

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Fig. 2 about here

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These results support models of neglect which postulate a dysfunction of large-scale right-hemisphere networks [66]. Parietal components of the network could determine the perceptual salience of extrapersonal

objects; frontal components 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. The network approach might prove important for patient diagnosis because a particular form of white matter disconnection might have greater predictive value than the localization of grey matter lesions. The demonstration of anatomically intact but functionally inactivated areas might also open perspectives for treatments (whether pharmacological or rehabilitative), aimed at restoring normal neural activity in these areas.

Although neglect commonly results from lesions in the territory of the middle cerebral artery, posterior cerebral artery strokes can also give rise to neglect signs. Also in these patients, the presence of neglect seems to correlate with inter-and intrahemispheric disconnection [67*]. Bird et al. [68*] located the maximal lesion overlap on a white matter tract linking the parahyppocampal gyrus to the angular gyrus, as tracked using DT-MRI of a normal individual.

Conclusion

Neglect remains a highly controversial topic, both concerning its mechanisms and its neural bases. Besides its clinical importance, its study has implications for our understanding of attention, consciousness, and perception. Research on the functional mechanisms appears to be moving from the description of dissociations in patients' performance to the dissection of the possible component deficits and of their modes of interaction. New, high-resolution imaging techniques are providing evidence relevant to the debate on the anatomical bases of neglect, shifting the focus from the study of cortical modules to large-scale brain networks. A huge explanatory gap still separates the functional and the anatomical descriptions of neglect, but it is a gap which seems now to be narrowing at a fast pace.

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* 68 Bird CM, Malhotra P, Parton A, Coulthard E, Rushworth MF, Husain M: Visual neglect following right posterior cerebral artery infarction. Journal of Neurology, Neurosurgery and Psychiatry 2006, 77:1008-1012.

This study on patients with infarcts in the territory of the right posterior cerebral artery indicated a possible disconnective correlate of neglect in white matter tracts running in the depth of the temporal lobe.

Figure legends

Fig. 1. Performance of a patient with left neglect two months after an ischemic lesion in the territory of the right anterior choroidal artery, when drawing a butterfly from memory, first with (upper panel), and then without (lower panel) visual guidance (while blindfolded), whereupon left neglect disappeared (reprinted from Ref. [19], with the authors' permission).

Fig. 2. Three long-range fronto-caudal white matter pathways in the right hemisphere of the normal human brain, with their cortical projections [61]. The arcuate fasciculus (red) and the human homologues of the second (yellow) and third (green) branches of the superior longitudinal fasciculus are shown.