Visual and motor neglect: clinical and neurocognitive aspects

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Abstract

Attention allows us to prioritize the processing of external information according to our goals, but also to cope with sudden, unforeseen events. Attention processes rely on the coordinated activity of large-scale brain networks. At the cortical level, these systems are mainly organized in fronto-parietal networks, with functional and anatomical asymmetries in favor of the right hemisphere. Dysfunction of these right-lateralized networks often produce severe deficit of spatial attention, such as visual neglect. Other brain-damaged patients avoid moving the limbs contralateral to their brain lesion, even in the absence of sensorimotor deficits (motor neglect). This paper first summarizes past and current evidence on brain networks of attention; then, it presents clinical and experimental findings on visual and motor neglect, and on the possible mechanisms of clinical recovery.

Keywords

Fronto-parietal networks; Visual neglect; Motor neglect; Consciousness; Spatial exploration

1. Networks of attention in the human brain

During a walk, you want to cross a busy road. At the pedestrian crossing, you look at the traffic light waiting for the green sign. When the green comes, you start to cross, but a bicycle cuts your way and you have to quickly avoid it. Your attention processes have allowed you to manage this situation in the best possible way, by selecting important information (voluntary attention on the traffic light) in order to maintain a finalized behavior (crossing the street), despite potential distractions (e.g., advertising panels on the road). However, attention also allowed you to react quickly and appropriately to an unforeseen and potentially dangerous event (automatic attention captured by the cyclist).

In the last decades, advances in human neuroimaging has provided extensive information on the neural implementation of these attentional processes [1, 2]. Thanks to this work, we now know that there is no single region in the brain that manages spatial attention. Instead, attention processes are controlled by large-scale fronto-parietal networks, with well-defined patterns of connectivity. The cortical nodes of the networks communicate quickly and efficiently with each other, thanks to large bundles of white matter (Fig. 1). These fronto-parietal networks direct our attention in space, for example towards the traffic lights before crossing the street. In general, each hemisphere of the brain directs attention towards the opposite side of space through a "dorsal" network of attention, including the superior parietal lobules, the frontal eye fields and the dorsolateral prefrontal cortex (PFC). These regions are connected the dorsal branch of the superior longitudinal fasciculus (SLF I).

An ongoing orientation (e.g., to the pedestrian traffic light), can be interrupted by an unforeseen and urgent event, such as the sudden arrival of the cyclist, which captures immediately the subject's attention. A second, more ventral fronto-parietal network deals with this important task of interrupting the ongoing attention activity, in order to redirect it to a new target. This ventral attention network includes the inferior parietal lobule, its junction with the temporal lobe, and the ventrolateral PFC. These regions communicate through the ventral branch of the superior longitudinal fasciculus, or SLF III. In most people, the ventral network of attention is asymmetric between the cerebral hemispheres: it is mostly active in the right hemisphere (RH), the non-dominant hemisphere for language, and much less in the language-dominant left hemisphere (LH) [1]. A similar, if less pronounced, asymmetry could exist for the dorsal attention network [3, 4], but this possibility is more controversial [5]. An intermediate branch of the superior longitudinal fasciculus, SLF II, connects the temporo-parietal node of the ventral attention network with the dorsolateral PFC, a node of the dorsal attention network [6]. SLF II thus allows direct communication between the dorsal (SLF I) and the ventral (SLF III) attention networks.

A further, even more ventral network is organized around the inferior fronto-occipital fascicle (IFOF; see Fig. 1), which links the ventrolateral PFC and medial orbitofrontal cortex to the occipital cortex, and thus allows top-down influence of PFC on visual areas. Also the IFOF network shows anatomical signs of asymmetry favoring the RH [7]. The right ventrolateral PFC may thus constitute a convergence zone between the visual occipito-temporal stream [8] through the IFOF, and the ventral attentional network through the SLF III. In addition to these cortical networks, subcortical structures such as the superior colliculus and the pulvinar nucleus of the thalamus also play important roles in attention processes [9]. Other subcortical nuclei, the basal ganglia, contribute to attentional processing by modulating PFC influence on visual cortex [10].

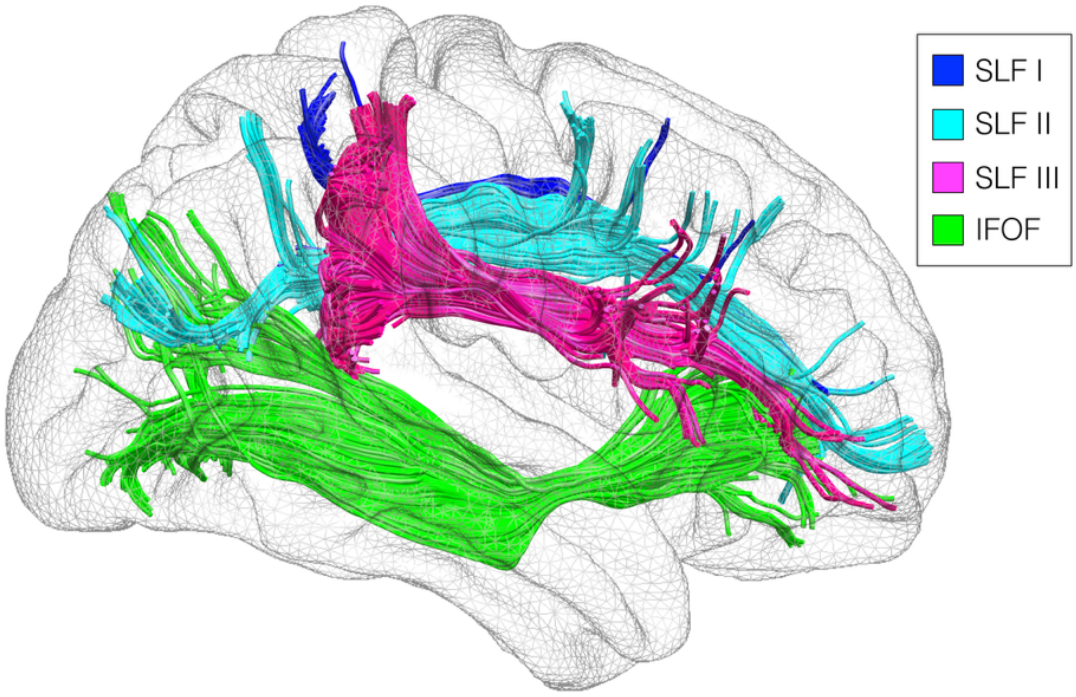

Fig. 1. Long-range white matter pathways in the right hemisphere connecting the attention networks. Figure courtesy of Michel Thiebaut of Schotten, reproduced from Ref. [3].

2. Clinical consequences of attention network dysfunction

Dysfunction of the above-described networks, especially in the RH, can have serious clinical consequences. For example, patients may become unable to process several stimuli when simultaneously presented (as in extinction [11, 12] and simultanagnosia [13]), or stimuli arising in a region of space contralateral to the brain lesion (visuospatial neglect) [14]. In these cases, a "wrong" object (that is, an object inappropriate to the current behavioral task) may win the competition and capture the patient's attention [15]. Thus, when patients with left visual neglect are presented with bilateral objects, they compulsorily orient their gaze towards right-sided stimuli, as if their gaze were "magnetically" captured by these stimuli [16, 17]; afterwards, patients find it difficult to disengage their attention from these stimuli in order to explore the left part of space [18-22], so that their space exploration may remain confined to a few right-sided objects [23, 24].

3. Clinical signs of visual neglect

Visual, or spatial neglect refers to patients' inability to orient their attention towards objects contralateral to their lesion (typically, left-sided objects after RH damage). As a consequence, patients may behave as if the left part of the world did not exist anymore. This condition can occur in the absence of elementary sensorimotor deficits, and is severely disabling in patients' everyday life. In the acute phase of a stroke, neglect can easily be detected by examining the posture and spontaneous behavior of the patients. They stay in bed with their heads turned to the side opposite to their hemiplegia (thus, most often

towards the right side), and do not respond to stimuli from the opposite, neglected space (typically the left side). For example, if someone questions them from the left, they may not answer, or they will respond to someone else standing on the right side. Any task involving vision leads to an even more exaggerated rightward gaze deviation. The deviation of gaze gradually disappears in the days following the stroke, but the tendency to be captured by right-sided items may persist in time.

At this stage, other behavioral signs may become apparent. Patients do not wash the left side of their body; they may shave, or make up only the right half of the face. They may forget to put their left sleeve or their left shoe, or let hanging the left branch of their glasses. Neglect is often evident in the near extra-personal space. Patients can eat food only on the right side of their plate, and read only the right half of the newspaper titles, without bothering about their lack of meaning (so-called neglect dyslexia).

Once patients are able to perform neuropsychological tests, their behavior often remains confined to the right side of their visual space. Those of them able to stand up show disorders of the control of the posture; patients may veer towards the left, probably because of impaired integration of visual, vestibular, somesthetic or graviceptive information. Several weeks or even months after the onset of the lesion, a substantial proportion of patients manage to compensate for neglect both in their daily lives and on neuropsychological tests. However, even in these patients, it is possible to detect more subtle signs of attention impairment. For example, they continue to begin their exploration of space from the right side [16, 25], while most healthy controls tend to start from the left side [26] – a phenomenon perhaps related to Western left-to-right reading habits. When these patients produce manual or vocal responses to lateralized objects on either side of space, they respond more slowly to left-sided targets than to right-sided ones, particularly at the beginning of the tests, as if attention were initially captured by right-sided items [27].

4. Deficits of spontaneous motility: Motor neglect

Motor neglect is another clinically relevant condition consequent upon unilateral brain damage. Patients with motor neglect avoid to move the limbs contralateral to their brain lesions. They may actually behave as hemiplegics, even in the complete absence of elementary sensorimotor deficits: they simply “forget” to use their contralesional limbs. Laplane and Degos [28] described 20 stroke patients with “pure” motor neglect (12 patients with right hemisphere lesions, eight with left hemisphere lesions), without substantial sensorimotor deficits or signs of visual neglect. Typically, these patients tend to use their ipsilesional limb even when the use of the contralesional limb would be more appropriate and convenient. No or little involvement of the contralesional limb occurs in gesture during speaking and in bimanual tasks (e.g., clapping, opening a bottle, buttoning or unbuttoning a dress). During walking, the contralesional limb may lag behind the ipsilesional limb, or it may lack normal swinging. Also, the characteristics of contralesional limb movements can be anomalous: movements can be delayed (hypokinesia), slowed (bradykinesia), and of reduced amplitude (hypometria). However, when explicitly asked to move their limbs these patients typically show normal strength and dexterity. Thus, diagnosis of motor neglect is at present exclusively clinical and subjective, based on the observation of patients’ spontaneous motor behavior, e.g. during activities such as tea preparation [29].

5. Tests of neglect

Several paper-and-pencil tests can uncover attention-related spatial deficits [30]. It is very important to evaluate these capabilities in the clinic, because neglect signs can be clinically elusive; and yet diagnosis is important because neglect patients should not be allowed to undertake activities requiring rapid reactions, such as driving for example. In addition, many of them do not fully recover from behavioral signs of neglect, which in turn can affect the recovery of their motor abilities [31]. These tests are also important during awake surgery for brain tumors, in order to prevent the appearance of post-operative neglect [32-34].

Given the strong influence of spatial position on neglect signs, it is important to carefully center the test sheets on the patient's midsagittal plane. Not all patients consistently show neglect on all these tests, consistent with the probable multi-component nature of this syndrome [35, 36], with different patterns of deficits occurring in different patients [37, 38]. To achieve good diagnostic sensitivity, it is thus important to have patients perform several visuospatial tests. Neglect tests can schematically be classified in visuo-perceptual tests, visuo-graphic tests and representational (or imaginal) tests.

Visuo-perceptual tests do not require substantial motor activity towards a certain sector of space. For example, one may present patients with a lateralized version of the Wundt-Jastrow illusion [39], or ask them to identify overlapping figures [16], or to read a short text [30]. Typically, patients do not consider information coming from the left half of the display: they do not suffer from a left-lateralized Wundt-Jastrow illusion, or do not detect left-sided overlapping images, words, or letters.

Visuo-graphic tests can be based on activities of copy, visual search, or line bisection (Fig. 2).

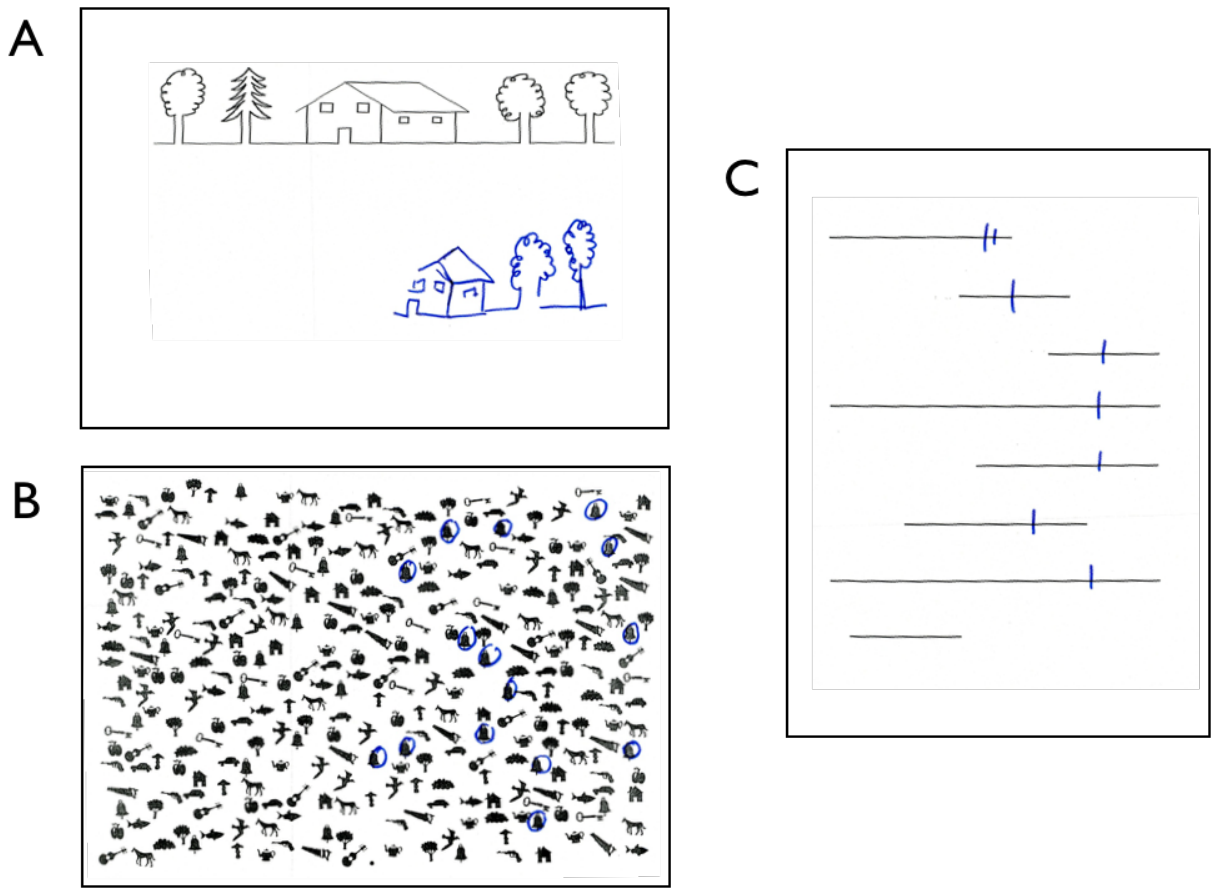

Fig. 2. Performance of a patient with left visual neglect on tests of copy (A), visual search (B), and line bisection (C). Figure originally published in Ref. [40].

Patients can be asked to copy geometrical or figurative drawings [41]. When copying, patients typically omit objects or details contained in the left half of the model (scene-based neglect). Sometimes, however, the patient can reproduce all the elements of the model independently of their spatial location, but neglect the left half of one or more items (object-based neglect). In visual search tests, patients are asked to find targets, such as lines [42], letters [43], stars [44], or bells [45]. Patients have to cancel out the target items, and typically omit to detect a variable proportion of left-sided targets. The difficulty of the task (e.g., when a target/distractor discrimination is required) may increase the number of left-sided omissions. In line bisection, patients are asked to mark the midpoint of horizontal lines. They typically misplace the bisection point rightward, especially when their attention is directed on the right extremity of the line [46].

Response time tests, analogous to those used to study spatial attention in normal participants, can provide more sensitive methods to detect subclinical biases in spatial attention [47]. For example, neglect patients often compensate for neglect on paper-and-pencil tests, but can remain slower in responding to left-sided targets than to right-sided targets [27], especially when engaged in a concomitant cognitive task, such as the inhibition of inappropriate responses [48].

Visual field defects, such as left homonymous hemianopia, can sometimes co-occur with neglect, for example when strokes damage the optic radiations or the primary visual cortex. However, they can also occur independently of neglect. Importantly, hemianopic patients without neglect try to compensate for their deficit, often to the point of a paradoxical contralesional deviation on line bisection [49], whereas patients with hemianopia and neglect deviate ipsilesionally (i.e., towards the side of the brain lesion, most often the right) [50]. Goldmann perimetry can usually discriminate between hemianopia and neglect, because non-hemianopic patients are typically able to detect the single targets presented in their left visual field despite their neglect. In rare cases, however, neglect can be so severe that patients can fail to report perimetry targets (pseudohemianopia). Presumably, in these cases the mere presence of the fixation point induces a stimulus competition with left-sided targets, which are therefore neglected. In one of these patients, removal of the fixation point just before target presentation was able to restore perception of left-sided targets [51]. The possibility of neglect-related pseudohemianopia should be kept in mind, especially with the now commonly used automated perimetry, where a trained perimetrist has less opportunity to interact with the patients and to observe their performance. In case of doubt, lateralized ERPs can demonstrate the absence of hemianopia by showing normal response of primary visual cortex to left-sided checkerboards.

As mentioned in section 4, diagnosis of *motor neglect* rests on clinical observation of patient's motor behavior, and on the exclusion of elementary motor deficits. However, objective diagnosis and quantification of motor neglect is now possible thanks to advanced techniques of movement recording. For example, upper-limb actigraphy can record spontaneous motor activity: patients wear wristwatch-like accelerometers during 24h, and perform their normal activities [26]. Differences in spontaneous activity between ipsilesional and contralesional limbs, when accompanied by normal motor behavior on command, can provide an objective diagnosis of motor neglect [27].

6. Models of visual neglect

It has long been recognized that visual neglect is a typical syndrome resulting from RH lesions [52, 53]. Early models [54, 55] held that attentional neurons of the parietal lobe, charged with spatial surveillance function, could have bilateral receptive fields in the RH, whereas they would be limited to the contralateral half of the space in the LH. According to this model, there would be little or no neglect after LH lesions because the attentional neurons of the right parietal lobe (spared by the lesion) can detect the stimuli occurring in the ipsilateral space. There would, however, be neglect for the left half of the space after RH lesions because the attentional neurons of the left parietal lobe cannot monitor the left (ipsilateral) half of the space. On the contrary, Kinsbourne [56 , 57] proposed that the basic asymmetry of neglect stems from LH preferential activation in verbally-mediated tests. This left activation, accompanied by a trans-callosal inhibition of the right, contralateral hemisphere, would automatically orient the gaze toward the right half of the space. These phenomena would be transient in normal subjects, but could become more stable (and thus result in left neglect signs) after right brain injury. Language activities (common in clinical tests) could further interfere with this general phenomenon, by activating the LH and causing a deviation of the gaze to the right.

Neuroimaging evidence gave some support to the Kinsbourne model, by showing a relative hyperactivation of the left superior parietal lobule as compared with its right hemisphere homolog in patients with left neglect [58]. The two structures reverted to a more balanced activity in the chronic phase, when signs of neglect had recovered. However, other left attentional hemisphere structures, for example in the PFC, had increased activity in the recovered phase as compared with the acute phase, thus suggesting a possible compensatory role of the nondamaged LH [59]. Consistent with this mixed evidence, behavioral results did not offer definitive support for either of the rival models. For example, according to the Kinsbourne model when a group of patients with various degrees of left neglect produce speeded manual responses to left- or right-sided targets, their responses to right-sided targets should decrease with increasing severity of neglect (as a result of increasingly stronger bias toward the right side); according to the Heilman/Mesulam model these responses should instead increase, because progressively less attentional resources are deployed in both hemispaces. The results of such a study [60] showed that not only the responses to left targets, but also those to right targets became progressively slower as neglect increased, consistent with the hypoattention account. However, the two regression lines were not parallel. With increasing neglect, responses to left targets increased more steeply than those to right targets did. Thus, a rightward attentional bias does occur in patients with left neglect, together with left hypoattention. However, this rightward bias is one of defective, and not enhanced, attention. Also, neglect patients' performance on perceptual estimation of line lengths [61] suggests that two independent deficits contribute to neglect signs: a deficit in attentional orienting to the left, perhaps depending on impaired functioning of RH attentional networks, and a tendency for attention to be captured by right-sided stimuli, possibly resulting from the activity of an isolated LH [62].

7. The connectional anatomy of neglect

Within the RH, the lesions responsible for signs of visual neglect tend to localize in the postero-inferior portions of the parietal lobe [53, 63]. However, signs of neglect have also been reported in patients with lesions affecting the frontal lobe [64, 65], the cingulate gyrus [55, 66], the thalamus [67] and basal ganglia [65]. It is possible that these various focal locations have no special role per se [68], but instead result in network-based dysfunction of the attentional circuits, especially those linked by SLF II and III (recent reviews in Refs. [14, 69-73]). Also, more ventral damage to the right-lateralized IFOF has been associated with visual neglect [74-76]. However, as mentioned above, damage to the LH homolog regions only rarely results in right-sided visual neglect [30, 77]. Signs of right-sided neglect have been observed after bilateral hemispheric damage, whether due to vascular strokes [78, 79], or to neurodegenerative conditions [80, 81]. This finding might indicate the necessity for some degree of RH dysfunction even for signs of *right-sided* neglect to occur. The right-lateralized SLF III network is a possible candidate site of RH dysfunction in patients with right-sided neglect [3].

As detailed in the previous section, an important aspect of left neglect behavior is a bias to explore the right portions of extrapersonal space. In experimental settings, this bias often induces the production of “inappropriate” rightward saccades, i.e., saccades towards nontarget stimuli on the right side. Eye movement recordings showed that this tendency could not be completely countered by endogenous orienting of attention, and was related to damage to SLF fibers leading to the RH FEF [17].

Motor neglect can result from unilateral lesions in the right or left hemisphere, without substantial asymmetries, at sharp variance with visual neglect. Lesion sites include the medial frontal premotor and motor regions [28, 82, 83], medial parietal regions [28, 82, 84], putamen, internal capsule and the thalamus [28, 82, 83, 85-87]. Lesion locations in the white matter include the corpus callosum, the fronto-parietal connections [28, 82], and the cingulum [29, 88]. The variety of lesion locations may suggest a heterogeneous nature of this condition, which still awaits a precise characterization in terms of pathophysiology.

By contrast, our knowledge of visual neglect and of its clinical recovery has witnessed important advances in recent years. Recent lesion-symptom mapping studies of visual neglect have confirmed the presence of damage to SLF II-III and IFOF networks in the RH [75, 89-93]. Electrophysiological evidence suggests a relative sparing of PFC activity in neglect patients [94, 95]. Activity in LH PFC might actually be causally related to neglect omissions: a MEG study demonstrated a specific increase of low beta synchronization activity in left frontal cortex before omissions of response to left-sided targets [96]. In an ERP study, attention-related PFC activity was preserved, but unable to counterbalance deficits in parietal-occipital activity [94]; however, in other patients PFC activity correlated with intentional, compensatory gaze shifts towards the left, neglected side [95]. Recovery from neglect has been related to the state of inter-hemispheric connectivity with the left, undamaged hemisphere [97, 98]. Evidence from diffusion-based MRI suggested an important role of the caudal portions of the corpus callosum, which connect the posterior nodes of the attentional networks, perhaps because the undamaged LH needs some access to information processed in the damaged RH to compensate for neglect signs [97, 99]. The status of more rostral portions of the corpus callosum can instead predict response to rehabilitation therapies such as prism adaptation: Patients with chronic neglect and caudal callosal disconnection, but intact body and genu, were more likely to respond to prism

adaptation therapy [100]. Prism adaptation could thus promote inter-hemispheric integration through these rostral callosal connections.

Clearly, the integrity of white matter pathways poses crucial connectivity constraints for compensatory brain plasticity from remote brain regions [59]. Preservation or recovery of inter-hemispheric connectivity might be important for shifting the role of the healthy left hemisphere in visual neglect, from exerting maladaptive effects [58], to promoting adaptive (compensatory) activity [62]. Perhaps only when the hemispheres can talk to each other, the left hemisphere can compensate for attention deficits induced by damage to the right hemisphere [99]. This hypothesis needs to be assessed by using structural, diffusion and functional neuroimaging in future longitudinal studies of neglect patients.

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