From competition to cooperation: Visual neglect across the hemispheres

P. Bartolomeo

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ABSTRACT

Visuospatial neglect is a frequent and disabling consequence of injuries to the right hemisphere. Patients with neglect show signs of impaired attention for left-sided events, which depends on dysfunction of fronto-parietal networks. After unilateral injury, such as stroke, these networks and their contralateral homologs can reorganize following multiple potential trajectories, which can be either adaptive or maladaptive. This article presents possible factors influencing the profile of evolution of neglect towards recovery or chronicity, and highlights potential mechanisms that may constrain these processes in time and space. The integrity of white matter pathways within and between the hemisphere appears to pose crucial connectivity constraints for compensatory brain plasticity from remote brain regions. Specifically, the availability of a sufficient degree of inter-hemispheric connectivity might be critical to shift the role of the undamaged left hemisphere in spatial neglect, from exerting maladaptive effects, to promoting compensatory activity.

KEYWORDS

Post-stroke cognitive deficits; brain connectivity; visual attention; recovery; rehabilitation

1. INTRODUCTION

Lesion-induced cognitive deficits place a huge burden on the daily life of patients and their families, and have a substantial impact on public health. Brain damage, even when it is focal in nature, such as in stroke, has effects which are not only local. It typically disrupts activity in highly distributed, large-scale neural networks, connected by long-range white matter tracts [1, 2]. After damage, these networks can reorganize following multiple potential trajectories [3], which can be either adaptive or maladaptive [4].

Dysfunction of fronto-parietal networks in the right, non-language dominant hemisphere often provokes signs of visual neglect, a disabling condition whereby patients do not pay attention to left-sided objects, and may behave as if the left part of the world did not exist [5-10]. Neglect predicts a poor functional outcome [11, 12]; clinical management and social reinsertion of these patients represent substantial societal problems.

Subcortical damage to long-range white matter tracts has emerged as a major cause of visual neglect and other post-stroke cognitive deficits [1, 2, 13, 14]. Damage to the tightly packed white matter fascicles is likely to be more disruptive for network activity than equivalent damage to cortical areas [13]. Today, diffusion MRI and white matter tractography permit the detailed anatomical study of white matter tracts *in vivo*. Such techniques are becoming increasingly important in studies of stroke-induced network dysfunctions [15-17].

Visusospatial attention relies on large-scale fronto-parietal networks in the human brain [18], linked by three branches of the superior longitudinal fasciculus (SLF I-III) [19, 20]. These branches display anatomical signs of hemispheric asymmetries favoring the right hemisphere [21], with a ventro-dorsal gradient of asymmetry, progressively decreasing from SLF II to SLF I [20]. A further, more ventral network is connected by the inferior fronto-occipital fasciculus (IFOF) [22] (Fig. 1). Partially overlapping fronto-parietal networks also control nonspatial aspects of attention, such as alertness [23], which is typically impaired in

spatial neglect [24]. Increasing alertness alleviates spatial bias in neglect patients [24], and also improves perceptual awareness of near-threshold targets in normal participants [25].

A vast amount of evidence from neurological patients indicates that network dysfunction in the SLF II-III and IFOF networks, rather than focal brain damage, is the critical precursor of many signs of visual neglect [7, 13, 16, 26-30]. The most frequent cause of such patterns of network dysfunction is stroke [15, 17, 31, 32], but signs of neglect can also be observed in other neurological conditions, such as brain tumors [33-35], brain surgery [16, 36, 37], or neurodegenerative diseases [38-42]. Specific lesional sites, such as the occipito-temporal cortex [43] or the cingulate gyrus (in addition to fronto-parietal damage [44]), may give rise to specific forms of neglect (respectively, stimulus-centered and motivational neglect). White matter damage may also produce specific patterns of neglect, depending on the affected circuits [31, 45]. Other component deficits of neglect, however, such as 'magnetic' attraction of attention towards the ipsilesional stimuli [46-48], and impaired spatial working memory [49-51] have proven more difficult to link to specific lesional patterns [52].The term motor neglect designates yet another condition, whereby patients underuse their contralesional limbs, even in the absence of elementary motor deficits [53, 54], sometimes to a degree mimicking hemiplegia. The lesional correlates of motor neglect, and its relationship to visual neglect, remain underdetermined [55, 56].

The network-based nature of visual neglect offers potential perspectives for its compensation, whether spontaneous or based on rehabilitation procedures [57]. After the injury, brain networks can follow multiple trajectories during post-stroke reorganization in different patients [3]. These trajectories can be either adaptive or maladaptive [4]. Disrupted activity of lesioned network nodes can potentially be compensated for by activity in different nodes, provided that the compensatory nodes can communicate with the rest of the system [58]. Network activity within and across the hemispheres can be restored or rebalanced, by

acting on the intact nodes of the damaged networks, or on their homologs in the healthy hemisphere [57, 59]. An intriguing possibility emerging from these considerations is that the connectivity profiles of individual patients may constitute crucial determinants of their individual response to injury and treatment.

Importantly, the identification of biomarkers of the likely trajectory of post-stroke cognitive deficits can improve the clinicians' ability to stratify patients and to reduce variability in trial outcomes. Biomarkers can assist clinical decisions for individual patients, by predicting the potential for recovery and by enabling clinicians to choose an appropriate rehabilitation strategy [60]. The following sections will examine potential factors influencing post-stroke recovery in time and space, as well as possible biomarkers targeting these factors.

2. WHEN: NEGLECT COMPENSATION IN TIME

The time since lesion occurred has a deep influence on compensation processes [3, 61]. During the acute/subacute phase of a stroke, remote effects of the lesion are described as *diaschisis* phenomena. The concept of diaschisis was introduced by von Monakov [62] to describe the effects of focal brain damage in anatomically intact areas that are connected to the lesion site [63, 64]. Diaschisis effects implicate not only remote loss of excitability, but also disinhibition leading to increased excitability, both in the lesioned hemisphere (ipsilateral diaschisis) and in the unaffected hemisphere (transcallosal or transhemispheric diaschisis) [65]. Murine models suggest that ipsilateral diaschisis is associated to the down-regulation of gamma-aminobutyric acid (GABA)A receptors alpha1, alpha2, alpha5 and gamma2 within the lesioned hemisphere, whereas up-regulation of receptors alpha3 in the contralateral hemisphere may lead to transhemispheric diaschisis. Thus, a sequential order of receptor modulation seems to occur in either hemisphere in the acute phase of a stroke [66].

Cortical hyperexcitability tends to increase in the early weeks in both hemispheres after a stroke, and to decrease thereafter. These processes may contribute to spontaneous

functional recovery. However, when they persist after the first weeks post-stroke they can assume a maladaptive role and hinder recovery [61]. Thus, the significance of post-stroke hyperactivity for functional recovery varies according to time. Four partially overlapping temporal epochs can be identified [3]: (1) an hyperacute phase within hours of the stroke, with local inflammation, oedema and distal diaschisis; (2) a subacute phase during the first weeks after the stroke, when most of the spontaneous recovery occurs and then reaches a plateau; (3) a chronic phase, beginning weeks to months after the stroke, associated with a 'normalization' of the activity and a stabilization of the deficits [61]; (4) finally, several months after the injury, rewiring of white matter fibers may occur, with axonal sprouting near the site of ischemic injury [67]. These mechanisms, which develop over different time frames, may be associated with different forms of functional recovery after stroke [3]. For instance, whereas recovery of motor deficits usually peaks within 30 days, language and other high cognitive functions may improve well beyond this phase, up to a year after stroke [61]. This difference in recovery rate suggests that partly distinct mechanisms may be at work in motor recovery or in cognitive recovery [68]. For example, the late occurrence of cortical rewiring might especially contribute to the recovery of cognitive functions [3].

Animal models of post-stroke recovery of function suggested the idea of time-limited windows of neuroplasticity following stroke in the adult brain. These time periods share molecular mechanisms with critical time windows in development [69]. For example, rehabilitation of motor deficits in the first few weeks after experimental stroke was more likely to be successful, in parallel with an increased number of branches and complexity of layer V neurons occurring at this early post-lesion period [70].

Although at the much longer time scale of several months, the finding that shorter lesion-rehabilitation intervals tended to predict better response to prism adaptation therapy in patients with chronic neglect [71] seems broadly consistent with these notions; the earlier the

intervention, the greater the potential for prism adaptation to induce compensation of neglect. This result suggests that anterior inter-hemispheric communication may favorably influence patients' response to prism adaptation especially during early temporal windows of opportunity.

Despite these considerations, however, the windows of neuroplasticity never completely close, and (suboptimal) recovery can still occur after the critical post-stroke period. Furthermore, the possibility exists of reopening developmental time windows in the adult brain [72]; thus, critical periods of plasticity might be reactivated even in the lesioned adult brain, e.g. by using noninvasive brain stimulation [73] or behavioral techniques such as prism adaptation therapy [71].

3. WHERE: NEGLECT COMPENSATION IN THE BRAIN SPACE

In general, the localization of the lesions in the brain is the best predictor of the occurrence of post-stroke cognitive impairment [74]. However, the importance of localization should not be construed as supporting a localistic view of regional specialization in the brain. Rather, strategically placed lesions, for example affecting the tightly packed fibers of long-range white matter tracts [13], are more likely than cortical lesions to disrupt the large-scale brain networks whose functioning is at the basis of cognitive processes [1]. Thus, the brain space should be conceived as a complex network of structural connections, or 'connectome' [75], The functional repertoires resulting from lesions to the connectome, or "disconnectome", are not only defined by white matter connections, but also by the highly stereotyped spatial distribution of strokes [76], depending on the vascular architecture of the brain.

A first spatial factor which may influence recovery is lesion size; large lesions are more likely than small lesions to impact the functioning of several brain systems, and hinder potential compensation from adjacent circuits. For example, the resolution of the ischemic penumbra may unmask compensatory activity from perilesional regions [69]. Follow-up of

motor recovery after experimental lesions of the internal capsule in two macaques suggested that the size of the lesion can induce distinct compensatory mechanisms for flaccid paralysis. Functional recovery required neural plasticity in the ipsilesional hemisphere for the smaller infarction, and in the contralesional hemisphere for the larger lesion [77]. Thus, lesion volume might influence the mechanisms of recovery, with predominantly intrahemispheric compensation for small lesions, and recruitment of circuits in the opposite, healthy hemisphere for larger lesions. More relevant to neglect, a mouse model of ipsilesional spatial bias after focal damage to the medial agranular cortex demonstrated that the extent of the postlesional bias, but not that of recovery, correlated with the lesion size [78]. This pattern of results suggests that recovery was based on neural plasticity not within the peri-infarct area, but in distal regions in the same or contralateral hemisphere. Broadly consistent with these notions, early evidence on human neglect patients showed that the volume of lesion influenced the presence and degree of post-stroke neglect [79].

A recent longitudinal study [80], which assessed neglect in 45 right-brain damaged patients in the subacute (<6 months) and chronic (> 1 year) phases of stroke, further specified the role of lesion volume in the evolution of neglect. Patients with chronic, persistent neglect tended to have larger lesions as compared with non-neglect patients; they had, however, similar lesion volumes as patients who eventually recovered from neglect, suggesting that lesion size *per se* is not a major determinant of the evolution of neglect in time. The results remain, however, consistent with an indirect role of lesion size; as stated above, large lesions are more likely than small lesion to impact several brain circuits, thus decreasing compensatory capacities.

Inter- and intra-hemispheric loci of lesions are more directly linked with the number and identity of lesioned circuits; as such, lesion location is an important factor determining the persistence of neglect signs in time. The laterality of the hemispheric lesion is perhaps the

most obvious aspect. It has long been known that signs of contralesional neglect are more frequent, severe and persistent after right hemisphere damage than after lesions in the left hemisphere [81, 82]. Right-sided neglect after left hemisphere damage may recover promptly because of the compensatory capacities of the right hemisphere attention networks, which may be able to take account information coming from both sides of space, whereas the competence of left hemisphere networks is more restricted to the right space [21, 83-86].

Consistent with this model, persistent right-sided neglect has been described after bilateral hemispheric damage, whether due to vascular strokes [87, 88], or to neurodegenerative conditions [38-40, 89]. Thus, some degree of right hemisphere dysfunction might be necessary even for signs of right-sided neglect to occur. The right-lateralized SLF III network is a possible candidate site for such right hemisphere dysfunction in patients with right-sided neglect [21].

Relatively less is known about the intra-hemispheric determinants of neglect evolution. Although, as mentioned above, neglect is a network-based condition, and can in principle occur from damage anywhere in the trajectory of dorso-rostral SLF II-III and IFOF, most patients with persistent neglect have retrorolandic lesions. A possible reason for this occurrence is that SLF II and III have spatially close origins in the inferior parietal lobule, but diverge when traveling rostrally; thus, damage at or near the inferior parietal lobule [90] is likely to concurrently disrupt both the SLF II and the SLF III networks [28]. In a study on 58 patients with strokes in the territory of the right middle cerebral artery [32], SLF II disconnection was the most likely lesion to predict chronic spatial neglect. However, 7 of the 38 patients showing chronic spatial neglect did not show neuroimaging signs of fronto-parietal disconnection; their lesions instead overlapped within the latero-dorsal portion of the thalamus.

Concerning more ventral lesions, Lunven et al. made a detailed description of a patient with chronic severe neglect on cancellation tasks at more than 8 years from a stroke in the occipito-temporal regions of the right hemisphere [91]. Neglect was, however, only present when the patient performed cancellation tasks with her right hand (controlled by the left hemisphere); performance reverted to normal when the patient used her left hand. White matter tractography demonstrated damage to the splenium of the corpus callosum, as well as a relative preservation of the right fronto-parietal network. Chronic, effector-dependent neglect may have emerged because the splenial disconnection deprived the right fronto-parietal networks from visual information processed by the left hemisphere.

An important variable for neglect compensation is the status of inter-hemispheric communication. Although surgical section of the corpus callosum does not typically determine signs of neglect [92] (but see Ref. [93]), splenial disconnection may contribute to neglect in patients with right hemisphere damage, whether it occurred before [94], or concurrently [91, 95]. In this case, callosal disconnection might prevent the left hemisphere from compensating for the deficits induced by right hemisphere damage, by taking charge of left-sided events [13]. In agreement with these notions, microstructural damage of the posterior corpus callosum has been shown to correlate with the clinical severity of neglect [96]. In the above-mentioned longitudinal study of 45 patients with unilateral strokes in the right hemisphere [80], the presence of signs of posterior callosal disconnection was able to predict the chronic persistence of neglect. The authors concluded that splenial disconnection may prevent fronto-parietal networks in the left hemisphere from taking into account visual information coming from the left hemispace. In a subsequent study [71] on patients with splenial disconnection and chronic neglect, the integrity of more anterior callosal connections appeared to be crucial for patients to respond to prism-based rehabilitation [97]. These results (summarized in Fig. 2) support the hypothesis that the healthy hemisphere has an important

role in the compensation for stroke-induced, chronic neuropsychological deficits [3], and suggest that prism adaptation can foster this role by exploiting sensorimotor/prefrontal circuits for neglect compensation. Thus, the status of different sectors of the corpus callosum may represent possible connectional biomarkers to predict neglect recovery, and to choose the appropriate rehabilitation procedures.

Further, confirmatory evidence on the role of the healthy hemisphere in neglect compensation came from a study on 20 patients with brain tumors affecting the right hemisphere, who were followed up before and after awake brain surgery [33]. Patients showed evidence for transient neglect signs in the acute post-operative phase; however, all of them had fully recovered when retested 3 months after surgery. It is likely that both the preservation of long-range white matter pathways within the right hemisphere, obtained thanks to intraoperative mapping [16, 98], and of the callosal connections with the left hemisphere, contributed to prevent the occurrence of chronic neglect in this population.

4. CONCLUSIVE REMARKS

Despite these encouraging results on the identification of connectional biomarkers for recovery of neglect, a word of caution is necessary. It is well known that patients who attain normal performance on paper-and-pencil tests may nevertheless keep showing clinical signs of neglect in everyday life [99]. This possibility calls for more ecological tests of neglect, which for example require patients to interact with real 3D objects [100]. Technology-enhanced versions of these tests are now being developed [101], which provide clinicians with convenient, fast, and relatively automatized procedures, that patients can even perform at home to follow-up the effects of rehabilitation.

Apparently recovered patients may also show subtle signs of spatial bias on paper-and-pencil tests. For example, they may keep starting to perform visual search tasks from the rightmost targets, even if they eventually find out all the targets [48, 102]. Normal

participants tend instead to start their search from the left side [103], possibly as a consequence of physiological pseudoneglect [104]. Moreover, these patients often keep showing deficits on more stringent tests of spatial or nonspatial attention, such as speeded response time tests, or on dual task paradigms [105-107].

Thus, functional recovery from neglect may be incomplete, as it often happens when behavioral recovery is sustained by compensatory processes. It is important to be aware of the possibility of these "subclinical" deficits, which do have clinical implications, for example in taking decisions about the patient's ability to drive. Patients with normal performance of paper-and-pencil tests, but left-right asymmetries of response times, might well be at risk of road accidents and should not be permitted to resume driving or to use dangerous mechanical devices.

In addition, neglect compensation can be domain-selective. For example, some neglect patients show signs of neglect for both real and imagined scenes [108, 109], perhaps as a result of disconnections between right-hemisphere attention networks and left-hemisphere systems important for the generation of visual mental images [110]. A few of these patients have been shown to selectively recover from visual neglect, while keeping to demonstrate neglect for their visual mental images [103, 111]. Such patients might have learned with time (and possibly the help of people around them) to compensate for their neglect in the visuospatial domain, but not in the less ecological imaginal domain. As a matter of fact, neglect patients are often reminded by relatives and hospital staff to explore the visual scene thoroughly, and could learn to appreciate the consequences of their omissions (e.g., while eating or reading a newspaper), but this is less likely to happen for imagined scenes [112]. Such 'dynamic' dissociations between preserved and impaired performance might also rely on changes in functional long-range brain connectivity. Further,

detailed reports on individual patients using advanced behavioral and neuroimaging techniques are required to assess these hypotheses.

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FIGURE LEGENDS

Fig. 1. Schematic representation of long-range white matter pathways in the right hemisphere of the human brain. Blue, SLF I; cyan, SLF II; purple, SLF III; green, IFOF. Tract reconstruction courtesy of Michel Thiebaut de Schotten.

Fig. 2. Schematic representation of the callosal regions whose anatomical integrity is important for recovery from neglect (red), and for response to prism adaptation therapy (cyan). Data from Lunven et al. [71, 80].