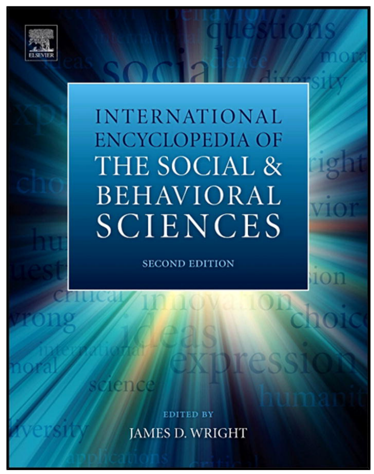

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Hemispatial Neglect, Neural Basis of

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Abstract

Patients with hemispatial neglect, a neurobehavioral deficit that manifests after a lesion that usually affects the right hemisphere, fail to process or attend to information appearing on the contralateral side of space. This deficit can arise in multiple modalities (visual, auditory, and somatosensory) and can adversely affect eye and hand movements. In addition to describing the phenomenon and its anatomical concomitant, the underlying mechanisms giving rise to this deficit are explored. The advent of cutting-edge neuroimaging and the recent development of new assessment and rehabilitation methods have also offered novel insights into the disorder and these are summarized here, too.

The Term 'Hemispatial Neglect'

One of the most dramatic deficits in spatial perception and action is hemispatial neglect ('neglect' for short), a neurobehavioral disorder in which a patient is unable to acknowledge, report, or otherwise make explicit use of information falling in the visual hemispace contralateral to the lesion (Bartolomeo and Chokron, 2001; Harvey and Rossit, 2012; Kerkhoff and Schenk, 2012). Neglect occurs more commonly and with greater severity after right than left hemisphere lesions in humans (Suchan and Karnath, 2011) and this asymmetry is consistent with the differential involvement of the right hemisphere in processes of attention and spatial representation, as revealed in many recent neuroimaging studies (Chica et al., 2011; Ptak and Schnider, 2011). Because of this hemispheric asymmetry, in this review, we will refer to neglect as 'left-sided' and to 'contralesional' as a lesion to the right hemisphere.

The Phenomenon of Hemispatial Neglect

Neglect is not an uncommon disorder and every year about 3–5 million patients present with neglect after sustaining a stroke (Corbetta et al., 2005). Moreover, about a third of these patients manifest a chronic form of the impairment, which can persist for more than a year postonset (Karnath et al., 2011; Rengachary et al., 2011). Neglect can be greatly debilitating in everyday life; individuals may fail to notice objects on the left of a scene, may ignore words on the left of a page or food on the left of a plate, may drive their wheelchair into the side of a doorframe, and may dress and/or shave only one side of their body. Neglect can also interfere with rehabilitation efforts by adversely affecting mobility, discharge destination, length of hospital stay, meal preparation, and independence in self-care skills (Barer, 1990; Bernspang et al., 1987) and, understandably, then, neglect can affect the outcome of rehabilitation and long-term prognosis.

Neglect is not restricted to the visual domain; patients may not orient to contralateral auditory information, may not detect a contralateral somatosensory stimulus and may even ignore contralateral odors (for review, see Kerkhoff et al., 2012). Neglect is also not restricted to sensory input; patients with neglect may plan and even execute movements more poorly to the contralateral than ipsilateral side and this holds both for upper limb movements as well as for eye movements. The reduction in the speed and the precision of movements to the left appears not to be solely a downstream consequence of the sensory impairment and thus, problems in computing the parameters of contralateral movements is yet another manifestation of neglect.

The failure to process information on the contralateral side cannot be attributed to either a primary motor impairment or to a hemianopia; even when information is presented to the intact visual field of a neglect patient, information in the contralateral hemispace is still neglected. Patients may even show neglect in the absence of visual input; for example, as revealed in a particularly elegant and dramatic experiment, patients may ignore the left side of a scene constructed entirely in visual mental imagery (Bisiach and Luzzatti, 1978) and may fail to search the left of a dark room (Hornak, 1992). Finally, patients can be cued to process information on the contralesional side through verbal or other visual instructions although, left to their own devices, they tend not to orient contralesionally. Taken together, these findings all rule out a primary sensory deficit as being causally linked to neglect.

Aside from the general characteristics of neglect as set out above, the exact manifestation of neglect across patients is not monolithic. Thus, some patients demonstrate neglect for the contralesional side of the body (personal neglect as in dressing only one side of their body) but show no deficits on clinical tests requiring scanning across space (for example, on drawing or cancellation tasks). Other patients can show extrapersonal or allocentric neglect, where they fail to respond to external, contralesional stimuli, and when they do, the neglect can be for information appearing in near space (peripersonal neglect) or far space (or upper or lower space, see below). Neglect occurs most frequently along the horizontal plane although 'altitudinal neglect,' in which information appearing in the upper rather than lower portion of an array (or vice versa) is ignored, may also occur (Pitzalis et al., 2001). Neglect may also occur along the radial dimension although this pattern is thought to be related to the need for a motor response and is less commonly seen when perception alone is tested.

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Finally, in some individuals, the severity of the neglect can be modulated by the nature of the information being processed; thus, the left side of items that 'belong' together or are connected perceptually is less subject to neglect than disconnected items (Behrmann et al., 1990; Tian et al., 2011; Ward et al., 1994). Whether different patterns of neglect are associated with different lesion sites is still controversial and this issue is discussed in greater detail in Section Different Forms of Neglect in Relation to Different Lesion Sites.

The Assessment and Diagnosis of Neglect

The diagnosis of neglect is generally rather straightforward – neglect is, in a standard manner, elicited in tasks in which the patient must either cross out items that appear randomly scattered on a piece of paper or must mark the midpoint of a single horizontal line and the neglect disorder can be elicited at the patient's bedside. Neglect is also typically observed when a patient is asked to draw or copy a simple picture such as a daisy or a clock and details on the contralesional side are generally omitted. A particularly popular test for hemispatial neglect, the Behavioral Inattention Test (Wilson et al., 1987), which consists of six subtests including drawing and line bisection, continues to be a measure of choice for many clinicians and researchers. The Birmingham University Cognitive Screen (BUCS; http://www.bucs.bham.ac.uk) is also useful and can be helpful in differentiating between different forms of neglect such as allocentric and/or egocentric neglect (Riddoch et al., 2010).

There have been other recent attempts to increase the sensitivity and reliability of assessment measures. The Sunnybrook Neglect Assessment Procedure, is the result of one such recent effort, and includes a small battery of tests that are quickly and easily administered and have high diagnostic differentiation (Leibovitch et al., 2012). Some bedside tests of hemispatial neglect, however, are still somewhat insensitive to subtle (but clinically relevant) forms of the disorder and considerable effort has been devoted to developing tools to address this issue. For example, the virtual reality lateralized attention test (Buxbaum et al., 2012) is an easy-to-administer computerized measure of hemispatial neglect that mimics the attentional demands of real-world tasks. In this test, participants name objects as they navigate (or are navigated) along a winding virtual path. Similarly, using virtual reality procedures, assessment techniques have been developed in which targets are placed at multiple locations and participants are required to locate the spatially disparate targets (Dvorkin et al., 2012). These latter, more dynamic, three-dimensional assessment tools offer a new approach, which may be valuable in identifying more subtle forms of the disorder and in tracking changes associated with interventions.

Underlying Mechanisms

A number of general interpretations have been advanced to account for the varied manifestations of neglect. For example, some have suggested that neglect arises from a deficit in orienting spatially to the contralesional side with a gradient of attention biasing attention to the ipsilateral side. Others have argued that the problem is one in which there is a rotation or translation of the egocentric frame of reference toward the ipsilesional side. Yet a third suggestion, the premotor theory of neglect, is that there is an imbalance between the spatial representations that control motor programs, and that this imbalance gives rise to an attentional deficit. Although described as alternatives, these differing interpretations may not be mutually exclusive and may refer to different aspects of a single deficit. What is clear at present is that, although they may diverge in detail, these explanations share a common perspective and that is that neglect is a higherorder, rather than sensory, spatial impairment.

One view of neglect, formalized by (Pouget and Driver, 2000) is that neglect reflects a partial loss or dysfunction of cells in the parietal cortex and other related neural areas. Because the number of neurons for representing information in different lateral positions is limited, damage to these neurons gives rise to a pathological gradient with a smooth decline for increasingly leftward locations and an off-center peak reflecting the peak activation on the ipsilateral side. Consistent with this idea, a spatial gradient has been incorporated into several neural network models that simulate neglect, and these theoretical models have successfully captured many aspects of neglect including extinction, performance on line-bisection and line cancellation tasks, and neglect dyslexia as manifest in various reading tasks (Mozer and Behrmann, 1990; Pouget and Sejnowski, 2001).

Alternatively, it has been argued that neglect behavior is best explained by the altered balance between the functioning of distributed default attentional cortical networks rather than by cell death, or structural damage, of specific regions. Recent studies investigating attentional control in neurologically intact individuals have demonstrated that attentional control is largely supported by two parallel networks, one dorsal and one ventral, each playing a specific role in attentional control (Corbetta and Shulman, 2011; Shomstein et al., 2010a,b; Vandenberghe et al., 2012). Corbetta and Shulman (2011) have argued that more ventral lesions to right parietal, temporal, and frontal cortices *directly* impair nonspatial functions (mediated by a ventral frontoparietal attention network) while also *indirectly* impacting the structurally intact more dorsal attentional network that is directly responsible for spatial attention. The fact that the behavioral gradient, described earlier, is known to be modulated by arousal and task instruction is then taken as further evidence that the underlying neural mechanisms are modulated by signals from other regions that are intact (areas within the dorsal network) rather than completely destroyed by structural damage. Perhaps related is the observation that neglect is accompanied by hypoperfusion (insufficient levels of oxygenation) of areas in the right angular and supramarginal gyrus and/or right superior temporal gyrus (Hillis et al., 2005; Khurshid et al., 2012), and that reperfusion, or rTMS, of these areas is associated with improvement of neglect (Cazzoli et al., 2010; Khurshid et al., 2012).

Lesion

As evident from the above discussion, much recent research has been concerned with demarcating the lesions that give rise to neglect and the relationship between the lesions and the neural correlates that have been identified with attentional networks in nonneurological individuals in recent functional imaging studies. Traditionally, visual neglect has been associated with lesions of posterior parietal cortex but more recently, there has been increasing disagreement concerning the neural concomitant of the disorder.

Recent Lesion Mapping in Patients with Neglect

Recent studies exploiting high-resolution structural imaging, in tandem with voxel-based mapping and lesion overlap analyses, have confirmed the standard brain-behavior relationship, pinpointing the temporoparietal junction and the angular gyrus as the neural basis of neglect. Several other studies, however, have identified additional regions such as the intraparietal sulcus as being critical for neglect – a lesion to this region affects the reorientation of the spatial focus of attention and the ability to select between competing stimuli (Gillebert et al., 2011; Vandenberghe et al., 2012). Karnath and colleagues, for example, have reported that neglect may be associated with damage to more anterior areas, including the superior temporal gyrus and insula (Karnath and Rorden, 2012). Others have argued for the involvement of several other critical regions in addition to damage to posterior parietal regions, including, for example, the frontal eye fields and cingulate cortex. Yet others have proposed that the site of the lesion is tightly coupled to the type of neglect, with more dorsal lesions resulting in deficits of top-down guidance of attention and more ventral lesions resulting in a neglect deficit affecting bottom-up attentional guidance. Finally, much recent work exploiting diffusion tensor imaging to map white matter integrity in lesion patients has revealed that visual neglect can result from, and be correlated with, damage to frontoparietal connections in the right hemisphere, and that these white matter changes adversely affect large-scale cortical networks that are important for orientation of spatial attention, arousal, and spatial working memory (Bartolomeo et al., 2012; Karnath and Rorden, 2012; Urbanski et al., 2011).

Different Forms of Neglect in Relation to Different Lesion Sites

Many patients with left neglect following right hemisphere damage have neglect that manifests both egocentrically (i.e., show neglect with left defined with respect to the midline of coordinates centered on the body) and allocentrically (i.e., show neglect with left defined with respect to the midline of coordinates centered extrapersonally). In one recent study, roughly two thirds of individuals with neglect displayed both allocentric and egocentric neglect, while the remaining patients showed pure egocentric neglect. Consistent with the findings reported in Section Recent Lesion Mapping in Patients with Neglect above, the lesions in the inferior frontal gyrus, precentral gyrus, postcentral gyrus, superior temporal gyrus (STG), middle temporal gyrus (MTG), insula, and surrounding white matters were more frequent in the neglect group than in the control group. Of greater interest here is that there is a differentiation in lesion site depending on the pattern of neglect; thus, lesions in the right STG, MTG, lenticular nucleus, and the surrounding white matter were more frequent in the group displaying both allocentric and egocentric neglect than in those with pure egocentric neglect (Yue et al., 2012). The exact neural underpinnings of the different manifestations of neglect is still controversial, however. For example, Riddoch and colleagues have argued that egocentric neglect was associated with more anterior lesions, including the superior temporal gyrus, the supramarginal gyrus, and middle frontal gyrus whereas, allocentric neglect was linked to more posterior lesions, including the middle occipital and temporal gyri and the angular gyrus (Riddoch et al., 2010). Note, however, that Vallar and colleagues have alternately proposed that allocentric neglect is associated with more ventral, occipitotemporal lesions (Vallar et al., 2003).

It is also interesting that reperfusing specific areas has differential impact on different forms of neglect: for example, reperfusion of dorsal frontoparietal cortex is associated with improvement in viewer-centered (egocentric) neglect, whereas reperfusion of a more ventral temporooccipital cortex, is related to improvement in allocentric, stimulus-centered neglect (Cazzoli et al., 2010; Khurshid et al., 2012).

Implicit Visual Information Processing

One of the most provocative claims in the research on neglect is that, despite the loss of phenomenal awareness of the contralateral information, patients are able to process a considerable amount of contralateral information implicitly and this information can be used to guide their behavior (Driver and Vuilleumier, 2001). An early observation suggested that these patients 'knew' more than their overt responses suggested (Kinsbourne and Warrington, 1962). Thus, for centrally presented words, patients with neglect dyslexia often retained word length in their erroneous responses, for example, producing MILKMAN for MAILMAN. The influence of the unattended left-sided information has also been observed in other lexical tasks, in which patients with neglect produced faster responses to a stimulus in the right field when it had been preceded by a brief presentation of an associated word in the neglected left field (Ladavas et al., 1997a,b).

Other innovative paradigms have been developed to explore this issue in greater detail, allowing for the probing the integrity of more rudimentary perceptual processes on the neglected (contralesional) side. Specifically, studies have shown some degree of processing of the contralesional stimulus when it can be grouped with the ipsilesional stimulus on the basis of bottom-up factors such as color and proximity (Driver and Halligan, 1991), or by brightness or collinear edges (Gilchrist et al., 1996; Rorden et al., 1997). This is also true when the contralesional information is grouped with the right information by a global outline (Farah et al., 1993), and when the contralesional information forms the left side of an illusory contour (Kanizsa-type figure) of a partially occluded figure (Mattingley et al., 1997), or of any well-configured object or whole (Gilchrist et al., 1996; Humphreys and Riddoch, 1994).

Although the findings reported above are provocative and of great interest, many of the studies employed designs in which stimuli presented to the neglected field were associated with stimuli presented on the right side of space by virtue of, for example, perceptual filling in, grouping by similarity, lexical relatedness, or semantic category. It remains possible, therefore, that the activation and processing of information on the neglected side occurs by virtue of the priming of the left-sided information by the intact right-sided information rather than being activated on its own merit (Boutsen and Humphreys, 2000; Brooks et al., 2005; Driver et al., 1992; Kumada and Humphreys, 2001; Mattingley et al., 1997; McGlinchey-Berroth, 1997). A recent study by Shomstein et al. (2010) employing semantically unrelated and task-irrelevant stimuli that avoids the possibility of priming information from the right to the left side, has nevertheless confirmed the processing of nonattended contralesional information. In this study, patients with left-sided neglect (and matched controls) judged whether successive complex checkerboard stimuli (targets), presented entirely to the intact right side of space, were the same or different. Concurrent with this demanding ipsilateral task, irrelevant distractor elements appeared on the unattended side and either changed or retained their perceptual grouping on successive displays, independently of changes in the ipsilesional, task-relevant, target. Changes in the grouping of the unattended task-irrelevant distractor produced congruency effects on the judgments of the ipsilateral attended targets to the same extent in neglect patients as in the control participants and this was true even in those patients with severe attentional deficits. These finding provide confirmatory evidence for the residual processing, at least to the level of perceptual grouping, of the neglected information. Much remains to be done to uncover the neural mechanisms that enable the processing of unattended information that is not available for overt report.

Perspectives on Rehabilitation

A diverse set of strategies has been adopted in studies designed to rehabilitate patients with neglect. While the intervention methods are numerous, there is not yet a single agreed-upon method that has proved to be the most effective. In a comprehensive literature review of cognitive rehabilitation following hemispatial neglect, Bowen and Lincoln examined the findings from 12 randomized controlled trials with 306 participants. Although the conclusion reached is that the overall effect of intervention was not statistically significant, cognitive rehabilitation did improve performance on some standardized neglect tests, including a reduction in the number of cancellation errors and an improvement in the ability to bisect the midpoint of a line. In a similar vein, an inclusive review of cognitive rehabilitation studies performed from 1998 to 2002 and then updated in 2005 (Cicerone et al., 2000, 2005) acknowledges the efficacy of cognitive rehabilitation, but also found that there is limited or insufficient evidence for the duration of treatment effects or relevance to everyday functioning (see also Rohling et al., 2009).

One of the most widely used rehabilitative methods, employed in clinical settings, is visual scanning or visual exploration therapy (VST or VET) in which patients are presented with an array of items and are asked to find an item embedded somewhere in the visual display. Of note is that this type of therapy is rather time-consuming with a reported minimum of 40 treatment sessions needed in order to achieve stable results (Antonucci et al., 1995; Kerkhoff, 1998). Empirical studies aimed at evaluating VST/VET's efficacy have yielded mixed results finding that, at worst, patients do not benefit from the method (Antonucci et al., 1995) or, at best, show very specific improvements (Kerkhoff, 1998).

It has been suggested that one of the central deficits in neglect is an orientation bias to the right, and therefore, several therapeutic techniques have been aimed at weakening the rightward bias and shifting the orientation bias centrally. Caloric vestibular stimulation in which iced water is introduced to the left ear and stimulates the vestibular apparatus has been shown to lead to a dramatic, albeit, short-term improvement in the disorder. This procedure has been shown to improve neglect-related disturbances of body perception, unawareness of hemiplegia, and postural imbalances, as well as the perception of the subjective straight ahead that is usually shifted to the right (Karnath, 1994; Rode et al., 1992, 1998). Vibration of the left neck muscles (which produces an afferent that is similar to twisting the trunk midline leftward) has also been shown to be successful (Johannsen et al., 2003; Schindler et al., 2002). Another approach to restoring interhemispheric imbalance that is currently being explored is rTMS and, although this is relatively new, some promising data are already available (see Cazzoli et al., 2010, for review).

Most recent rehabilitative efforts have been focused on prism adaptation as a technique showing potential for long-lasting effects. Patients wear glasses with lenses that shift visual information several degrees to the right (anywhere from 10° to 20°). When goggles are first placed on the patient, the patient performs motor actions, typically consisting of reaching out and touching a visual target that is placed randomly in right and left visual fields. As a consequence, patients will make erroneous reaches proportional to the degree of visual shift. If, however, patients are allowed to observe the last part of the action, they quickly learn to correct for the discrepancy. Following the adaptation period, the goggles are removed and patients are asked to make the same type of reaching movements again. Just as during the adaptation, patients make erroneous reaches only this time shifted in the opposite direction from the target (i.e., to the left of the actual target). Studies using this technique have shown that, following a brief (in some studies as short as 15 min) prism adaptation procedure, there is an increase in attentive behaviors toward the neglected side. Patients also showed increased exploratory behaviors toward the previously neglected side and this benefit persists even after the glasses have been removed (Ladavas et al., 2011; Serino et al., 2006, 2007, 2009; Turton et al., 2010). What sets this intervention apart from the previous attempts to alleviate unilateral neglect is that the observed amelioration generalizes across several different clinical measures, including wheelchair navigation, postural control, and neglect of mental imagery. In addition, the effects can persist for as long as 4 days (in rare cases 5 weeks) after a single adaptation procedure (Frassinetti et al., 2002; Pisella et al., 2002). The neural basis of the improvements remains poorly understood and may involve plasticity in some brain areas, although the parietal lobe is notoriously nonplastic

(Kolb and Cioe, 1998). It is also possible, however, that whatever change is observed may arise from involvement of other postural alterations (such as the shift of the viewer-midline more leftward).

Many other forms of treatment are also being explored. For example, in recognition of the fact that patients with neglect often have deficits in nonspatial forms of attention, too, some intervention approaches have focused on improving vigilance or sustained attention. One recent successful study of this type had patients monitoring long streams of novel visual scenes and, by virtue of this tonic and phasic alertness training, the researchers were able to demonstrate improvement in spatial as well as nonspatial forms of attention (Van Vleet and Degutis, 2012).

Concluding Remarks and Future Directions

As is clear from this review, hemispatial neglect is a heterogeneous and complicated disorder that defies simple explanation, and there remains a pressing need to understand what psychological and neural alterations give rise to this disorder. A further issue that requires additional investigation is the relationship of the spatial and nonspatial deficits in patients with neglect and their underlying neural correlates (Corbetta and Shulman, 2011). Much also remains to be determined regarding the underlying spatial map or frame of reference that defines neglect and whether the different manifestations of neglect arise from different underlying lesions and require different types of intervention.

An additional pressing issue concerns the fate of the neglected information; whether this information is processed normally and in a rich and detailed fashion but is somehow not available for conscious or explicit report continues to be hotly debated and highly controversial (Esterman et al., 2000). Promising studies using functional magnetic resonance imaging have shown differences in brain activation in the striate and extrastriate regions of the contralateral hemisphere for stimuli that have been extinguished compared with those that are reported (Driver and Vuilleumier, 2001; Marzi et al., 2000; Rees et al., 2000; Vuilleumier and Rafal, 2000) and further explication of the neural dynamics that support representations of nonattended information remains to be undertaken.

A final issue to resolve concerns the role of the parietal/temporal cortex in relation to other cortical regions that are involved in spatial processing. The parietal/temporal cortex does not have a monopoly on spatial processing and regions such as the frontal cortex and parahippocampal regions also contribute importantly to spatial representations. How these different areas work separately and/or together to give rise to our unitary visual experience remains unclear but neuropsychological studies with patients suffering from hemispatial neglect allow us to observe some of the representations and processes that ultimately contribute to our unified spatial experience. These findings together with those obtained from functional imaging studies with normal subjects, single-unit recordings from nonhuman primates and computational analyses continue to provide new insights into this perplexing disorder.

See also: Attention, Neural Basis of; Cognitive Neuropsychology, Methods of; Cognitive Neuroscience; Parietal Lobe; Perception of Action Space: Using Multiple Frames of Reference; Visual Streams: Dorsal and Ventral.

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