Spatial hemineglect in humans

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Abstract

The paper reviews the main findings of studies of hemispatial neglect after acquired brain lesions in people. The behavioral consequences of experimentally induced lesions in animals and electrophysiological studies, which shed light on the nature of the disorder, are briefly considered. Neglect is behaviorally defined as a deficit in processing or responding to sensory stimuli in the contralateral hemispace, a part of the own body, the part of an imagined scene, or may include the failure to act with the contralesional limbs despite intact motor functions. Neglect in humans is frequently encountered after right parieto-temporal lesions and leads to a multicomponent syndrome of sensory, motor and representational deficits. Relevant findings relating to neglect, extinction and unawareness are reviewed and include the following topics: etiological and anatomical basis, recovery; allocentric, egocentric, object-centered and representational neglect; motor neglect and directional hypokinesia; elementary sensorimotor and associated disorders; subdivisions of space and frames of reference; extinction versus neglect; covert processing of information; unawareness of deficits; human and animal models; effects of sensory stimulation and rehabilitation techniques. © 2000 Elsevier Science Ltd. All rights reserved.

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Abbreviations: MCA, middle cerebral artery; BA, Brodman area; SSA, subjective straight ahead; CT, computerized cranial tomography; (f)MRI, (functional) magnetic resonance imaging of the brain; 2DG, 2-desoxyglycose; rCBF, regional cerebral blood flow; PET, positron emission tomography of the brain; SC, superior colliculus; PmS, posterior middle-suprasylvian cortex (in cats).

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1. Introduction

Neglect (synonymous with: hemispatial neglect, hemiinattention, hemisensory neglect, hemineglect) denotes the impaired or lost ability to react to or process sensory stimuli (visual, auditory, tactile, olfactory) presented in the hemispace contralateral to a lesion of the human right or left cerebral hemisphere. Besides the aforementioned aspects of sensory neglect, motor neglect may occur and manifest itself as the reduced use or nonuse of a contralateral extremity (arm, leg) during walking or bimanual activities. Finally, neglect may occur in the imagination of spatial scenes (representational neglect). By definition, neglect is not merely the result of elementary sensory (i.e. hemianopia, hemisensory loss), motor (i.e. hemiparesis) or cognitive/emotional disorders (i.e. reduced intelligence, depression). Table 1 summarizes the most frequent neglect phenomena in these different categories.

2. Anatomy and recovery

2.1. Etiology and lesion localization

The most frequent etiological cause of neglect in humans is (often large) infarctions in the territory of the right, less often the left middle cerebral artery (MCA; Vallar, 1993), causing lesions which center on the inferior parietal cortex (Brodman areas, BA 40, 7). Accompanying damage to adjacent structures such as the optic radiation, the insula, dorsolateral frontal cortex (BA 4, 6, 44, 45, 46) and superior temporal cortex (BA 22, 37) is frequently apparent (Smania et al., 1998). Furthermore, neglect occurs after posterior thalamic (Cambier et al., 1980) or basal ganglia lesions (Damasio et al., 1980), as a result of intracerebral bleedings, but has never been described following pure occipital lesions (Smania et al., 1998; Vallar, 1993). Occasionally, neglect after lateral frontal lesions has been reported (Husain and Kennard, 1996) where similar lesions in animals regularly lead to contralesional neglect (Rizzolatti et al., 1983; Deuel and Collins, 1984). Neglect may also result from tumors or traumatic injuries of the aforementioned areas (Vallar, 1993). In general, severe and multimodal neglect is caused by very large rightsided lesions which encroach on parietal, temporal, and regions of occipital or frontal cortex as well as subcortical structures (Vallar and Perani, 1986).

Contralesional neglect occurs in some 33% of left-hemisphere and more than 50% of right-hemisphere
lesioned patients (Stone et al., 1991) when tested immediately (within 7 days) after lesion onset. The absolute percentage of neglect depends critically on the criterion or test used but the asymmetry in the occurrence of contralesional neglect has been found across different samples and methods (Schenkenberg et al., 1980). Recovery is considerably quicker and more complete in neglect after left-hemisphere lesions as opposed to right-hemisphere lesions (Stone et al., 1991). Thus, there is a clear hemispheric asymmetry showing that neglect is more frequent, more severe and more permanent following right-hemispheric lesions. However, transient rightsided neglect after left unilateral lesions occurs in some cases (Welman, 1969; Peru and Pinna, 1997; Kerkhoff and Zoelch, 1998). More long-lasting rightsided neglect occurs in patients with bilateral cerebral lesions (Weintraub et al., 1996).

2.2. Mechanisms of recovery

Recovery from the most obvious signs of neglect (i.e. the tendency to orient to the ipsilesional side and the lack of visual exploration in the contralesional hemispace) has been noted in the majority of patients within the first 6 months (Lawson, 1962; Hier et al., 1983). In the remaining 25% neglect may persist for up to 12 years (Zarit and Kahn, 1974) and performance in tasks which are sensitive to neglect may decline again after cessation of apparently successful rehabilitation treatment in the clinic (Paolucci et al., 1998; Hier et al., 1983). Recovery from neglect is more prominent after left compared with right-sided cerebral lesions (Stone et al., 1991). Furthermore, recovery from “frontal” neglect is more rapid and more complete in humans than from the classical “parietal” neglect syndrome (Mattingley et al., 1994a). Substantial recovery is less likely after large lesions and in those patients with diffuse brain atrophy in addition to the focal right hemispheric lesion (Levine et al., 1986)

Little is known about the mechanisms guiding spontaneous recovery and/or those enabling treatment-guided improvements during rehabilitation. Pantano et al. (1992) reported a concomitant increase in regional cerebral blood flow (rCBF) in the posterior areas of the damaged right hemisphere and the anterior areas of the intact, left hemisphere probably including the frontal eye fields after a specific neglect treatment in their patients. Only the left frontal activation, in the region of the frontal eye fields, covaried with improved visual scanning behavior after treatment. The authors concluded that the left (intact) frontal eye fields are crucial for recovery of visual scanning in neglect. In a later PET study with three neglect patients, this finding was not uniformly replicated (Pizzamiglio et al., 1998).

In this study, behavioral recovery seemed to covary with improved blood flow in surviving areas of the lesioned hemisphere.

Similar results have been obtained in primate studies where neglect was induced by lesioning the frontal polysensory association cortex. Metabolic mapping for local glucose utilization (2-DG) showed a widespread reduction of glucose in ipsilesional striatal and partially thalamic nuclei connected with the frontal lobe whereas no reductions were found in cortical areas

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1 Since leftsided neglect after right cerebral lesions is the most frequent type of neglect the term “neglect” in this review refers always to leftsided neglect in humans if not indicated otherwise. Of course, this does not exclude the fact that rightsided neglect after uni- or bilateral lesions may occur (more rarely) as well.

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Table 1
Summary of sensory, motor and representational neglect phenomena occurring after unilateral lesions in humans

<table>
<thead>
<tr>
<th>Type of neglect</th>
<th>Definition and typical behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>Patient searches for stimuli with eye- and head-movements preferentially in the ipsilesional hemispace. Omission of contralesional stimuli during reading, writing, drawing of geometric stimuli, bisecting horizontal lines, or eating from a plate. Ipsilesional deviation of the perceived subjective straight ahead.</td>
</tr>
<tr>
<td>Auditory</td>
<td>Patient does not react to sound/speech stimuli from the contralateral hemispace. He/she may turn to the ipsilesional side when addressed from the contralesional. When several speakers are present the patient responds preferentially to the most ipsilesional one, irrespective of who has spoken. Ipsilesional deviation of the perceived auditory midline position in front space.</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>Ignoring of tactile stimulation (i.e. touch) or painful stimuli (cold/hot stimuli, jammed fingers in wheel or spokes of the wheelchair) on the contralesional body half. Mislocalization of tactile stimuli in this part. Subjective shift of own body-midline (i.e. position of the spine) to the ipsilesional side.</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Ignoring smells delivered to one nostril. Rarely observed in daily life since stimuli are easily detected with the other nostril.</td>
</tr>
<tr>
<td>Motor</td>
<td>Reduced use of contralesional arm/leg which is not completely attributable to a sensorimotor loss. Reduced arm sway during walking; reduced use of contralesional arm during bimanual activities (i.e. eating, carrying loads); dragging behind the contralesional leg/foot during walking.</td>
</tr>
<tr>
<td>Representational</td>
<td>Patient describes few items located in the contralesional part of an imagined scene (i.e. a famous city place, the own living room or house), but describes much more items when describing the same scene from a different perspective (180° rotated).</td>
</tr>
</tbody>
</table>
3. Allocentric spatial deficits

Because damage is invariably widespread and compromises multiple neural systems, principally located in the parieto-temporal cortex (in human neglect) as a result of large lesions a variety of deficits are encountered in neglect. These may be analyzed with respect to different aspects of spatial cognition. A distinction may be drawn between allocentric, egocentric and object-centered deficits. Allocentric space is defined in this context as concerning the spatial relationship between two stimuli separated in space, i.e. the length of two lines or the two halves of a bisected line. In a broader sense, allocentric relationships define spatial relations between two or more stimuli in three-dimensional space, including those entailed in spatial navigation. In contrast, egocentric deficits relate to spatial impairments in relation to the patient’s own body or specific body parts, i.e. the subjective estimate of her/his tactile body midline, the auditory or visual sense of straight ahead in relation to the sagittal midline of the body or head. Object-centered (or environment-centered) deficits indicate hemispatial deficits or omissions in the contralesional half of one object, i.e. a face or a clock face (see below). In contrast to the allocentric and egocentric deficits which fit relatively easy into a left-right or contralesional/ipsilesional dichotomy of space (impairments in left/contralesional hemispace, normal or nearly normal performance in right/ipsilesional hemispace) object-centered neglect means that a patient ignores the left/contralesional part of one object (i.e. a word, a drawing, or a face), regardless of the object’s location in space (Walker, 1995; Olson and Gettner, 1996).

One of the most frequent allocentric deficits investigated in patients with visual neglect is horizontal line bisection (Schenkenberg et al., 1980; Burnett-Stuart et al., 1991), a task originally devised to measure spatial judgments in hemianopic patients without neglect (Axenfeld, 1894; Lohmann, 1911). These patients bisect a horizontal line in most cases too far to their blind hemifield (Kerkhoff, 1993; Barton et al., 1998) whereas neglect patients without hemianopia place their bisection mark too far to their ipsilesional side thus reproducing a too large line segment in their contralesional hemispace (Halligan et al., 1990; Halligan and Marshall, 1991b; Barton et al., 1998; cf. Fig. 1A). In a variant of this task termed line extension (Fig. 1B) the subject views only the part of the line displayed in the ipsilesional hemispace and subsequently estimates how long a bar has to be extended to the contralesional hemispace until both parts appear as equally long. In this task neglect patients typically oversize the line segment in their neglected hemispace — just as they do in line bisection (Fig. 1B).

![Fig. 1. Survey of deficits in allocentric visuospatial tasks in patients with leftsided visual neglect.](image-url)
Similarly, neglect patients overreproduce a horizontal distance displayed in their contralateral hemispace when the “reference” distance is displayed in their ipsilateral space (Fig. 1C). The same phenomenon is observed when a horizontal bar has to be reproduced in the left hemispace (Fig. 1D). Here patients reproduce the bar in the contralateral hemispace too long, which has been termed “size distortion” (Harvey et al., 1995; Milner and Harvey, 1995; Milner et al., 1998). In contrast, neglect patients show veridical coding of vertical bars (Fig. 1E) and of symmetrical, global shapes like circles (Fig. 1F). This disturbed size coding may remain a purely perceptual phenomenon since it does not necessarily imply disturbed adjustment of finger grip aperture when scaling the size of an object in grasping (Pritchard et al., 1997). Together, these results indicate a non-veridical coding of within-object (length of an object) and between-object (distance between objects) spatial extension in the horizontal plane which is not found when vertical size cues are apparent. The advanced interpretation for these allocentric spatial disorders is that the contralateral hemispace appears “constricted” or “distorted” in relation to the ipsilateral hemispace (Milner et al., 1998). As a consequence, elongated objects presented in this hemispace have to be larger in order to match the length of an object in ipsilateral hemispace. This has been found for horizontal object-size, and as well for the horizontal distance between objects (Kerkhoff, 2000; see also Karnath and Ferber, 1999 for different results and interpretations). Measures of perceptual distortions in patients with neglect may be quite sensitive since they may reveal size distortions even after apparent recovery of other signs (line bisection; Harvey and Milner, 1999).

4. Egocentric spatial deficits

It is a relatively new idea that neglect is not only found in relation to the left half of space but more precisely in relation to what is left of the patient’s trunk midline, head sagittale or even the position of the patient’s hand in space. In one of the early studies on that topic (Heilman et al., 1983) neglect patients were required to point towards their subjective straight ahead (SSA) in relation to their trunk midline. The patients’ responses were ipsilesionally deviated to the right side while non-neglecting patients with left hemispheric lesions showed quite accurate pointing results. Similar results are obtained when neglect patients have to indicate their visual SSA without pointing (Fig. 2A).

If egocentric deficits are related to the body midline or certain body parts modifications of their position in space might influence neglect. In an early study examining this question (Bisiach et al., 1985), neglect patients had to tactually explore a honeycomb-shaped board with their ipsilateral hand to find a marble. The authors found that neglect covaried with the position of the trunk-vertical axis and with the head/eye-axis. Shifting either the trunk or the head to the left in relation to the stationary honeycomb-board reduced the number of omissions in the tactile neglect task. Karnath (summarized in Karnath, 1997) has investigated the influence of body-and-head position in more detail. In a saccadic reaction-time study, it was found that leftward trunk-rotation but not head-rotation improved the delayed reactions to visual targets appearing in contralateral hemispace (Karnath et al.,

![Fig. 2. Representative egocentric deficits in neglect. (A) Deviated visual judgments of neglect patients (without visual field defects) when indicating the position of a diode in total darkness in relation to their bodily subjective straight ahead position. The judgments were similarly shifted to the ipsilesional, right side in two distances (1.2 and 3 m), indicating a rotation of the visual subjective straight ahead (SSA) in front space (redrawn after Ferber and Karnath, 1999). (B) Ipsilesionally shifted visual search area in total darkness (solid line) and similarly shifted tactile search area (with the ipsilesional hand, not drawn) with blindfolded neglect patients (cf. Karnath and Perenin, 1998). Search areas are drawn schematically and not to scale. (C) Judgments of the subjective visual and tactile vertical, horizontal and oblique orientation matches in a patient with left-sided neglect (upper two polar plots) and a matched normal subject (lower two plots). Each thin black lines represents the result of one trial. Visual tests were taken with stimuli displayed on a PC-screen via software (Kerkhoff and Marquardt, 1995), tactile tests employed the judgment of a metal bar mounted on a vertical board in front of the patient (Kerkhoff, 1999a). Note the counterclockwise tilt of perceptual judgments in both modalities in the neglect patient. Together, these results indicate a subjective rotation of sensory space in the frontal plane going beyond the shift of the SSA in the sagittal plane (A) in neglect patients.](image-url)
1991). This role of the trunk-sagittale as one major anchor for determining left versus right in space in relation to the observer has been replicated in several subsequent studies using line bisection and reading tasks (Chokron and Imbert, 1995; Schindler and Kerkhoff, 1997; Vuilleumier et al., 1999). However, the trunk midline is not the only axis that might be important for spatial orientation: the head sagittale plays a similar important role as suggested by behavioral and neurophysiological studies (behavioral: Bisiach et al., 1985; Kerkhoff and Schindler, 1997; Vuilleumier et al., 1999; neurophysiological: Andersen et al., 1989, 1990, 1997; Duhamel et al., 1997). Other types of egocentric or body-centered deficits in neglect are summarized in Fig. 2. Patients with pure neglect (without field defects) often show an ipsilesionally deviated subjective estimate of straight ahead (Fig. 2A) which seems to be anchored to the trunk midline, although not every neglect patient shows this deficit (Bartolomeo and Chokron, 1999). The visual and tactile fields of search in neglect patients (as measured by optoelectronic devices) are shifted to the ipsilesional, right side (Fig. 2B), even when no external stimulus is present.

However, the deviations of spatial orientation in the horizontal plane are not the only ones encountered in neglect. These patients can also show a tilt of their subjective vertical or horizontal or judgments of whether two obliquely oriented stimuli are parallel, in their frontal plane (Fig. 2C). Hence, a 90°-oriented, vertical bar has to be oriented to 100° (tilted counterclockwise) to be perceived as vertical by a neglect patient. This deficit occurs both in the visual (Kerkhoff and Zoelch, 1998) and tactile (Kerkhoff, 1999a) modality and indicates that the spatial anchoring of subjective, egocentric space is disturbed in neglect patients in at least two spatial planes: the horizontal plane, leading to the pathological, ipsilesionally oriented body orientation (cf. Fig. 2A,B), and the frontal plane, leading probably to abnormal posture of the head, trunk and legs during sitting and stance, as found in neglect patients (Rode et al., 1997, 1998; Perennou et al., 1998, 1999).

5. Object-centered neglect

When we look at or imagine an object we are aware of its structure. Consider the face of a friend of yours, your watch or the letter ‘d’. We know that in order to transform the letter ‘p’ from ‘d’, we have to rotate the letter ‘d’ in the plane of the page. Likewise, you know if and on which side your friend has a birth mark on his face, or on which side of your watch the date is indicated. This kind of structural awareness very likely depends on a neural system with two features: neurons selective for locations as defined relative to a reference frame around an object, and an arrangement of several of such neurons so that their spatial fields form a map of object-centered space (Olson and Gettner, 1995, 1996). Patients with spatial neglect may copy or mark every feature in an array, yet they may fail to reproduce the left part of an object (leftsided numbers on a clock face, a flower, or the left part of a word, cf. Fig. 3).

Hillis and Caramazza (1991) described a patient with rightsided neglect dyslexia who made reading errors chiefly at the end of a word — irrespective in which visual field the word appeared, or if it were printed from left to right, right to left or vertically from top to bottom. In all these experimental modifications, the errors occurred at the end of the word. These results support the idea that meaningful words form a kind of “perceptual unit” (Baylis et al., 1994) and have an object-centered representation. Likewise, faces may be coded in a similar way which fits neatly the observation of leftsided neglect for the contralateral half of objects or faces (Walker, 1995).

Which factors do determine that a patient neglects the left half of an object? Is the gravitational vertical
or the intrinsic vertical of an object the relevant variable? To decide between these two possibilities, rotated figures with critical elements on the left or right side of the intrinsic figure axis have been utilized. Some patients persist in showing neglect of the contralesional part of the rotated object (Driver et al., 1994). This type of axis-based neglect demonstrates neatly that neglect might be attached to the object’s intrinsic axis and not necessarily to the physical, left side of an object (but see Farah and Buxbaum, 1997, for an alternative interpretation).

6. Representational neglect

Neglect is not restricted to perception or action in the contralesional part of external space. It may occur as well when subjects have to scan their inner spatial representation of a scene. Bisiach and Luzzatti (1978) reported in their famous experiment two patients who were unable to recall specific locations on the left side of the Piazza de Duomo in Milano when they imagined facing it from a particular vantage. When they had to describe the square from a 180°-rotated perspective they recalled the omitted details on their left from the previous condition but neglected now particular items on their left side which were on the right side in the prior test condition. The authors concluded that their patients had an unilateral representational deficit for one hemispace. In later studies, these results were confirmed experimentally using an elegant technique (Bisiach et al., 1981). Similar deficits are found when patients are required to recall cities from their country (Bartolomeo et al., 1994; Rode and Perenin, 1994 cf. Fig. 4).

Representational neglect seems to be less frequent than frank visual neglect: only some 25% of the latter patients show representational neglect when they are required to recall cities located on the left or right side of a map of their own country (Beschin et al., 1997; Bartolomeo et al., 1994). Typically, the patients recall easily cities located on the right side of the map and fail to report those located on the contralesional, left side — just as in the Piazza de Duomo example described above. Clinically, similar deficits can be suspected when patients have to remember where on the ward their bedroom is or when they have to recall details from their home, i.e. the living room.

7. Motor neglect and directional hypokinesia

Two types of deficient motor behavior in neglect have to be distinguished clearly: the reduced spontaneous use or complete nonuse of the contralesional hand, arm or leg during motor activities (termed motor neglect; cf. Laplane and Degos, 1983; von Giesen et al., 1994) and the slower execution of arm movements with the ipsilesional hand or arm towards the contralesional hemispace (termed directional hypokinesia, Heilman et al., 1985; Bisiach et al., 1990; Mattingley et al., 1994c; Bisiach et al., 1995). The latter is associated with a delayed movement initiation and a reduced movement velocity and is probably a rare form of neglect (Milner et al., 1993). Akin to the directional hypokinesia for leftward arm movements, neglect patients show delayed (Sundquist, 1979) and hypometric (Girotti et al., 1983) saccadic eye movements to left hemispace and their pattern of visual search is shifted to the ipsilesional hemispace (Chédru et al., 1973; Ishiai et al., 1987; Hornak, 1992; Karnath et al., 1996; as depicted in Fig. 2B).

In contrast, motor neglect affects only the contralesional extremity; the use of the neglected hand/arm often can be prompted by the allocation of attention to it (Ghika et al., 1998), similar to the cueing effects in sensory neglect (see Section 14). This motor neglect is not a result of a paresis which can be excluded by the examination of magnetic evoked potentials (Von Giesen et al., 1994). Patients with motor neglect have often lesions involving the thalamus, basal ganglia or the frontal cortex but spare the primary sensorimotor cortex (Laplane and Degos, 1983). Motor neglect is also found as a transient phenomenon after unilateral ventrolateral thalamotomy for the treatment of hemicparkinsonism (Vilkki, 1984). Similar to the results of the 2-DG mapping studies in primate neglect (Deuel and Collins, 1984) imaging investigations in humans (PET, Von Giesen et al., 1994) indicate a more widespread metabolic dysfunction in the premotor, prefrontal, cingulate and partially parietal cortex of the

![Fig. 4. Example of representational (imaginal) neglect in a patient asked to visualize mentally the map of France and to name as many towns as possible during a limited period of time (2 min). The number at the bottom indicates the number of recalled cities in the two conditions. Temporary remission through caloric (vestibular) stimulation is seen on the right side of the figure. Reproduced from Perenin (1997), with permission from Springer-Verlag.](image-url)
Table 2
Frequently associated deficits in neglect. Percentages are based on studies with neglect patients after right hemisphere lesions, or on right-hemisphere lesioned patients in general and may differ between studies. In patients with small, circumscribed parietal lesions, other percentages are obtained (indicated by "*, see Ghika et al., 1998). In the rightmost column diagnostic procedures are suggested to differentiate between elementary sensory or motor deficits and neglect-related impairments. If the peripheral sensorimotor pathways are intact VEP, SEP and transcranial magnetic stimulation should reveal largely normal results

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Frequency (%)</th>
<th>Source</th>
<th>Procedures for differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual field defects (hemianopia, quadrantopia)</td>
<td>70–90</td>
<td>Vallar and Perani, 1986; Kerkhoff, 1999a</td>
<td>Visually evoked potentials (VEP), Vallar et al., 1991; Spinelli et al., 1994; De Keyser et al., 1990; Special perimetry, Walker et al., 1991</td>
</tr>
<tr>
<td>Hemianaesthesia (impaired position and pain sense in contralesional limbs)</td>
<td>63</td>
<td>Vallar et al., 1995b; Vallar et al., 1997; Sterzi et al., 1993; Ghika et al., 1998</td>
<td>Somatosensory evoked potentials (SEP); Cueing of patient’s attention to the neglected limb; Ghika et al., 1998 Transcranial magnetic stimulation of motor cortex; Von Giesen et al., 1994</td>
</tr>
<tr>
<td>Hemiplegia/paresis</td>
<td>100</td>
<td>Sterzi et al., 1993</td>
<td>Transcranial magnetic stimulation (TMS) of motor cortex Von Giesen et al., 1994</td>
</tr>
<tr>
<td>Pseudoparesis of the hand*</td>
<td>90</td>
<td>Ghika et al., 1998</td>
<td>Transcranial magnetic stimulation (TMS) of motor cortex Von Giesen et al., 1994</td>
</tr>
<tr>
<td>Abnormal finger and hand postures*</td>
<td>67</td>
<td>Ghika et al., 1998</td>
<td>–</td>
</tr>
<tr>
<td>Ipsilesional deviation of body posture in stance</td>
<td>70</td>
<td>Rode et al., 1997; Hesse et al., 1994</td>
<td>Posturography; Rode et al., 1997 Measurement of prolonged “silent periods” in the EMG after TMS; Classen et al., 1997</td>
</tr>
<tr>
<td>Increased pain, avoidance of contralesional limb use*</td>
<td>34</td>
<td>Ghika et al., 1998</td>
<td>–</td>
</tr>
<tr>
<td>Contralateral gaze palsy (tonic ipsilesional eye deviation)</td>
<td>30–50</td>
<td>De Renzi et al., 1982; Tijssen and Gisbergen, 1993</td>
<td>–</td>
</tr>
<tr>
<td>Visuospatial and tactualspatial disorders, impaired time perception</td>
<td>90</td>
<td>Kerkhoff, 1999a; Basso et al., 1996</td>
<td>Evaluation of spatial perception; Kerkhoff and Marquardt, 1995</td>
</tr>
<tr>
<td>Fatigue, reduced sustained attention</td>
<td>–</td>
<td>Robertson et al., 1997</td>
<td>–</td>
</tr>
</tbody>
</table>
injured hemisphere in motor neglect than the lesion shown by the structural CT/MRI scans. Classen et al. (1997) studied the neurophysiological basis of motor neglect and found an exaggerated “silent period” in the electromyogram of small hand muscles after transcranial magnetic stimulation. According to their results, this “silent period” might considerably delay the initiation of directed motor activities of the contralateral extremities, and thus lead to the symptoms of hypokinesia, underutilization of the contralateral extremities as well as delayed movement initiation (Classen et al., 1997).

8. Elementary sensory, motor and associated disorders

Most patients with neglect have low-level sensory and motor impairments as well as other associated deficits (see Table 2). This often creates a diagnostic dilemma in the clinical examination of these patients since it may be difficult to decide whether a patient has for instance hemianopia or neglect or both. Examinations with evoked potentials and magnetic stimulation of the motor cortex may be used to test the integrity of the peripheral sensorimotor pathways up to their primary cortical representation (Table 2).

The frequent co-occurrence of associated disorders is explained by the characteristically large lesions of neglect patients which cause damage to many adjacent structures such as the optic radiation, the pyramidal tract, temporal, occipital, frontal and other cortical or subcortical areas. Nevertheless, well-examined single cases demonstrate that neglect is not caused by such associated deficits, although it is almost certainly aggravated by their presence. Despite the phenomenological similarity of both types of deficit (i.e. in the sense of a hemivisual deficit) there is a fundamental difference between the two disorders, illustrated in Fig. 5.

To summarize, the hemianopic patient without neglect has a largely intact, abstract spatial representation of both hemispaces (left, right)\(^2\) including his

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\(^2\)It has been proposed recently that primary visual cortex is also involved in high resolution visual imagery (Kosslyn et al., 1999). Consequently, striate cortex lesions might cause not only hemianopia but also a unilateral imagery deficit similar to that of neglect patients. However, clinical experience with purely hemianopic patients does not support such a hemi-imagery deficit, at least not on a coarse level. Possibly, such hemi-imagery deficits require lesions upstream area 17 (Goldenberg, 1993).
own body, while the neglect patient without hemianopia may have an intact peripheral visual system apparently sufficient to perceive his environment and own body — but fails because this sensory information is compromised at a higher level of space representation. The same reasoning holds true for the somatosensory, auditory or olfactory modality.

9. Subdivisions of space and different frames of reference

9.1. Behavioral dissociations in different sectors of space in neglect

We subjectively experience our surrounding space as well as our body in space as a single and coherent multisensory unit, including imagined space and back space as well. Far extrapersonal space, peripersonal or reaching space, near and ultranear space (personal space), as well as imagined (or representational) spaces are usually distinguished (see Fig. 6).

Why are these distinctions? First, there is a behavioral evidence from neglect patients and those with other spatial disorders that these different space systems may partially dissociate. Second, there is an increasing physiological evidence indicating that different brain areas code different aspects of space (see Section 9.2). The behavioral dissociations in-patients have been interpreted in terms of this distributed coding of space in our brain.

Neglect may occur selectively in near space (Halligan and Marshall, 1991a; Mennemeier et al., 1992) or be more severe in far space (Cowey et al., 1994). Such dissociations are rare (Guariglia and Antonucci, 1992) and often task-dependent (Keller et al., 1999), and in most patients neglect occurs in near and far space (Pizzamiglio et al., 1989). Nevertheless, such dissociations show that there is probably not one single all-purpose space map in our brain — as suggested by introspection. Furthermore, these space maps are probably dynamically calibrated, for instance by tool use (Berti and Frassinetti, 2000), so that far space may be remapped into near space when we reach targets with a stick in far space. Similarly, it is very likely that different sensory space maps interact with each other in creating a unified space map (Knudsen and Brainard, 1995). In a recent study concerning the influence of vision on auditory space, we found a rapid recalibration of auditory space in neglect patients by a few minutes of visual motion stimulation (Kerkhoff et al., 2000). This suggests plasticity and continuous reorganization of space maps by sensory or motor experience, particularly in neglect patients. Apart from the dissociations in external space, neglect may occur solely in the representation of space (Guariglia et al., 1993; Beschin et al., 1997) while sparing external space.

9.2. Neurophysiologic and functional imaging evidence for different types of space coding in the brain

There are several distinct space maps coding different sectors of space (Graziano and Gross, 1995; Olson and Gettner, 1995; Rizzolatti et al., 1997; Colby, 1998). Many areas participating in space representation are motor areas (Rizzolatti et al., 1997) located in frontoparietal cortex. One important area is located in the ventral premotor cortex; neurons in this area discharge when the arm or head of the animal moves. Many cells are bimodal, thus responding to visual and/or tactile stimulation within a particular body or space sector around the animal. Although these cells are chiefly activated through moving stimuli it has recently been shown (Graziano et al., 1997) that such neurons can also tonically signal the presence of an object in darkness following its silent removal so as to deceive the monkey that it is still present. This indicates that a spatial representation can be generated or held in memory by the monkey on the basis of previous experience — just as when we recall where we positioned the alarm clock beneath our bed.

Another type of oculocentric space representation has been shown in another cortical area, the monkey’s ventral intraparietal cortex (VIP; Colby, 1998). The bimodal cells in this area seem to code “ultraneural” space since they react to cutaneous and/or visual stimuli in a particular sector of the animal’s body, principally around the mouth and extending up to 30 cm into surrounding space (Colby and Duhamel, 1996). Two types of neurons were found in this area. First, bimodal neurons, that signaled the presence of stimuli very close (ultranear) to the animal. The second type were trajectory neurons, which responded to movements of stimuli — apparently coding the point where a stimulus might contact the animal’s body (Colby, 1998). Trimodal cells coding near space have been found in the ventral premotor cortex reacting to tactile, visual and auditory stimuli in front space, and in part also to auditory and tactile stimuli presented behind the monkey’s head (Graziano et al., 1999). This study shows that there is a physiological correlate of sensory space behind the head for cutaneous or acoustic stimuli. Cells in the monkey’s supplementary eye field seem to code space in yet another, more abstract spatial manner (Olson and Gettner, 1995). These cells react to stimuli around an object irrespective of the position of that object in space — exactly as in the case of object-centered neglect of a word-part (Hillis and Caramazza, 1991).

Imaging investigations support the physiological results summarized above. Fink et al. (1997) investi-
gated object-based and space-based perceptual judgments in normal subjects with PET. They found partially overlapping, in addition to diverging neural activations in the medial parieto-occipital cortex indicating separable representations of objects versus the space between objects. These results were largely replicated in another study (Honda et al., 1999) showing that object-based spatial judgments activates ventral stream areas bilaterally. In addition, they found that the coupling of object-centered coding with a motor response by the subject resulted in right-sided posterior parietal and bilateral frontal activations (ventral premotor, dorsolateral prefrontal and anterior supplementary motor areas, Honda et al., 1999). In yet another imaging study (Galati et al., 2000), it was showed that egocentric and allocentric coding of space in humans is represented in partially overlapping, but also diverging anatomical regions. While egocentric space coding activated a large fronto-parietal network with greater activations in the right hemisphere, a small fronto-parietal subset of the activated areas was activated during an allocentric space task. This finding explains why ego- and allo-centric signs of neglect often coexist (due to overlapping neural circuits), and secondly, why egocentric signs of neglect are more frequently entailed than object-centered signs (due to the larger network for egocentric space coding).

In summary, there is a growing evidence that there are numerous representations of space and objects in space in our brain. How exactly these different space maps are integrated and coordinated remains to be established. However, some details concerning the merging of sensory space are already known. Bimodal and trimodal neurons are likely to participate in “binding” different sensory space maps together. Furthermore, subcortical structures (superior colliculus, SC; Meredith and Stein, 1985, 1986a, 1986b; Stein et al., 1988; Knudsen and Brainard, 1995), the pulvinar nuclei (Grieve et al., 2000) and cortical areas (anterior ectosylvian cortex of the cat; Stein et al., 1988; Wallace et al., 1992; Wilkinson et al., 1996, the likely homologue of the temporo-parietal cortex in humans), are involved in intersensory integration. Furthermore, parietal cortex (Lateral intraparietal cortex, cf. Batista et al., 1999) serves as a sensorimotor interface for visually guided reaching movements. Thus, various cerebral structures are involved in creating a unified space map — similar to our introspective feeling of a unitary sense of space.

10. Extinction versus neglect

In contrast to neglect, extinction is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented, or when two actions have to be performed with both hands simultaneously (see Table 3). By definition, the processing of a single stimulus or action should be intact or only marginally impaired because otherwise an elementary sensory or motor deficit should be suspected. In that case, sensory extinction may nevertheless be examined with uni- and bi-lateral stimulation in the intact visual hemifield or body side (cf. Rapcsak et al., 1987; Ladavas et al., 1990).

Hence in contrast to extinction, neglect can readily be observed when only one stimulus (i.e. a laser spot; Karnath, 1994) or no external stimulus at all is present, i.e. when describing a scene from memory (Bisiach and Luzzatti, 1978) or when searching for a nonexistent visual target in complete darkness (Hornak, 1992). Apart from the inherent differences between neglect and extinction, their distinction is further strengthened by the differential lesion sites associated with them. Patients with sensory extinction often have subcortical (basal ganglia) lesions (Vallar et al., 1994), whereas neglect patients most frequently have parietal lesions (see Section 2). This distinction may be less clear in light of the recent report by Smalian and colleagues (Smalian et al., 1998) who described visual extinction in four patients with lesion of the anterior parietal lobe (BA 1,2,3) which extended posteriorly (BA 39, 40). De Renzi et al. (1984) reported patients with auditory extinction whose deficits were dissociable from both visual extinction and as well from severe visual neglect. Their patients with persistent auditory extinction had neither subcortical nor

<table>
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<th>Table 3</th>
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<td>Definition and description of extinction phenomena occurring after unilateral brain lesions in humans</td>
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| General definition | Inability to perceive two sensory stimuli when presented simultaneously at different locations (one contralesionally, one more ipsilesionally located). By definition, single, unilaterally presented stimuli in the contra- and ipsilesional location should in most trials be perceived correctly in order to rule out an elementary sensory defect. |
| --- |
| Sensory extinction | When two visual, auditory or tactile stimuli are presented simultaneously the patient frequently does not report (“extinguishes”) the more contralesional stimulus. |
| Crossmodal extinction | The more contralesional stimulus of two stimuli presented in different modalities is extinguished (i.e. a visual stimulus on the left and a tactile stimulus on the right side). |
| Motor extinction | When bimanual actions are required the patient frequently “forgets” to use the contralesional hand/arm. |
parietal lesions but had sustained largely superior-temporal lesions which involved the auditory pathways.

Since extinction may occur with diverse lesion sites—just as neglect—the search for differential mechanisms might be more rewarding. Exactly such a criterion for differentiation was recently reported by Smania et al. (1998) in reaction-time experiments for visual stimuli delivered in contra- and ipsilesional hemispace (see Fig. 7).

This study shows that neglect patients when responding to a single visual stimulus have a gradient of reaction time increase in the contralesional hemispace and a paradoxical reaction time decrease in the ipsilesional hemispace around 10° eccentricity. In contrast, extinction patients and the normal control subjects respond more slowly to more eccentric, compared with more central visual targets. A similar reaction-time advantage for the more ipsilesional stimulus over the more contralesional one has been reported by Ladavas et al. (1990).

Visual extinction can be reduced by using stimuli that are perceptually “grouped” (Ward et al., 1994) into a coherent “Gestalt” or when the two stimuli show the same, (e.g. horizontal) orientation and appeared in a paracentral area of ± 8° in the visual field (Pavlovskaya et al., 1997). The beneficial effect of co-oriented stimuli on visual extinction seems to only hold true for the central visual field (Pavlovskaya et al., 1997). This may be explained by the known long-range horizontal interactions in visual cortex which evidently may remain intact in patients with extinction. In a unique single-case study, Mattingley et al. (1997a, 1997b) showed that extinction no longer occurred when two visual stimuli form one perceptual object. The authors concluded from this that preattentive mechanisms occurring presumably in “early” visual cortical processing stages are intact in visual extinction.

Tactile extinction is usually tested with light touches on the back of the patient’s left and right hand (Bender, 1952, 1977), or more quantitatively with same or different tactual surfaces delivered to either or both hands (Schwartz et al., 1977) and the patient has to identify both tactual surfaces beyond the mere detection of a touch (Schwartz et al., 1977). In some cases, tactile extinction may be so severe that real objects held in the contralesional hand are extinguished when another object is held in the ipsilesional hand simultaneously (Berti et al., 1999). However, general testing is accomplished when the hands are placed adjacent to each other (left hand left of body midline, right hand right of body midline). Crossing the position of the hands, so that the left hand is positioned in right hemispace and vice versa, significantly reduces the tactile extinction rate on the contralesional left hand significantly (apparently 30%, cf. Smania and Aglioti, 1995). This indicates—as in egocentric neglect phenomena—a modulating influence of hand position in relation to the midline of the body or head. Moscovitch and Behrmann (1994) investigated tactile extinction with touches on the patients’ left and right wrist. They reported that tactile extinction always occurred for the more contralesional, leftsided stimulus, independent of whether the hand was placed palm up or palm down. This indicates that spatial information in the somatosensory system is not coded in somatotopic coordinates but in a more abstract, body-centric frame of reference. Remy et al. (1999) found in a PET-study that tactile extinction is associated with reduced activity in the secondary somatosensory cortex, but not in the primary somatosensory cortex, suggesting that processing of bilateral tactile stimuli requires a “higher” stage in somatosensory processing.

Apart from unimodal extinction, crossmodal extinc-
tion may also occur. Mattingley et al. (1997b) showed in three patients that stimuli in different modalities (i.e. touch and vision) may extinguish each other. Likewise crossmodal extinction of visual and tactile stimuli near the face region was recently shown (Ladavas et al., 1998) indicating an integrated visuo-cutaneous space map around the subject’s head (see Section 9.2). Finally, motor extinction has been reported when a patient has to act with both hands simultaneously (Robertson and North, 1994).

To summarize, extinction phenomena are nearly as diverse and dissociable as neglect phenomena. They may occur in any modality, dissociate from each other and from neglect as well although they may often occur in conjunction, possibly due to damage of overlapping neural circuits. They are modulated in part by similar spatial principles as neglect (i.e. egocentric manipulations). As neglect, extinction phenomena are strongly modulated by attentional and expectational factors, as well as fatigue (Bender and Teuber, 1946; De Renzi et al., 1984).

11. Covert processing of information

Since the neglect of sensory stimuli in neglect patients is not per se caused by an elementary deficit (see Section 8), it is most likely that the patients have seen, heard or felt the stimuli but deny their presence. This leads one to question on which level of processing the contralesional deficit arises, or up to which level the incoming information concerning the neglected stimulus is still preserved, albeit partially. Volpe et al. (1979) examined four patients with right parietal lesions and visual extinction. During unilateral tachistoscopic presentation of drawings or words, all performed nearly perfectly in both hemifields. However, during bilateral stimulus presentation two failed to identify any stimulus in the left contralesional hemifield, while the other two correctly identified 23% and 46% of items. In contrast to their inability to identify the leftsided stimulus explicitly, all four patients were able to decide if both stimuli presented in bilateral stimulation were identical or not. Though two patients claimed that they did not perceive anything in the contralesional hemifield, and that the task was senseless for them they performed correctly (88%, 100%) when forced to guess if both stimuli were identical or not. In a subsequent investigation (Berti and Rizzolatti, 1992), this finding was replicated and extended showing that extinction patients were also able to decide if both stimuli belonged to the same category of objects (i.e. fruits, animals).

In another type of experiment Marshall and Halligan (1988) showed drawings of two houses to a neglect patient. The houses were arranged vertically over each other and were identical except that fire emerged from the left side of one house. Their patient indicated that both houses were identical, thus ignoring the fire on the left, but when asked in which house she preferred to live she always chose the house without flames. Bisiach and Rusconi (1990) replicated these results only partially in four neglect patients; two preferred the house with the flames on the left side, thus indicating no covert processing.

Residual, but unconscious processing of somatosensory information in tactile extinction has also been reported as well (Maravita, 1997). In another study (Peru et al., 1997) covert processing was investigated with chimeric stimuli. Chimerics are figures constructed of two halves that normally do not belong together (i.e. left half of a cow combined with the right half of a horse). The two halves were either semantically (same category) or perceptually (similar form) related to each other or were completely incompatible to each other. Interestingly, the number of leftsided extinction errors was minimal when the perceptual discrepancy between the chimerics was maximal. Thus, perceptual conflicts (based on object shape) were more effective in reducing the extinction errors than semantic conflicts (Peru et al., 1997). Electrophysiological evidence shows that nonextinguished visual stimuli in the contralateral visual field (during bilateral stimulation) are associated with activations of the P1 and N1 components which were absent during extinguished trials (Marzi et al., 2000).

Together, these results indicate that visual and tactile information may be well represented at a preattentive level (Peru et al., 1997) and sometimes even up to a categorical (Berti and Rizzolatti, 1992) or semantic (McGlinchey-Berroth et al., 1993) level of stimulus processing in neglect and extinction. Nevertheless, it seems unlikely that every patient shows this type of intact, covert processing. Feinberg and colleagues (Feinberg et al., 1994) also found confabulations regarding the identity of stimuli flashed in their contralesional hemifield which were in no way related to the shown target. These interesting studies show that covert or unconscious processing of visual information is not only found in hemianopic patients with hindsight following occipital lesions (Stoerig and Cowey, 1997) but also to an even higher level of processing in parietal neglect and extinction (see Driver and Mattingley, 1998 for review).

12. Unawareness of deficits

Unawareness of disease (also termed anosognosia) is frequent in cerebral diseases (McGlynn and Schacter, 1997) but in no way exclusively coupled with neglect, since it occurs also with Wernicke’s aphasia (Lebrun,
1987), severe amnesia, dysexecutive (problem-solving) deficits after frontal lobe lesions (McGlynn and Schacter, 1990), or psychiatric disease (McGlynn and Schacter, 1997). Historically, unawareness for hemiplegia (Babinski, 1914) and cerebral blindness (Redlich and Dorsey, 1945) was described several decades ago. Since both types of unawareness are frequent in neglect (Bisiach et al., 1986) unawareness of hemiplegia and/or hemianopia is viewed as a frequently associated, but dissociable disorder (Feinberg et al., 1994) in neglect. In the acute phase of neglect, the patient is mostly unaware of his deficits and their cause, and can not imagine further consequences. This is in contrast to patients with elementary hemisensory deficits, i.e. left-sided, homonymous hemianopia without neglect, who often show awareness of their impairments and can therefore describe them in detail (see Table 4 for two contrasting case examples).

Table 4
Case examples of a patient with leftsided, homonymous hemianopia (HH), without neglect, and a patient with leftsided neglect (N), without hemianopia. E: Examiner. Both patients had objective deficits in reading (omissions on the left side of the text; slowness of reading, omissions of single lines) as well as in visual exploration of the environment (causing bumping into objects on their left side, or failing to perceive them in time). Based on Kerkhoff (1999c).

Anamnese with a left hemianopic patient without neglect
E: Did you experience any significant changes in vision since your illness (brain infarction)?
HH: Yes, I have problems perceiving things on my left; and reading is a problem.
E: Why is reading a problem?
HH: It is slower than before my illness and more exhausting. Sometimes I omit words on my very left.... or I omit a whole line. I only realize it at the end of a sentence when it doesn’t make sense...
E: Do you have any other visual impairments?
HH: Yes, sometimes I bump into things or persons on my left, or detect them rather late...
E: What about your orientation outside the clinic, can you find your way?
HH: It’s difficult, especially when many people are around, on places... or when I have to find one particular thing, i.e. in a supermarket,... when it is on the left..

Anamnese with a left hemineglect patient without hemianopia
E: Did you experience any significant changes since your illness (brain infarction)?
N: No, I haven’t realized any changes. Except... the spectacles don’t fit.
E: Do you have problems with reading?
N: No, not really.
E: Do you omit words or syllables on your left side?
N: No, I don’t think so.
E: Have you noticed that your vision is impaired on your left side?
N: The left eye is fine, no problem.
E: Do you bump sometimes into things or persons walking on your left side?
N: Rarely! Well, sometimes it occurs, but that is because there are so many people in this hospital, and they don’t care...
E: Can you find your way inside the clinic, and outside?
N: I find everything that I want to find.

As in neglect, multiple dissociations can also occur in (un)awareness for certain deficits. Hence, a patient may deny the paresis of her left arm but acknowledge reading problems or cognitive problems. Likewise, unawareness for hemiplegia is dissociable from neglect for the left side of the body (personal neglect, cf. Adair et al., 1995).

Recent analyses of the behavior and lesions in patients with unawareness of hemiplegia (Ellis and Small, 1997) revealed that it is dissociable from visuospatial neglect, and that most patients (87%) show deep white matter or basal ganglia lesions. Although transient unawareness for hemianopia is found in the first week after various lesion sites in pure hemianopia (Ceesla et al., 1997) more chronic unawareness of field defects is most often found after right parietal lesions (Koehler et al., 1986). In contrast to many neglect patients, hemianopic patients with temporal or occipital lesions (and thus probably without neglect) rapidly gain insight into their visual problems in daily life and learn from their daily experience (i.e. omissions in reading, bumping into objects, Kerkhoff, 1999b).

To summarize, unawareness of the disorder is frequently associated with, but not causally linked to, neglect and extinction, and is caused by separable white matter lesions (for hemiplegia) and parietal lesions (for hemianopia). It is likely that other types of unawareness (i.e. for visuospatial disorders like the tilted visual vertical and horizontal in Fig. 2C) are associated with slightly different lesion sites. This would suggest a distributed, patchwork-like cerebral network for awareness and consciousness of deficits in sensory, motor, cognitive or emotional areas (see McGlynn and Schachter, 1997). Focal lesions to this distributed network would then lead to a variety of distinct and dissociable phenomena of unawareness. Milner (1995) has suggested that elaborate awareness may require the ventral stream and its connections to memory structures while the dorsal visual stream is more engaged in unconscious, rapid visuomotor behavior.

13. Models

13.1. Early sensory theories

Early models of neglect and extinction have stressed the importance of low-level sensory impairments as well as a generalized deterioration of cognitive and intellectual functions (Bender, 1952; Battersby et al., 1956). Although such disorders certainly have an aggravating effect they cannot be the core deficit since both neglect and extinction occur without elementary sensorimotor impairments (cf. Section 8). Current models can be grouped in four main categories: atten-
tional, representational, transformational, and cerebral balance theories (cf. Table 5).

13.2. Attentional theories

According to the orienting vector model, proposed by Kinsbourne (Kinsbourne, 1987, 1993), both hemispheres contain a kind of orienting vector that directs attention to the contralateral hemisphere. These orienting tendencies are not only active in the exploration of external space but also of internal spatial representations (Kinsbourne, 1993). Lesion to this putative vector in the right hemisphere therefore leads to a hypoexploration of the left hemispace and a hyperattention for stimuli located in the ipsilesional, right hemispace due to the intact attentional vector in the healthy left hemisphere which operates in right hemispace. According to this theory, every unilateral hemispheric lesion should produce contralateral neglect — which obviously is not the case (see Section 2). Another critical point of the theory is that it fails to explain why there is this striking hemispheric asymmetry in the frequency and severity of spatial hemineglect. This would require the assumption of a stronger right-hemispheric attentional vector and a weaker left-hemisphere vector.

This is exactly what two other theories of neglect by Heilman and coworkers (1995) and Mesulam (1998) have proposed. Heilman and Van Den Abell (1980) proposed some 20 years ago that the right hemisphere might be dominant for attention in both hemispheres while the left is only specialized for the right hemispace. Mesulam later restated this idea in anatomical terms. His theory states that the right hemisphere contains a neural network for directed visuo- or tactile-spatial attention which is specialized for both the left and right hemispace, while the comparable system in the left hemisphere subserves only the right hemispace. The neural network includes the lateral premotor cortex (frontal eye fields), posterior parietal cortex, cingulate cortex and subcortically the basal ganglia and thalamus (Mesulam, 1998). While the more anterior areas in each hemisphere are relevant for shifting the focus and guiding exploration posterior areas in the parietal cortex deal with visual salience of stimuli in external space (see Fig. 8A). Lesions to the right hemisphere would produce left neglect while left hemisphere lesions lead only rarely to contralateral neglect since the stronger right-hemispheric attentional system may compensate for the deficit as a result of its bilateral attentional focus. This model is supported by imaging studies for tactile-spatial (Gitelman et al., 1996) and visuospatial attention (Nobre et al., 1997; Gitelman et al., 1999) in healthy subjects. In both studies, a stronger right parietal activation was found in most but not all subjects that would neatly explain how right neglect may occur sometimes after leftsided lesions, but is nevertheless rare. Furthermore, the different stations of

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**Table 5**

Summary of current neglect theories (see text for further details)

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<th>Theoretical school</th>
<th>Neglect viewed as</th>
<th>Neglect results from an impairment in the representation of the contralateral space and body (Bisiach and Luzzatti 1978; Bisiach et al., 1981).</th>
<th>Each hemisphere contains a topographically organized memory map of the contralateral visual world (Gaffan and Hornak, 1997), which is disrupted in neglect.</th>
<th>Different parts of extrapersonal and body space are motorically coded or represented by different neural structures. A lesion of these structures causes contralateral neglect (Rizzolotti et al., 1997).</th>
<th>Acting in space requires a transformation of the various sensory input informations from sensory (visual, auditory, tactile, olfactory) into motor coordinates which operate in body-part-centered coordinates (eye-, hand-, arm-, head-centered, Vallar, 1997; Karnath, 1997; Colby, 1998). This coordinate transformation is thought to be impaired in neglect.</th>
<th>Neglect studies in cats indicate that is not the absolute level of neural activity within each cerebral hemisphere that determines neglect but the relative (in)balance between cortical and subcortical structures in the lesioned and intact hemisphere (Lomber and Payne, 1996; Payne et al., 1996). Complex, excitatory and inhibitory interactions occur on a cortical and subcortical level between the lesioned and the nonlesioned hemisphere, probably via callosal fibres (Payne et al., 1991).</th>
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<td>Attentional theories: Neglect is viewed as</td>
<td>An exaggeration of the orienting of attention towards the ipsilesional side (ipsilesional hyperattention, Kinsbourne (1987).</td>
<td>A deficit in disengaging attention from an ipsilesional focus towards a new stimulus on the contralesional side (Posner and Driver, 1992).</td>
<td>As a result of damage to a neuronal network preferentially elaborated in the right hemisphere for the directing of attention towards the ipsilesional space and body (Heilman and Van Den Abell 1980; Nobre et al., 1997).</td>
<td>The result of damage to a visual salience map located predominantly in the human right hemisphere (Anderson, 1996).</td>
<td>Perception of sensory events requires their mental representation. Neglect results from an impairment in the representation of the contralesional space and body (Bisiach and Luzzatti 1978; Bisiach et al., 1981).</td>
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Without intending to offer a complete model of neglect it is suggested (Milner, 1995, 1998) that neglect results from a dysfunction of the ventral stream while visuomotor functions are thought to be largely spared because of the integrity of the visuomotor functions in the dorsal stream.
the neural network would explain why neglect occurs after lesions to structures as divergent as the thalamus, basal ganglia, the dorsolateral frontal lobe and posterior parietal cortex.

Posner and Driver (1992) have argued that the disengagement of attention from a current ipsilesional focus to a contralesional stimulus is the core deficit in neglect patients. In support of their “spotlight-of-attention” theory, it was found that patients with superior parietal lesions show such disengagement deficits and that valid cueing of their attention towards a target appearing later in the contralesional hemispace reduced this deficit significantly (Posner et al., 1984). Similarly, Baynes et al. (1986) found that both left and right hemisphere lesions cause a slowing of reaction several times but only right parietal lesions cause a selective deficit in the orienting of attention towards the contralesional left hemispace. In support of this theory, Steinmetz and colleagues (1994; Steinmetz, 1998) found that parietal neurons of macaques are engaged in covert attentional shifts towards the contralateral hemispace.

While Posner’s theory could explain why neglect patients have difficulties in directing their attention to left hemispace, it would probably not explain why they search preferentially in their ipsilesional hemispace in total darkness and in the absence of sensory stimuli (cf. Hornak, 1992; Karnath et al., 1996), or why the visual or auditory SSA is ipsilesionally deviated in neglect.

Recently, an elaborated mathematical model of neglect has been proposed by Anderson (1996) which makes rather explicit assumptions about the strength and spatial distribution of the left- and right-hemispheric hypothesized attentional vectors (see Fig. 8B). The model assumes a weaker and more contralaterally (around 10–20° eccentricity towards the right side) shifted salience function of the healthy left hemisphere and a stronger salience function operating in both hemifields — similar to the model of Heilman and Watson (1995), and Mesulam (1998). Furthermore, Anderson’s model assumes that the salience functions of the two hemispheres add (cf. Fig. 8B, lower plot). Disruption of the stronger right hemisphere salience function would lead to left neglect while damage to the left hemisphere salience system would be compensated by the bilaterally operating right hemisphere system. Simulations of this model can effectively explain the typical line bisection effects (Burnett-Stuart et al.,

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**Fig. 8.** Schematic illustration of the neglect model by Mesulam (A) and the salience model by Anderson (B). (A) The circles represent visual targets in the left and right hemispace, the arrows attached to the circles represent the attentional vectors (short arrows: left-hemisphere vectors; large arrows: right hemisphere attentional vectors). Below the figure, the two hemispheres of a brain are drawn schematically. Anterior areas are thought to be responsible for active exploration and shifting of the attentional focus, while posterior areas contain a salience map for visual targets in the two hemispheres. (B) The salience functions of the two cerebral hemispheres are drawn in the top figure (small curve: left hemisphere salience function; large curve: right hemisphere salience function). The lower figure shows the combined function.
Bisiach and colleagues formulated a model of topological space representation (Bisiach and Luzzatti, 1978; Bisiach et al., 1981). This model assumes that every sensory event has a representation. This mental representation can be activated either through sensory afferences or by memory engrams. More particularly, the model assumes that this topological space is not coded veridically in neglect patients. Their left side of representational space is enlarged whereas the right side is constricted compared with normal subjects (Bisiach et al., 1996). In contrast to the premotor theory by Rizzolatti (see below), this model does not detail where and how this topological space representation is created. This model is compatible with the recent evidence in patients with a unilateral temporal lobe removal (Hornak et al., 1997) and experimentally induced neglect in monkeys (Gaffan and Hornak, 1997; see review in Gaffan and Hornak, 1999). According to these findings, widespread cortical areas in each cerebral hemisphere interact with each other in memory retrieval to produce a retinotopically organized representation of the contralateral visual world. Lesioning of the temporal cortex — which is often but probably not always included in neglect patients — would then produce a hemi-amnesia for things occurring in the contralateral hemispace. This is compatible with Bisiach’s theory. One possible problem with this theory is the explanation of the hemispheric asymmetry in neglect.

A more physiologically oriented theory of neglect states that space representation is enabled by the activity of premotor cortical structures (Rizzolatti et al., 1997) which are linked closely to attention (Sheliga et al., 1995). According to this view, space is motorically coded by actions towards positions in certain space sectors (cf. Section 9.2). A lesion to these specialized premotor structures would then cause a neural representational deficit leading to neglect in a certain space sector. Since attention and movement towards targets in contralateral space are intricately connected, this theory would encompass attentional and motor neglect phenomena as well. Moreover, it is not incompatible with the more cognitive representational account of Bisiach, although it differs from the latter in that it does not hypothesize one topological spatial map but rather a number of decentrally organized (Rizzolatti et al., 1983) space maps, which relate to the different motor effectors (Rizzolatti et al., 1997).

13.4. Transformational theories

These theories assume that the transformation of sensory (input) information into motor (output) action, which is necessary due to the different reference frames or ‘format’ in which sensory and motor informations are coded in the brain is impaired in spatial neglect (Jeannerod and Biguer, 1987, 1989). Since such coordinate transformations are likely to be computed in parietal cortex (Andersen, 1995; Andersen et al., 1997) a parietal lesion causing neglect might impair such transformations. In a variant of this original account both Vallar (1997) and Karnath (1997) have proposed that this coordinate transformation seems to work with a consistent error, i.e. the straight ahead direction is not coded as 0° but as +15° to +20° ipsilesionally, thus causing the observed shift in the subjective straight ahead and the deviated visual and tactile exploratory patterns (Fig. 2A, B). The two theories differ in their assumptions regarding the type of spatial error. Vallar postulates a translation of the egocentric midsagittal representation in relation to the trunk midline while Karnath assumes a rotation around the subject’s body midline (see Fig. 9).

While the assumptions of both models (at least in front space) would fit the observed data on egocentric deficits in neglect, it remains unclear exactly how this “error term” in the coordinate transformation models is created and on which physiological grounds it is based. The transformational theories do not deal with allocentric and object-centered neglect and do not attempt to explain these phenomena in their framework.

Fig. 9. Schematic demonstration of translation of the auditory subjective straight ahead (SSA, left figure) and rotation of the auditory SSA (right figure) in leftsided neglect. The translational results (redrawn based on data by Vallar et al., 1995a) indicate a similar shift of the SSA in front and back space towards the right, ipsilesional side by 15–20°. In contrast, the rotational hypothesis is based on a rightsided shift of the SSA in front space and a corresponding leftward shift of the SSA in back space. Note that these results are not due to peripheral hearing deficits since pure tone audiometry reveals normal peripheral hearing functions in these patients.
13.5. Cerebral balance theories

Although some of the attentional theories in a way imply an imbalance of psychological attentional mechanisms in the two hemispheres in neglect, there are more direct experiments and theories favoring this account on a physiological level. Sprague (1966) showed, in a pioneering experiment in cats, that hemianopia caused by a cortical lesion can be improved by abrating the SC on the opposite side to the cortical damage or by cutting the intertectal commissure. In an extension of this experimental philosophy, Payne, Lomber and coworkers (Lomber and Payne, 1996; Payne et al., 1996) by reversible deactivation studies through local cooling of the posterior middle-suprasylvian cortex (PmS) or SC postulated that there are dynamic interactions in spatial attention based on the level of neural activity in these structures of both hemispheres. As reported earlier with unilateral SC lesions (Sprague, 1966) and small unilateral perisylvian lesions in cats (Hardy and Stein, 1988), cooling of these same structures causes a profound visual hemineglect of the contracooled hemispace (Payne et al., 1996). Subsequent cooling of the homologue area in the other hemisphere completely abolished the neglect behavior, or created now a neglect contralateral to the second cooled hemisphere if the cooling temperature was slightly lower than that in the originally cooled hemisphere (Geraerts and Vandenbussche, 1999).

Together these results indicate that the PmS in cats — like the SC — is engaged in directing visuospatial attention to the contralesional hemispace. More importantly for human neglect models, it is not the absolute level of activity within a cortico-subcortical spatial-attentional network but the ratio of neural activity in these structures within cerebral structures of one hemisphere and between the two hemispheres. This cerebral (in)balance theory has implications for our thinking of neglect and for the development of treatment techniques. Although cooling of the healthy hemisphere in a patient with left neglect from a right parietal lesion is of course impossible for ethical reasons alternative methods might be developed to either strengthen the lesioned hemisphere or weaken the healthy hemisphere by specific sensory stimulation maneuvers. For instance, stimulating the right hemisphere via leftsided somatosensory magnetic stimulation might increase neural activity in the lesioned hemisphere. Transcranial magnetic stimulation of the parietal cortex in the healthy hemisphere would lead to a transient decrease of activity in this hemisphere and might consequently reduce leftsided neglect by changing the cerebral (in)balance. Moreover, optokinetic stimulation of one visual hemifield might specifically activate cortical and/or subcortical structures in the contralateral hemisphere (Pizzamiglio et al., 1990; Brandt et al., 1998;
Dieterich et al., 1998) thus modulating neural activity in a way that reduces neglect (see Section 14).

1.3.6. One model or a synthesis of models?

Given the multiple and dissociable phenomena of spatial neglect and the characteristically large lesions in neglect patients, it seems unlikely that any one model can explain all features of neglect. Rather, every model is able to explain some features but not other, and vice versa. Furthermore, some theories are compatible with each other although this point is rarely admitted by their proponents. For instance, the shift of the SSA and visual exploration towards the ipsilesional hemispace by about 15°–20° in left neglect is equally well explained by the transformational theory as well as the salience model. Likewise, the reaction-time data by Smania et al. (1998), with the pathological reaction-time decrease in the neglect patients around 15°–20° ipsilesionally is consistent with both accounts. Finally, it would be possible to test the hypothesis whether the deficit in the disengagement of attention (Posner et al., 1984) is modulated by egocentric parameters, i.e. the position of the head, hand or trunk in space, thus combining attentional and transformational approaches. Finally, many of the sensory stimulation experiments described below are compatible with the idea of a cerebral (in)balance between various neural relay stations of a network distributed within and across both hemispheres.

To conclude, mutual influences between the theories and research paradigms in the study of neglect in particular, and space coding in general, might be more fruitful than strict demarcations between the various ‘claims’. Finally, the recent animal work on neglect (Lomber and Payne, 1996; Payne et al., 1996) deserves more attention.

14. Modulation of neglect, extinction and unawareness by sensory stimulation

A variety of different techniques (see Vallar et al., 1997) has been used to influence neglect behavior (Fig. 10). Caloric (ice–water) stimulation of the contralateral ear (usually the left) or warm water stimulation of the ipsilesional ear (the right in patients with left neglect) stimulates the horizontal ear canal of the vestibular system and leads to a tonic deviation of the eyes towards the contralateral hemispace thereby reducing sensory neglect for some 10–15 min. This procedure also improves neglect-related disturbances of the body scheme on the contralateral side of the body as well (Rode et al., 1998) and in some cases transiently relieves the patient from his/her anosognosia for the left hemiplegia (10–15 min; Rode et al., 1992). An easier and more tolerable stimulation procedure is optokinetic or slow visual motion stimulation with large-field visual displays containing stimuli all moving to the left or right. Leftward motion (in case of left neglect) temporarily reduces the line-bisection error (Pizzamiglio et al., 1990; Mattingley et al., 1994b). Similarly slow motion stimulation towards the neglected hemispace reduces the “size” and “space” distortions transiently (cf. Fig. 10B, Kerkhoff, 2000) and temporarily reduces tactile extinction (Nico, 1999). However, negative effects have also been observed with this procedure in a line-extension task with leftward optokinetic stimulation (Bisiach et al., 1996). It is likely that fast optokinetic stimulation leads to constant changes in eye-position which may render the perceptual task more difficult for a patient. We have found that slow motion stimulation (velocity: 7.5°/s) is completely sufficient to observe full normalization in perceptual neglect tasks (Kerkhoff, 2000). This further indicates that the motor component of the optokinetic nystagmus obtained with high-speed stimulation is not crucial for the modulatory effect on neglect (Mattingley et al., 1994b).

Another simple stimulation is ‘cueing’ the patient to attend to stimuli in the contralesional hemispace (Fig. 10C). Cueing may simply be the verbal command to look further to the left or to require the patient to read a letter located on the left side of a line before he is allowed to attempt bisection (Riddoch and Humphreys, 1983) or to display flickering stimuli in the contralesional hemispace (Butler et al., 1990). Lin et al. (1996) have recently elaborated this cueing paradigm. They showed that circling of a digit at the left end of a line and the tracing of the complete line with the right index finger was the most effective cueing procedure: it led to a complete normalization of the line bisection error in left neglect.

Vibration of the contralesional neck muscles leads to a temporary shift of the SSA towards the contralesional hemispace (Karnath et al., 1993) and reduces neglect-related omissions of visual stimuli in this hemispace. A similar transient effect can be achieved through selective rotation of the head (Schindler and Kerkhoff, 1997; Kerkhoff et al., 1999b) or trunk (Karnath et al., 1991; Schindler and Kerkhoff, 1997; Spinnell and Di Russo, 1996) towards the left hemispace while fixation remains straight ahead (Fig. 10D, E). Similar effects have been reported with different body positions (upright versus supine). The activity of the otoliths of the vestibular system is reduced in a supine body position. Positioning neglect patients in a supine position reduces neglect (i.e. in line bisection; Mennemeier et al., 1994; Pizzamiglio et al., 1997).

Apart from passive arm positioning active movements of the contralesional, left arm in left hemispace further leads to a temporary reduction of sensory
neglect phenomena (Robertson and North, 1993). Another influential factor is cueing with alerting stimuli, i.e. a sudden beep. This leads to an immediate alertness reaction and temporarily improves visual neglect (Robertson, 1999). Transcutaneous electro-neural stimulation (TENS) is widely used in physiotherapy, i.e. to treat stays or to stimulate muscles. TENS of the left hand has a small effect on perceptual neglect (Vallar et al., 1995c) but this effect is much weaker than vibration of the left neck (Karnath, 1995). Scherder et al. (1995) obtained similar beneficial effects in Alzheimer’s disease suggesting that TENS probably increases the arousal level. In contrast, Guariglia et al. (1998) reported small, but significant improvements in representational neglect and drawing after leftsided and deteriorations after rightsided stimulation of the neck with TENS, thus suggesting a more specific effect.

All these different methods show that neglect is considerably influenced by sensory, attentional or gravitational factors. This elucidates mechanisms crucial to the genesis of neglect and might in the future help to find effective, systematic rehabilitation techniques.

### 15. Rehabilitation approaches

Despite recovery of the most obvious signs of hemineglect a considerable portion of neglect patients — especially with large right-hemispheric lesions — is severely impaired in functional activities of daily living (ADL), i.e. dressing, eating, transfer from bed to the wheelchair, wheelchair navigation or reading. Neglect patients have a delayed recovery from hemiplegia (Paolucci et al., 1996), postural problems (Rode et al., 1997) and require further ambulant treatment after discharge from the hospital (Paolucci et al., 1998). Few neglect patients recover in a way that allows them to live independently or even return to their premorbid job. Neglect is therefore a major negative predictor of recovery from brain lesions (Denes et al., 1982; Paolucci et al. 1996; Katz et al., 1999).

Early treatment approaches for neglect, which began in the 1970s (Diller and Weinberg, 1977), were mainly based on clinical experience and were less theory-driven than more recent approaches to the syndrome (Robertson, 1999). Since disturbed visual exploration of space is one of the most obvious deficits in neglect patients, this was one that received most attention in

### Table 6

Summary of treatment techniques with permanent improvements (unshaded part of table) and experimental procedures yielding transient improvements (lightly shaded part of table) in patients with hemispatial neglect

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basic therapeutic/modulating principle</th>
<th>Practicability/outcome/transfer/source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual exploration</td>
<td>Improvement of search strategy and speed using paper-pencil and wide-field projection devices. Reduction of critical omissions by systematic strategy</td>
<td>Easy to realize in a rehabilitation setting; Limited transfer to daily activities; Needs numerous training sessions (i.e. 40) (Antonacci et al., 1995; Kerkhoff, 1998)</td>
</tr>
<tr>
<td>Limb activation</td>
<td>Improvement of visual neglect by acting with the contralesional arm (usually the left) in the contralesional hemispace. Such activities are believed to activate attentional circuits in the lesioned hemisphere</td>
<td>Easy to use in clinic and at home; Demonstrated transfer to daily activities; Often not applicable due to severe contralesional sensorimotor deficits (arm/hand) (Robertson and North, 1993; Robertson, 1999)</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>Amelioration of neglect phenomena by activating sustained, nonlateralized attentional capacities by stimuli which have an alerting quality (i.e. brisk tone)</td>
<td>Easy to use in different daily situations (i.e. self-care); Transfer to non-trained activities and to the tactile modality (Schindler et al., 1999)</td>
</tr>
<tr>
<td>Neck muscle vibration</td>
<td>Vibration of left dorsal neck muscles leads to a shift of subjective space towards the contralesional hemispace</td>
<td>Easy to realize; portable, low-cost; Small effects in cancellation tasks; Very small/insignificant effects in treatment (Pizzamiglio et al., 1996)</td>
</tr>
<tr>
<td>Spatial perception</td>
<td>Feedback-related training of visuospatial deficits in neglect; reduction of uncertainty in space perception transcutaneous electro-neural stimulation of the left neck muscles by low-voltage current</td>
<td>Transfer to daily activities; Requires relatively few training sessions (&lt;12, cf. Kerkhoff, 1998)</td>
</tr>
<tr>
<td>TENS</td>
<td>Exploiting the sensory-motor recalibration effect during readaptation after a previous prism exposure</td>
<td>Easy to realize; Significant but as yet transient effects (up to 72 h); Repeated prism exposure might yield enduring effects (Rossetti et al., 1998)</td>
</tr>
<tr>
<td>Prisms</td>
<td>Using coherent visual background motion to shift attention to contralesional hemisphere</td>
<td>Requires technical facilities; Strong effects on visual/motor neglect and extinction (Mattingley et al., 1994b; Kerkhoff et al., 1999b; Kerkhoff, 2000; Nico, 1999)</td>
</tr>
<tr>
<td>Optokinetics</td>
<td>Improvement of neglect by caloric (cold-water) stimulation of the horizontal ear canal (contralesional ear)</td>
<td>Marked improvements in perceptual neglect and unawareness; Transient effects (15 min); Uncomfortable (Karnath, 1994)</td>
</tr>
<tr>
<td>Vestibular stimulation</td>
<td>Reduction of neglect by verbal, visual or auditory stimulation; facilitation of attentional shifts to contralesional space</td>
<td>Easy applicable procedures with small but only transient beneficial effects (Brunner and Kirsch, 1995; Lin et al., 1996)</td>
</tr>
<tr>
<td>Cueing</td>
<td>Easy to use in clinic and at home; Transfer to non-trained activities — Stability of improvements questionable (Robertson et al., 1995)</td>
<td>Easy to use in different daily situations (i.e. self-care); Transfer to non-trained activities and to the tactile modality (Schindler et al., 1999)</td>
</tr>
</tbody>
</table>
treatment studies (Diller and Weinberg, 1977; Weinberg et al., 1979). Later studies have implemented a similar approach and compared the training of efficient scanning in neglect patients with nonspecific cognitive training (Antonucci et al., 1995) or combined it with specific visuospatial training (Weinberg et al., 1979) patients. Cognitive training has only minor effects on neglect, while specific visuospatial training ameliorates the associated spatial problems, but does not influence visual scanning. Table 6 summarizes evaluated treatment approaches as well as stimulation techniques with transient effects that might eventually become effective techniques of treatment.

As in other areas of neurorehabilitation, pharmacological treatments have been suggested for different types of disorders (Feeney and Hovda, 1985; Kertzman et al., 1990; McDowell, 1991; Müller and von Cramon, 1994; Huber et al., 1997). Treatment of neglect with dopaminagonists was prompted by the observation that experimental reduction of dopamine unilaterally in monkeys (Apicella et al., 1991) and rats (Carli et al., 1985) causes neglect-like deficits in these animals. Fleet et al. (1987) reported improved scanning in two neglect patients following application of a dopamine agonist. However, the opposite effect was reported in a recent study (Grujic et al., 1998) Evidently no firm conclusion is at present possible concerning pharmacological stimulation in the rehabilitation of neglect.

In contrast to the variety of stimulation and rehabilitation procedures that are being proposed for neglect, very little is known about how extinction can be treated. Since it persists even when the most overt neglect signs have recovered (Karnath, 1988) treatments of extinction clearly would be of practical importance. Goldman (1966) described impressive and stable improvements in 20 brain damaged patients with tactile extinction following a teaching strategy with the aim to direct the patient’s attention to the extinguished side and improve his/her awareness for the contralateral stimulus. This shows that the allocation of attention (cueing) is also helpful in extinction. Another, more physiologically oriented promising treatment approach is somatosensory magnetic stimulation of the contralesional hand. This procedure led to an increase in the identification rate in bilateral tactile stimulation by some 40%, in one patient (Heldmann et al., 2000). Since the testing took place some 30 min after the end of the magnetic stimulation, this indicates that the effect is not merely a short-lived “on/off” stimulation effect but obviously has enduring effects lasting over the stimulation period. Possibly, repetitive stimulation of this type might help to rehabilitate tactile extinction more permanently than the short-lived sensory stimulation maneuvers reported above.

Despite the improvements that have been made in the last decade in the development of theory-based treatment techniques for neglect and extinction, the patients often remain impaired at the end of clinical rehabilitation. This shows that the efforts so far are only partially effective. Therefore, the scientific development of effective treatment techniques in this field is urgently required. The increasing physiological, anatomical, neuropsychological and cognitive knowledge concerning sensory, motor and representational aspects of space coding in health and pathology will hopefully help to develop such treatments for the severely disabled patients with neglect. In exchange, the results obtained with such new methods will influence our current thinking of normal spatial processing in the human brain.

Table 7
Outstanding questions and topics for further research

- Neglect is often multimodal. What is the exact interplay between these different modalities and which principles guide this type of multisensory interaction and integration?
- Models of human neglect have payed little attention to recent contributions of animal experimentation in the domain of neglect. Integrating these findings will probably lead to another, novel view of the mechanisms and possible modulations of neglect.
- Auditory and somatosensory neglect are not well understood. The more sophisticated technical examination of space in these two modalities might improve our understanding of the cortical organisation of auditory and somesthetic space.
- Are representational neglect and unilateral, scene-based memory deficits related to each other? The study of this relationship might help to understand how short- and long-term memory feed into spatial imagery in neglect.
- How do extinction and neglect relate to each other? Is extinction a completely different disorder from neglect, or does it simply reflect a less severe, residual form of it?
- Which treatment methods for the rehabilitation of neglect are effective? How can different treatment approaches be combined effectively to reach a maximal outcome for the patient?
- Which mechanisms guide spontaneous recovery and enable improvements during systematic rehabilitation? Functional imaging may be useful to evaluate which cortical and subcortical regions in the damaged and healthy hemisphere contribute to these two processes. Such studies could complement the physiological basis for current behavioral rehabilitation studies.
16. Outstanding questions

It has become obvious that hemineglect is a multi-component syndrome resulting from damage to a number of cerebral structures, and hence neural circuits relevant for sensory, motor and cognitive functioning in the brain. Although much progress has been made in the last two decades, many issues are presently still unresolved or controversial (summarized in Table 7).

Most of the open questions center around the issue of how our subjective, introspective feeling of one perceptual, motor and cognitive space (including our own body) is accomplished although so many different egocentric, allocentric and object-centered neural representations of different spatial aspects exist in our brain. How these are interwoven (Driver and Spence, 1998) and how they relate to awareness is a fascinating research task for the next years to come.

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