
Objectives: To review the existing literature on treatments of unilateral neglect, to synthesize findings, and to offer recommendations for future studies.

Data Sources: Computerized databases including MEDLINE and PsychINFO.

Study Selection: All studies investigating treatment(s) of unilateral neglect.

Data Extraction: Authors reviewed design and other methodologic issues.

Data Synthesis: Unilateral neglect is a common consequence of right-hemisphere stroke. It is well recognized that the disorder is heterogeneous and has numerous subtypes. There have been numerous studies showing that arousal, hemispheric activation, and spatial attention treatments may all improve neglect, at least transiently. Despite these promising outcomes, little consensus exists as to whether 1 treatment is more efficacious than others, in part because cross-study differences in methodology render meta-analyses difficult, and in part because many studies fail to document duration of treatment effects or generalization to daily activities. One possibility is that these varied and diverse treatments may all be effective, reflecting redundancy in neural circuits devoted to attention and action in space, and consequent flexibility of the spatial processing system. It remains possible, however, that different subtypes of neglect may respond differentially to treatment of various sorts. Most existing studies of neglect have relied on very small populations of neglect patients, whose neglect is characterized only generally.

Conclusion: Methodologic shortcomings hinder assessment of the efficacy of various types of neglect treatment. In the future, these shortcomings could be addressed with larger studies of well-characterized patients that evaluate duration of treatment effects and include functional measures. In addition, the role of overarching variables, such as reduced arousal, requires consideration. The ultimate goal of these studies might be the development of triaging strategies wherein neglect patients are assigned to treatments of most likely benefit on the basis of neuroanatomic and behavioral profiles.

Key Words: Arousal; Attention; Cerebrovascular accident; Dopamine; Hemispatial neglect; Motor activity; Motor skills disorders; Perceptual disorders; Rehabilitation; Spatial behavior; Treatment outcome.

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HE HALLMARK OF THE syndrome of unilateral neglect is a failure to report, orient toward, or respond to stimuli on the contralesional side of space that cannot be attributed to sensory or motor dysfunction. In addition to deficits in attention to the area within reaching space (peripersonal neglect) and beyond (extrapersonal neglect), patients with neglect may exhibit personal neglect, a deficit in grooming or dressing the contralesional sides of their bodies. For example, patients with personal neglect may fail to shave 1 side of the face or comb the hair on 1 side of the head. The neglect syndrome includes anosognosia or unawareness of deficit in 20% to 58% of patients. Neglect is a relatively common consequence of lesions to the right inferior parietal lobe, and is also seen after damage to the right frontal lobe, thalamus, and basal ganglia. The reported incidence of neglect in right-hemisphere cerebrovascular accident (RCVA) patients varies widely from 13% to 81%, in part because of cross-study differences in subject selection, lesion location, and assessment procedures. The disorder is relatively less common after left-hemisphere cerebrovascular accident (LCVA). Neglect has a significant impact on rehabilitation: compared with stroke patients without neglect, patients with the disorder have relatively poor functional outcomes, even after controlling for differences in overall severity.

The presence of neglect may be determined on the basis of a left-right asymmetry in performance on a variety of measures, including line cancellation, letter cancellation, reading, drawing, mental imagery, attention to the body, and naturalistic action tasks. Neglect is not a unitary disorder, but a complex constellation of symptoms with different manifestations across patients. Patients may neglect the contralesional side of near (peripersonal) and not far (extrapersonal) space, or vice versa. Some patients with neglect are predominantly deficient in moving attention and action into and toward contralesional space, a subtype of the syndrome known as motor neglect, whereas others have primary deficits in attending to or perceiving contralesional space. The personal subtype of neglect may also dissociate from neglect of peripersonal space. There is preliminary evidence to suggest that neglect subtype may be associated with lesion location: perceptual neglect has been associated with parietal lesions and motor neglect with frontal lesions.

Several neurocognitive models have been used to explain neglect phenomena, not all of them mutually exclusive. On the basis of the evidence that RCVA patients exhibit decreased attention and arousal when compared with patients with LCVA, that dopaminergic receptors may be asymmetrically lateralized to the right hemisphere, and that RCVA patients with neglect have decreased arousal compared with RCVA patients without neglect, it has been proposed that neglect results from damage to predominantly dopaminergic right-hemisphere subcortical and cortical structures that mediate both general arousal and attention to the contralesional hemi-
space. This suggests an orienting bias to the right.35

A second account attributes neglect to damaged right-hemisphere dominant attention-shifting mechanisms, resulting in an orientation bias to the ipsilesional hemispace.34 Support for this account comes from evidence that neglect patients are superior, relative to controls, at detecting stimuli in the ipsilesional space. This suggests an orienting bias to the right.35

A final group of accounts suggests that neglect is attributable to a deficit in an internal representation of the contralesional side of space, or asymmetric allocation of visual attention to this internal representation.32,33 A related account suggests that neglect of contralesional limbs (personal neglect) may be caused by impaired representation of the left side of an internal body schema.38

A recently recognized property of spatiomotor coding in the frontoparietal dorsal processing stream39 is that visuomotor information is progressively transcoded into multiple coordinate systems. Although the process is not strictly linear, as a general rule spatial information about object location progresses from a form of information relevant to the eye, to a format relevant to the limbs for the purpose of action. Incoming visual information is initially coded in retinotopic coordinates, meaning that the axes of the reference frame used to define location are at the center of the retina.

Oculocentric coding is similar in that stimuli are mapped with respect to the geometric center of the eye. However, unlike retinotopic receptive fields, which are fixed to retinal coordinates and move with the eye, the excitability of oculocentric neurons is systematically modulated by gaze position.40 Information about the position of the eye in the orbit is combined with retinotopic target position information to achieve a more stable head-centered representation of target location. Coding of the location of the target with respect to the head is then integrated with information about the position of the head on the neck, derived in part from the vestibular system, to map target location in body-centered reference frames, which include torso-, shoulder-, arm-, and hand-centered coordinates. The latter are particularly important in planning and performing movements to targets.41,42

Lateralized damage to mechanisms involved in the representation of these frames of reference, or to the procedures involved in the transformation of location information from 1 frame of reference to another, may result in an error in the coding of contralesional space that manifests behaviorally as hemispatial neglect. For example, on the basis of evidence that the subjective midline is shifted to the right in neglect patients, 1 account posits that neglect results from a rightward error in the calculation of the body-centered reference frame.43,44

These 3 groups of accounts have guided the development of a variety of neglect treatments. Some of these have been discussed in previous reviews.45,46; in our review, we attempt to provide a comprehensive summary of most of the attempted treatments to date, organized by a theoretical framework. Under ideal circumstances, the efficacy of treatments targeting arousal, attention-shifting, or spatial representational deficits would speak to the adequacy of the theories that motivated the treatments. As will become clear, however, though several treatments targeting each of these (and other) putative deficits show initial signs of promise, methodologic and other concerns render any conclusions premature. We will examine the efficacy of each treatment, briefly discuss some of the properties of the brain’s representation of space and action relevant to potential treatment response, and conclude with some suggestions for the design and implementation of future neglect treatment studies.

TREATMENTS TARGETING AROUSAL DEFICITS

Dopamine Agonist Therapy

There are several lines of evidence that decreased levels of the neurotransmitter dopamine may be implicated in neglect. Data from studies with animals indicate that ascending dopamine systems projecting to the neostriatum, frontal cortex, and cingulate gyrus are involved in sensory orienting, arousal, and motor intention.47 In addition, dopamine levels correlate with neglect severity.45 Neglect can be induced by injections of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into the caudate nucleus of monkeys.46 Finally, the dopamine receptor agonist apomorphine reduces neglect in lesioned animals,47,50 and the dopamine receptor blocker spiroperidol reverses this treatment effect.48 These data suggest that dopamine agonists might effectively treat neglect in humans.

Consistent with this possibility, Fleet et al51 showed that 15mg/d of the dopamine agonist bromocriptine was effective in reducing neglect on a battery of clinical tests in 2 patients with large right frontotemporoparietal infarctions. Neglect worsened on discontinuation of the medication. Geminiiani et al52 showed that 2mg of apomorphine significantly improved neglect in 4 patients. Three patients showed relative improvement in motor as compared with perceptual tasks, suggesting that decreased dopamine levels may underlie the motor component of the neglect syndrome (but see later). Recently, Hurford et al53 studied the efficacy of 20mg/d of methylphenidate (Ritalin), which also has dopaminergic properties, and has been shown to be effective in improving speed of mental processing in patients with traumatic brain injury44 (TBI) and attention deficit disorder.55 Methylphenidate was found to be as effective as 30mg/d of bromocriptine in a patient with chronic neglect caused by middle cerebral artery (MCA) stroke. Improvements from both medications were maintained after they were discontinued.

Although these studies are encouraging, other investigations have yielded conflicting findings. A recent study examined the performance of 7 neglect patients on a computerized target search paradigm and found increased exploration of ipsilesional (right) hemispace with just 2.5mg of bromocriptine.56 This finding is difficult to interpret because bromocriptine may inhibit dopamine receptors at low doses.57,58 However, Barrett et al59 reported a patient with motor neglect caused by right MCA stroke whose performance on a line bisection task declined on a larger dose of 20mg/d of bromocriptine. At this dose, inhibitory effects are not expected. The investigators suggested that bromocriptine activated the intact dopaminergic system of the left hemisphere, but could not activate the damaged right-hemisphere dopamine system, thereby exacerbating the ipsilesional bias. They59 also suggested the possibility that the presence of right subcortical involvement in these patients may prevent dopamine transmission to the right parietal spatiomotor subsystem.59 Finally, it may be relevant that changes in cerebral metabolism have been found in both the right and left hemispheres of patients recovering from neglect,60,61 consistent with neuronal plasticity involving regeneration of damaged regions, and compensation and substitution by undamaged areas. The effect of these changes on the uptake of medication is unknown.

Phasic Averting Treatments

Another group of treatments targeted at improving arousal uses external sources of stimulation. For example, Robertson et al62 reported data from 8 chronic neglect patients with various right-hemisphere lesions who were taught a self-alerting paradigm. Initially, the trainer provided direct auditory feedback to
attend to a task. Subjects were then taught to provide their own auditory feedback, and the ratio of subject feedback to examiner feedback was gradually increased. Patients significantly improved on several neglect and attention measures immediately after training, and these improvements were maintained for 2 weeks. In a related study, Robertson et al\(^63\) showed that auditory feedback, and the ratio of subject feedback to examiner feedback was gradually increased. Patients significantly improved on several neglect and attention measures immediately after training, and these improvements were maintained for 2 weeks. In a related study, Robertson et al\(^63\) showed that an auditory tone sounded before a left visual stimulus improved awareness of the left visual field in 8 neglect patients, the majority of whom had suffered right MCA strokes. Maintenance of the treatment effect was not assessed.

**Summary and Discussion of Treatments**

**Targeting Arousal**

Although initial investigations of treatments targeting arousal and attention deficits are promising, there are several unanswered questions. Medication studies of neglect to this point have solely investigated dopamine agonists, and it remains to be seen whether medications predominantly acting on other neurotransmitters (eg, glutamate agonists, selective serotonin reuptake inhibitors) would be equally or even more effective. In addition, for both medication and altering treatments it is not clear whether patients with involvement of certain brain regions (eg, subcortical) or with certain neglect subtypes (eg, motor neglect) might be more or less amenable to treatment. As is the case for all of the treatments examined in this article, an important goal will be the development of treatment studies with larger groups of well-characterized patients. Duration of treatment effects should be assessed, as should the impact of treatment on functional measures.

**TREATMENTS TARGETING DEFICIENT VISUAL ATTENTION**

Based in part on findings that neglect patients fail to explore the left hemispace and are abnormally oriented toward the right hemispace,\(^29\) scanning training attempts to improve attention to the neglected hemispace. Table 1 summarizes a number of studies.
that used this method. Weinberg et al65,66 and Gordon et al66 have shown significant improvements in neglect after scanning training in a number of studies, but in most cases, the long-term effect of treatment is not reported. In 1 of these studies,66 control patients who engaged in conventional rehabilitation or leisure activities performed equivalently to the experimental patients at 4 months postdischarge. Another recent study67 compared the effectiveness of general cognitive stimulation with visuospatial training. The spatial training group showed significant relative improvements on a neglect battery. The cognitive stimulation group was then given the visuospatial training and also showed significant improvements in the neglect battery. Maintenance of improvement was not reported.

Although visuoperceptual training has some experimental support, Robertson et al66 were unable to show differences between 20 patients who received a computer-based scanning program and 16 control patients. In addition, it has been observed that training effects in scanning studies are often limited to tests that share characteristics of training stimuli90,91 (but see Antounucci et al92). Finally, and most critically, studies thus far have not attempted to assess whether treatment effects generalize to activities of daily living.90,91

**TREATMENTS TARGETING SPATIAL REPRESENTATION DEFICITS**

**Hemispheric Activation Approaches**

It has been shown in several studies that even small movements of the left hand on the left side of space may result in significant reductions in neglect. As can be seen in table 2, active movements of the contralesional upper or lower extremity have significantly improved walking trajectory,72 reading,73,74 and cancellation performance75 in patients with neglect. A meta-analysis of the activation literature76 found large effect sizes for both group and single-subject studies of contralesional limb activation that support their therapeutic effectiveness.

In contrast, several investigations indicate that neglect does not improve with movements of the ipsilesional extremity, or of bilateral extremities, possibly because of competition from the intact left hemisphere.77-79 The results of passive range of motion (PROM) of the left extremity have been inconclusive, with some investigators reporting improvements with PROM,80 and others finding no effects.81 Robertson82 has proposed that limb activation exerts its benefit by virtue of its effects on overlapping neural systems representing personal (body surface) and peripersonal (near body) space. When the left limb is used, there is enhancement of the left portion of the representation of personal space. When the left limb is used in the left hemispaces, this enhancement is accompanied by corresponding activation of the left portion of the peripersonal representation. It is this reciprocal activation in multiple corresponding spatial sectors that is putatively critical to the beneficial effect (see also Rizzolatti and Camarda83).

Although the activation approach to treatment of hemispatial neglect appears promising, replication of limb activation effects has been unsuccessful by some investigators,84 who have suggested that the effects may be patient specific. Additionally, because bilateral limb movements appear to mitigate positive treatment effects, it is not clear whether traditional therapeutic activities may actually diminish the effects of limb activation treatment.79 As with other treatments, few data on functional consequences of limb activation treatment are available. Perhaps the greatest impediment to this treatment is that it requires active motion of the hemiplegic extremity, a capacity that is absent in many patients with neglect.85

**Constraint-Induced Therapy**

A treatment technique that has received recent attention as a treatment for unilateral neglect86 is constraint-induced therapy (CIT). CIT is based on the principle of learned nonuse, which suggests that after repeated unsuccessful experiences with hemiparetic limbs, patients may learn to avoid their use, even when the limbs have the potential to function adequately.87,88 Consequently, the neural representation of the hemiparetic limb gradually weakens, resulting in diminished potential for use. CIT attempts to reverse learned nonuse by using a mechanical restraint, such as a sling or mitt, on the intact extremity. One frequently used protocol involves wearing a restraint for approximately 90% of waking hours over several weeks.88 The effectiveness of CIT has been studied with a variety of populations, and has been successful in eliciting long-term functional improvements in patients with chronic stroke and TBI.89-92 A recent study by Liepert et al93 which used transcranial magnetic stimulation in 13 chronic stroke patients, showed that CIT increased ipsilesional cortical limb representation.

In 1 of the few investigations of neglect patients, CIT was compared with traditional rehabilitation therapy (neurodevelopmental technique) in a large sample of chronic stroke patients that included 7 RCVA patients with neglect.94 Patients completed a 2-week program of 7 daily hours of physical training while wearing a restraint on their intact extremity for approximately 90% of waking hours. Although both treatments were beneficial, CIT resulted in significantly greater improvements in contralesional arm use than the neurodevelopmental technique in 3 patients with neglect. Because no measures of neglect were used, the effect of CIT on neglect symptoms (eg, visual attention to contralesional space) awaits further investigation.

One potential problem with the application of CIT to the neglect population is that the requirement for active wrist and hand extension may eliminate most patients with neglect, who frequently exhibit dense hemiparesis.85 On the other hand, because nonuse of the contralesional limbs in the neglect syndrome may result in part from personal neglect, rather than frank motor disability, this treatment may have promise with this population.

**Treatments Targeting Intact Dorsal Stream Functioning**

The seminal work of Ungerleider and Mishkin19 suggests that visual information bifurcates into 2 major parallel processing streams: a dorsal stream concerned primarily with spatial representation (the where system), and a ventral stream predominantly involved in perception and recognition (the what system). More recently, Milner and Goodale55 provided evidence suggesting that the where system might be characterized more accurately as the how system in that it is primarily concerned with spatiomotor programming for actions such as reaching and grasping. Furthermore, Goodale et al56 provide evidence that information in the dorsal stream may have access to the motor system without conscious awareness. This phenomenon was recently exploited by Robertson et al.97 who hypothesized that information available to the dorsal action system might ameliorate neglect. Patients who showed neglect on a task requiring them to indicate the center of metal rods were nevertheless able to reach and grasp the rods at their center of balance.97 In a subsequent study, these researchers98 showed that 16 acute and chronic patients with neglect temporarily improved on line bisection and star cancellation tests...
<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Design</th>
<th>Intervention</th>
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<td>Joanette et al</td>
<td>Case study</td>
<td>Left vs right active pointing</td>
<td>1 session</td>
<td>3</td>
<td>1–7mo</td>
<td>Visual stimuli detection</td>
<td>Increased detection of stimuli with left hand pointing only</td>
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<td>Hommel et al</td>
<td>Quasi experimental</td>
<td>Passive tactile, white noise, and verbal auditory stimulation</td>
<td>1 session</td>
<td>14</td>
<td>1mo</td>
<td>Drawing task</td>
<td>Improvements noted only with &quot;white noise&quot;</td>
<td>—</td>
</tr>
<tr>
<td>Halligan et al</td>
<td>Case study</td>
<td>Left vs right hand performed; starting position of hand varied</td>
<td>1 session</td>
<td>1</td>
<td>2.5mo</td>
<td>Line bisection</td>
<td>Left hand better than right hand with hand at midline; right hand better when started on left than right</td>
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<tr>
<td>Robertson and North</td>
<td>Single-subject design</td>
<td>Left active finger movements in left and right space with or without visual input; right active finger movements in left space</td>
<td>1 session</td>
<td>1</td>
<td>3mo</td>
<td>Letter cancellation</td>
<td>Left finger movements in left space improved performance with or without vision</td>
<td>—</td>
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<tr>
<td>Robertson et al</td>
<td>Single-subject design</td>
<td>Scan to left arm; scan to left arm with active movements and alerting device; left active movements with alerting device</td>
<td>10–44hr</td>
<td>2</td>
<td>1–2mo</td>
<td>Letter cancellation, telephone dialing, reading, star cancellation, line orientation</td>
<td>Improvements with all treatments</td>
<td>Gains maintained at 6wk (scan to left arm with active movement and alerting device); partially maintained at 3wk (left active movements with scanning device)</td>
</tr>
<tr>
<td>Robertson and North</td>
<td>Single-subject design</td>
<td>Active vs passive hand and leg movement</td>
<td>1 session</td>
<td>1</td>
<td>3mo</td>
<td>Letter cancellation, tactile extinction</td>
<td>Active movements in left hemispace improved letter cancellation, not tactile extinction; no effect with passive motion</td>
<td>—</td>
</tr>
<tr>
<td>Robertson et al</td>
<td>Quasi experimental</td>
<td>Active left hand movement vs no movement during ambulation</td>
<td>1 session</td>
<td>5</td>
<td>0.5–5mo post-CVA/TBI</td>
<td>Deviation from center of door frame</td>
<td>Improvement with hand movement in 4 RCVAneg subjects</td>
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<tr>
<td>Robertson and North</td>
<td>Single-subject design</td>
<td>Active left hand movement vs bilateral active hand movement</td>
<td>1 session</td>
<td>2</td>
<td>3mo</td>
<td>Reading task</td>
<td>Improvements with left hand movement only</td>
<td>—</td>
</tr>
<tr>
<td>Vallar et al</td>
<td>Quasi experimental</td>
<td>TENS sensory stimulation to right or left neck</td>
<td>1 session</td>
<td>14</td>
<td>1–4mo</td>
<td>Line cancellation, letter cancellation</td>
<td>Improvement with left posterior neck TENS; decreased performance with right posterior neck TENS</td>
<td>No difference after 30min</td>
</tr>
<tr>
<td>Worthington</td>
<td>Case study</td>
<td>Active left hand movement in left space with hand visible (visuomotor cueing) vs active movement on lap</td>
<td>10 session; 1 per wk</td>
<td>1</td>
<td>4mo</td>
<td>Reading</td>
<td>Both treatments improved performance</td>
<td>Only visuomotor cueing gains maintained at 3 and 18mo</td>
</tr>
<tr>
<td>Guariglia et al</td>
<td>Quasi experimental</td>
<td>TENS sensory stimulation to right or left neck</td>
<td>1 session</td>
<td>9</td>
<td>3–8mo</td>
<td>Mental imagery, drawing, shape comparison</td>
<td>Significant improvement with left TENS for all tasks</td>
<td>—</td>
</tr>
<tr>
<td>Robertson et al</td>
<td>Single-subject design</td>
<td>Active left hand movement in left space to turn off buzzer</td>
<td>18 session</td>
<td>1</td>
<td>18mo</td>
<td>Baking tray task, hair combing, route finding</td>
<td>Improvement in all tasks</td>
<td>Only baking tray improvements maintained at 9d</td>
</tr>
<tr>
<td>Cubelli et al</td>
<td>Quasi experimental</td>
<td>Left, right, and bilateral active hand movements</td>
<td>1 session</td>
<td>10</td>
<td>1–11mo</td>
<td>Letter cancellation</td>
<td>No improvements in 9 patients; 1 patient improved with left hand movement</td>
<td>—</td>
</tr>
<tr>
<td>Brown et al</td>
<td>Single-subject design</td>
<td>Left vs right active hand movements</td>
<td>1 session</td>
<td>4</td>
<td>1–2mo</td>
<td>Letter detection, eye movements, reading</td>
<td>Improvement in reading with left hand movement</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: RTBIneg, right-hemisphere traumatic brain injury with neglect; TENS, transcutaneous electric nerve stimulation.
immediately after they grasped metal rods at their centers. Edwards and Humphreys report data from a single patient supporting the potential efficacy of the grasping treatment technique. The clinical application of these findings has not yet been investigated.

Mental Imagery Training

As noted earlier, in 1 prominent group of accounts, neglect patients may have a deficient internal representation of contralateral space and/or of the contralateral limbs. Recent evidence suggests that mental simulation of movements results in a pattern of neural activation in spatiomotor circuits similar to that seen with actual movements. These 2 lines of evidence suggest that mental simulation of movements results in a pattern of neural activation in spatiomotor circuits similar to that seen with actual movements. The subjects initially misreach to the right. After repeated exposure, this effect has been observed in both healthy controls as well as neglect patients.

Prism Treatment

Prism lenses have been used in the treatment of neglect with some success. The prisms cause an optical deviation of the visual field to the right, so objects appear farther to the right than is actually the case. While wearing the prisms, subjects initially misreach to the right. After repeated exposure, the subjects correct the reach trajectory to accurately grasp target objects, in effect overriding the visual input. The effect has been observed in both healthy controls as well as neglect patients.

Rossi et al investigated the use of Fresnel prisms in a heterogeneous population of acute stroke patients with either visual extinction or homonymous hemianopia. Patients were randomly assigned to control or treatment groups. The latter group wore prisms over their affected hemifield during all daily activities for 4 weeks. Patients also wore prisms during outcome testing (measures of neglect, visual fields, functional performance). The treatment group showed significant improvements on neglect tests as compared with controls, but there were no differences on measures of visual fields or functional performance. It remains possible, however, that the mixture of hemianopics and extinction patients may have masked improvement occurring in 1, but not the other, group.

Eye Patching and Hemispatial Glasses

Hemispatial glasses consist of a standard eyeglass frame with the ipsilesional (right) hemifields of both lenses blocked out by a light-deflecting lens or an opaque patch. Full-eye patches completely eliminate visual input into the covered, ipsilesional (right) eye. The rationale is that because each superior colliculus of the midbrain receives input from the contralateral hemifield of each eye, but predominantly from the contralateral eye, both techniques reduce input to the left superior colliculus, which then releases its inhibition over the right superior colliculus. This, in turn, improves visual functioning in the left hemifield.

Arai et al reported 10 patients with neglect (1–31mo post-CVA) who wore hemispatial glasses during testing with line bisection, line cancellation, and figure copying tasks. The glasses resulted in apparent improvements in some patients, and no effects or exacerbation of neglect in others. No data were reported enabling distinctions between patients who did or did not profit from the treatment. Another recent study compared half-eye and full-eye patching. Both treatment groups wore their respective devices continuously for a 3-month period. Outcome measures included change in scores on the FIM instrument and left-sided performance on a computerized visual task. There were significant improvements in attention to the left visual field in the half-patch compared with the other groups. FIM results were difficult to interpret, however, because the half-patch group had lower FIM scores at baseline; thus, effects of regression to the mean cannot be ruled out.

Caloric Stimulation

If cold water is irrigated into the external ear canal, the vestibular-ocular reflex induces a slow phase of nystagmus toward the stimulated ear. If warm water is used, the slow phase of nystagmus is directed away from the stimulation. These phenomena have been exploited to overcome right visual biases in neglect patients. It has been proposed that cold contralateral and warm ipsilesional caloric stimulation improve neglect through their influence on the vestibular system's contribution to the representation of space, rather than through changes in eye movements per se.

As shown in table 3, caloric stimulation has been shown to reduce personal and extrapersonal neglect in a number of investigations by eliciting a slow phase-left, fast phase-right nystagmus. Improvements in tactile sensitivity and motor function have also been observed. Finally, caloric stimulation has been successful in ameliorating anosognosia, spatial representation, and somatoparaphrenic delusions, such as the conviction that the patients' arm belongs to a stranger. Symptoms of neglect have also been exacerbated through the elicitation of a slow phase of nystagmus toward the right visual field.

Although these studies appear encouraging, 1 major problem is that the effects of caloric stimulation are of limited duration (table 3). It is not clear whether habitation or, alternatively, longer term improvements might be elicited by repeated treatments. Additionally, most studies have involved acute patients, and the potential benefits in chronic patients are not well understood.

Optokinetic Stimulation

Optokinetic stimulation as applied to the treatment of neglect induces a slow phase-left, fast phase-right nystagmus via exposure to stimuli moving from right to left at a rate of approx-
### Table 3: Caloric Treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Design</th>
<th>Intervention</th>
<th>Duration of Treatment</th>
<th>Number of Subjects</th>
<th>Time Postinjury</th>
<th>Outcomes Measured</th>
<th>Results</th>
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<tbody>
<tr>
<td>Rubens110</td>
<td>Case study</td>
<td>Left or right ear with warm or cold caloric</td>
<td>2 sessions</td>
<td>18</td>
<td>4–7d</td>
<td>Line cancellation, reading, extrapersonal neglect</td>
<td>Improved performance with cold left/warm right stimulation</td>
<td>–</td>
</tr>
<tr>
<td>Cappa et al111</td>
<td>Case study</td>
<td>Left ear cold or right ear warm caloric</td>
<td>1 session</td>
<td>4</td>
<td>1–2d</td>
<td>Line cancellation, circle cancellation, anosognosia scale, personal neglect test154</td>
<td>Improved cancellation and personal neglect for all pts; improved anosognosia for 2 pts</td>
<td>Return to baseline after 15min</td>
</tr>
<tr>
<td>Vallar et al112</td>
<td>Single-subject design</td>
<td>Left ear cold or right ear warm caloric</td>
<td>1 or 2 sessions</td>
<td>3</td>
<td>2–12d</td>
<td>Extrapersonal neglect, personal neglect, anosognosia scale, sensory testing156</td>
<td>Improvements in extrapersonal neglect, anosognosia, hemianesthesia with both cold and warm stimuli; greater improvement with cold stimuli</td>
<td>Return to baseline after 30–60min</td>
</tr>
<tr>
<td>Bisiach et al113</td>
<td>Case study</td>
<td>Left ear cold caloric</td>
<td>1 session</td>
<td>1</td>
<td>11d</td>
<td>Verbal report of delusion</td>
<td>Decreased somatoparaphrenic delusions</td>
<td>–</td>
</tr>
<tr>
<td>Rode et al117</td>
<td>Case study</td>
<td>Left ear cold caloric</td>
<td>2 sessions</td>
<td>1</td>
<td>6mo</td>
<td>Extrapersonal neglect, line crossing, personal neglect, anosognosia scale, visual-sensory motor clinical examination</td>
<td>Improvements in extrapersonal neglect, anosognosia, and hemiplegia; no changes in hemianopia or sensation</td>
<td>Informal observation showed return to baseline</td>
</tr>
<tr>
<td>Geminiani and Bottini116</td>
<td>Case study</td>
<td>Left ear cold caloric</td>
<td>1 session</td>
<td>5</td>
<td>1mo</td>
<td>Line cancellation, anosognosia scale, personal neglect, mental representation2</td>
<td>Improved performance in line crossing, anosognosia, and mental representation</td>
<td>–</td>
</tr>
<tr>
<td>Vallar et al114</td>
<td>Quasi experimental</td>
<td>Cold caloric contralateral to lesion</td>
<td>1 session</td>
<td>19</td>
<td>Mn 14d post-CVA</td>
<td>Sensory testing</td>
<td>R group better than L group immediately poststimulation; improved extinction in a subgroup of R patients</td>
<td>No difference between groups after 30min</td>
</tr>
<tr>
<td>Vallar et al115</td>
<td>Case study</td>
<td>Right ear cold caloric</td>
<td>3 sessions</td>
<td>1</td>
<td>6wk</td>
<td>Line cancellation, Token test, object naming, digit span, sentence repetition159</td>
<td>Improvements in line cancellation only</td>
<td>Return to baseline after 30-min delay</td>
</tr>
<tr>
<td>Bottini et al118</td>
<td>Single-subject design</td>
<td>Left ear cold caloric</td>
<td>6 sessions</td>
<td>1</td>
<td>4wk</td>
<td>Tactile stimulation during PET scan</td>
<td>Improved sensation poststimulation; PET showed interaction between touch and vestibular stimulation</td>
<td>–</td>
</tr>
<tr>
<td>Rode et al117</td>
<td>Quasi experimental</td>
<td>Cold caloric contralateral to lesion</td>
<td>1 session</td>
<td>9</td>
<td>Mn 2.5mo</td>
<td>Motor function, personal neglect, anosognosia154</td>
<td>Improved performance all measures RCVA only</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: Pts, patients; R, right; L, left; LTBIneg, left hemisphere TBI with neglect; PET, positron emission tomography.
Aspects of neglect. Deficits in position sense,\textsuperscript{121-123} motor optokinetic stimulation has been reported to improve several outcomes in neglect patients. For example, subjects might be asked to denote the center of a line presented against a right-left background. The duration of the effects of optokinetic stimulation is approximately 30° to 45° per second.\textsuperscript{120,121} Neglect outcome measures are typically administered while the subject is receiving the optokinetic stimulation. For example, subjects might be asked to scan targets against a right-left background. The training was also given to 5 chronic neglect patients, 4 of whom showed improved performance in right stimulation and 3 in left stimulation. Treated subjects showed relative improvement on neglect tests as well as FIM scores, and some differences between groups were maintained at 1-month follow-up.

### Table 4: Optokinetic Treatments

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Interventions</th>
<th>Duration of Treatment</th>
<th>Number of Subjects</th>
<th>Time Postinjury</th>
<th>Outcomes Measured</th>
<th>Results</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzamiglio et al\textsuperscript{122}</td>
<td>Quasi experimental; Left vs right optokinetic stimulus</td>
<td>1 session</td>
<td>10 controls; 10 RCVA; 10 RCVA neg</td>
<td>RCVA mn 8mo; RCVA neg mn 7mo</td>
<td>Line bisection</td>
<td>Left optokinetic stimulation improved performance; right stimulation decreased performance in RCVA neg</td>
<td>--</td>
</tr>
<tr>
<td>Vallar et al\textsuperscript{123}</td>
<td>Quasi experimental; Left vs right optokinetic stimulus</td>
<td>1 session</td>
<td>10 controls; 10 RCVA; 10 RCVA neg; 10 LCVA</td>
<td>Mn 10mo</td>
<td>Forearm proprioception</td>
<td>Left optokinetic stimulation improved performance; right stimulation decreased performance in RCVA neg</td>
<td>--</td>
</tr>
<tr>
<td>Vallar et al\textsuperscript{123}</td>
<td>Quasi experimental; Left vs right optokinetic stimulus</td>
<td>1 session</td>
<td>8 LCVA; 8 RCVA; 8 RCVA neg</td>
<td>RCVA- mn 2.5mo; RCVA neg mn 3.5mo; LCVA mn 3.25mo</td>
<td>Forearm proprioception</td>
<td>Left optokinetic stimulation improved proprioception; right stimulation decreased proprioception in RCVA neg</td>
<td>--</td>
</tr>
<tr>
<td>Karnath\textsuperscript{120}</td>
<td>Quasi experimental; Left vs right optokinetic stimulus</td>
<td>1 session</td>
<td>3 RCVA; 6 CVAneg</td>
<td>RCVA- mn 58d; RCVA neg mn 308d</td>
<td>Judgment of &quot;straight ahead&quot;</td>
<td>Left stimulation improved and right stimulation impaired proprioception in RCVA neg</td>
<td>--</td>
</tr>
<tr>
<td>Vallar et al\textsuperscript{123}</td>
<td>Quasi experimental; Scanning program with computer, reading, copying, and figure description; optokinetic stimulation</td>
<td>40 sessions for scanning program; optokinetic stimulation given only at baseline and after scanning program</td>
<td>8 RCVA neg</td>
<td>Mn 7mo</td>
<td>Line cancellation,\textsuperscript{12} letter cancellation,\textsuperscript{142} reading, Wundt-Jastrow Area Illusion Test,\textsuperscript{14} forearm proprioception</td>
<td>Left optokinetic stimulation improved proprioception; scanning program improved letter cancellation and reading</td>
<td>--</td>
</tr>
<tr>
<td>Vallar et al\textsuperscript{123}</td>
<td>Single-subject design; Left vs right optokinetic stimulus</td>
<td>1 session</td>
<td>2 RCVA neg; 2 LCVA</td>
<td>No data available</td>
<td>Contralateral grip strength</td>
<td>Contralateral optokinetic stimulation improved performance in RCVA neg</td>
<td>Return to baseline after 10min</td>
</tr>
</tbody>
</table>

Abbreviation: RCVA-, right-hemisphere stroke without neglect.

Approximately 30° to 45° per second.\textsuperscript{120,121} Neglect outcome measures are typically administered while the subject is receiving the optokinetic stimulation. For example, subjects might be asked to denote the center of a line presented against a right-left moving background on a video monitor. As shown in table 4, optokinetic stimulation has been reported to improve several aspects of neglect. Deficits in position sense,\textsuperscript{121-123} motor skills,\textsuperscript{124} body orientation,\textsuperscript{120} and perceptual neglect\textsuperscript{124,125} have temporarily improved during optokinetic stimulation. A recent functional magnetic resonance imaging study of optokinetic stimulation showed bilateral activations in subcortical and cortical sensorimotor circuits.\textsuperscript{126}

Several factors may limit the success of optokinetic stimulation therapy. The duration of the effects of optokinetic stimulation has not been well investigated, but appears to be limited to when the stimuli are being applied.\textsuperscript{124} In addition, as with caloric stimulation, the effect of repeated treatments has not been investigated, so it is not clear whether habituation or more permanent improvement may occur.

#### Neck Vibration Therapy

Muscle vibration activates muscle spindles that provide afferent information to the central nervous system. The stimulation is interpreted as a change in muscle length; thus, in the absence of visual input, perceived distortions of body shape and orientation may result.\textsuperscript{127,128} In healthy subjects, unilateral vibration of the posterior neck musculature gives rise to the illusion that both the head and stationary targets are displaced contralaterally.\textsuperscript{129,130} Vibration of the left posterior neck musculature has recently been investigated as a potential treatment for neglect. Karnath et al\textsuperscript{143} showed that 3 neglect patients improved in their detection of objects in the left visual field during such vibration. The investigators suggested that the vibration shifted the perceived position of the head-on-trunk to the right, thereby displacing the perceived sagittal midline of the body to the left and improving the representation of space. The duration of treatment effects has not been reported.

#### Trunk Rotation Therapy

Another treatment that targets the representation of space is trunk rotation therapy. Karnath et al\textsuperscript{144} showed in 4 subjects that rotating the trunk to the left improved latencies to detect targets in the left visual field. Similar results were reported in a subsequent study. Spinelli and DiRusso\textsuperscript{131} found improved visual evoked potentials in 4 neglect patients whose trunks were rotated to the left. As with neck vibration, positive results have been interpreted in terms of changes in the body-centered representation of space caused by a shift of the perceived midline to the left.

In a recent study,\textsuperscript{132} neglect patients stood in a supportive device permitting trunk rotation while scanning for visual targets. There were 11 acute patients each in control and treatment groups. Treated subjects showed relative improvement on neglect tests as well as FIM scores, and some differences between groups were maintained at 1-month follow-up. The training was also given to 5 chronic neglect patients, 4 of whom showed improved performance in right stimulation and 3 in left stimulation. Treated subjects showed relative improvement on neglect tests as well as FIM scores, and some differences between groups were maintained at 1-month follow-up.
whom showed relative improvements in both neglect and FIM scores. One problem with the study, however, given evidence that functional training such as standing may be superior to traditional therapy,\textsuperscript{133,134} is that it is possible that the improvements noted were the result of additional time spent in standing, rather than an effect of the trunk rotation and/or scanning treatment. Further studies of standing therapy with and without the rotation and scanning component are required.

**Summary of Treatments Targeting Spatial Representation Deficits**

A number of methods appear potentially successful in treating neglect by attempting to shift or remap the representation of space. There are, however, several outstanding concerns. Sample sizes have frequently been small, and there is often little or no investigation of functional outcome. For some treatments, such as optokinetic and vestibular stimulation, treatment effects are of limited duration, and the efficacy of repeated treatment has not been investigated. Even if repeated treatment proves successful, it is likely to be difficult to achieve in the rehabilitation environment. On the other hand, though prisms, trunk rotation, and neck vibration therapy may be relatively easily integrated into physical rehabilitation programs for patients with neglect, additional evidence of their efficacy is required.

**DISCUSSION**

On the basis of the review of the literature presented here, one might conclude that neglect must be relatively easy to remediate. Indeed, at least short-term benefits have been observed from treatments targeting arousal deficits (medications, alerting treatment), visual attention deficits (scanning treatments), and a putatively impaired representation of space (vestibular and optokinetic stimulation, motor activation, motor imagery, neck vibration, trunk rotation). When one considers the recalcitrance of other common cognitive and neurologic disorders (eg, aphasia) to treatment, these findings are encouraging. There is undoubtedly every reason to continue to investigate treatments of neglect.

On the other hand, there are several issues marred current understanding of the benefit of these various treatments, some mentioned previously. In many cases, effects of treatment appear to be relatively evanescent, and it is not clear whether repeated treatments would result in greater benefit or, alternatively, habituation. In many cases, treatment effects have been assessed only with paper-and-pencil or computerized tasks, and the functional effects of treatment remain unknown. Many studies have small sample sizes, and the pattern of patients’ neglect (and, sometimes, lesion localization) are poorly characterized. Various neglect assessment protocols and outcome measures have been used, rendering cross-study comparisons and statistic meta-analyses difficult. Finally, with rare exceptions, there have been no studies directly comparing the efficacy of treatments of 2 or more types.

One possibility is that all of the treatments reviewed are potentially effective with nearly all neglect patients. Although this may appear relatively implausible, one might argue that the richness and redundancy of the spatiomotor system predicts just such a possibility. An important property of the action system is its flexibility. Given that spatial information about target locations is simultaneously mapped with respect to several different reference frames centered on different effectors, remediation of the putative coding deficit in any of these frames may potentially benefit the overall, emergent representation of space. Thus, for example, in keeping with what Robertson\textsuperscript{82} suggested when explaining the benefits of limb activation therapy, an intervention that activates the left hand-centered representation not only augments attention to and/or representation of objects near the left hand, but also may affect the left portion of the torso-centered spatial representation. Similarly, interventions that target the vestibular system affect representation of the position of the head on the neck, and this in turn influences the contribution of this coding to the torso-centered reference frame and, likely, to reference frames centered on the shoulder and arm as well. Interventions that improve oculomotor scanning to the left side of space not only influence scanning mechanisms, but also are likely to affect the head-centered and higher spatial representations. On this argument, treatment of the deficit by using any of the systems contributing to spatial representation (eye, head, hand) may affect spatial representation as a whole.

Yet, it remains possible (and, we believe, likely) that this prediction of a response to nearly all therapies by nearly all neglect patients is overly simplistic. There are at least 3 potential reasons for a more guarded optimism. First, many patients with neglect suffer relatively large lesions in the distribution of the right middle cerebral artery that affect both cortical and subcortical structures.\textsuperscript{135} These lesions disrupt significant portions of the right hemisphere’s spatiomotor coding and arousal network, rendering it likely these patients will respond poorly to any treatment. A related concern is that frequent concomitants of right-hemisphere damage (decreased arousal, depressed affect, poor insight and anosognosia, as discussed by Jehkonen et al\textsuperscript{136} and Starkstein et al\textsuperscript{137} are likely to play an important role in treatment response (and in maintenance of treatment benefit) above and beyond that predicted by specific spatiomotor deficits. These factors clearly require further investigation. One possibility is that it will be necessary to treat such overarching problems before, or concomitant with, treatment aimed at specific spatiomotor deficits.

A third concern is that many studies have shown that improvement putatively occurring in a given spatiomotor circuit (eg, the oculomotor system) does not in fact generalize to untreated circuits (eg, the left hand and arm-centered spatiomotor system), suggesting limited cross-talk between systems mediating spatiomotor activities of different effectors. Even bearing these concerns in mind, it is nevertheless important to continue to refine our models of neglect as they may bear on development of targeted treatment. For example, it may prove to be the case that the subtypes of neglect described earlier (motor, perceptual, personal, extrapersonal) reflect differential damage to different portions of the spatiomotor coding system. The near (peripersonal) type of neglect might be a function of damage to circuits coding trunk- and limb-centered representations (ie, the space within reaching distance). Conversely, neglect of far (extrapersonal) space might reflect damage to retinotopic and oculocentric representations (ie, the space reached only through eye movements). If such distinctions prove correct, they predict different patterns of neglect on the basis of lesion locus (the extrapersonal subtype being relatively inferior, in parieto-occipital regions; the peripersonal subtype reflecting relatively superior damage within the dorsal where or how system). Such insights could guide treatments targeted at remediating neglect primarily by focusing treatment on the damaged system, or those targeted at compensation by focusing treatment on intact systems. On the basis of lesion locus and performance on a brief screening battery, it might at some point be possible to triage patients into treatment of most likely benefit.

To reach this point, however, it may be useful if future studies of neglect treatment adopt the following guidelines: (1)
incorporate standardized test protocols that measure a range of neglect phenomena, including personal, peripersonal, motor, and perceptual neglect to establish subtype(s) of neglect in each patient and to facilitate cross-study meta-analyses; (2) attempt to study larger samples including patients who represent several different neglect subtypes or, alternatively, who represent the most common subtypes (ie, peripersonal, perceptual neglect) and analyze data bearing subtype distinctions in mind; (3) incorporate measures of basic arousal and affect to explore their relationship to neglect symptoms and to treatment effects; (4) carefully characterize lesion locus and attempt to analyze data for differential treatment effects in patients with differing lesions; (5) use patients for whom stable pretreatment test scores can be established (ie, relatively chronic patients) or, alternatively, if using acute patients, statistically characterize trajectory of pretreatment natural recovery to assess whether treatment significantly changes this trajectory; (6) match control (nontreatment) groups on demographic and severity characteristics; (7) assess treatment effects not only immediately after treatment, but also at some delay (eg, hours to days); and (8) for treatments in which improvements are noted on measures of impairment, incorporate measures of the functional effects of the treatment and duration of the functional effects.

CONCLUSION

The current health-care environment renders it difficult to perform treatments other than those that are clinically common and accepted. Nevertheless, we believe that through careful treatment studies, it will be possible to gather increasing evidence of the efficacy of at least some treatments. This, in turn, will enable us to garner additional support for changes in current clinical practice.

References


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