Rehabilitation in practice

Hemispatial neglect: approaches to rehabilitation

Victoria Singh-Curry and Masud Husain UCL Institute of Neurology, UCL Institute of Cognitive Neuroscience and National Hospital for Neurology and Neurosurgery, London, UK

This series of articles for rehabilitation in practice aims to cover a knowledge element of the rehabilitation medicine curriculum. Nevertheless they are intended to be of interest to a multidisciplinary audience. The competency addressed in this article is ‘The trainee consistently demonstrates a knowledge of the pathophysiology of various specific impairments including cognitive dysfunction including perception’ and ‘management approaches for specific impairments including cognitive dysfunction including perception’. The article focuses on hemispatial neglect as a common and difficult to manage problem in clinical practice.

Introduction

Hemispatial neglect is a syndrome that commonly follows unilateral brain injury, especially right hemisphere stroke. The most striking feature of neglect is an inability of the patient to orient towards and attend to stimuli – even their own body parts – in contralesional space (the left side for patients with right hemisphere lesions).1,2 Some of these patients are also unaware of their deficit (anosognosia), making the disorder a particularly difficult syndrome to rehabilitate.3 Persistent neglect is often associated with poor functional outcome.4

The heterogeneity of neglect makes rehabilitation a complex challenge

Neglect has proven notoriously difficult to treat effectively despite intensive efforts with single techniques.5,6 This can at least partly be attributed to the fact that the syndrome does not seem to be caused by disruption of just one cognitive process. Careful testing demonstrates that different combinations of neuropsychological deficit may be seen across this patient population.4 Figure 1 illustrates just a few of the common bedside tests used to assess neglect. Some patients show deficits on all these tasks, but many show impairments on only some. Moreover, the combination of cognitive deficits varies across patients. For this reason, it is unlikely that a single therapeutic intervention will suit all of these individuals.

The heterogeneity of neglect is likely to be based on the known diversity in brain lesions responsible for producing the syndrome. Figure 2 demonstrates some of the cortical sites that are associated with neglect when lesioned. In general, the right inferior parietal lobe (IPL), inferior frontal gyrus (IFG) and temporoparietal junction (TPJ) are most consistently implicated,7,8 although damage to analogous left hemisphere regions may sometimes be associated with the syndrome. Subcortical strokes can also lead to neglect because of remote effects such as hypoperfusion of overlying cortical regions or the...
Figure 1  Common tests used to assess hemispatial neglect. (a) Star cancellation: Subjects are asked to circle all of the small stars. This patient has only been able to cancel those on the far right side of the page. (b) Copying scenes/objects: The patient was asked to copy the whole of the scene displayed at the top; however, they managed only the trees on the right of the drawing. (c) Writing and copying from memory: When asked to write a paragraph of text, this patient has started at the left hand margin, but subsequent lines move further and further rightwards. Only the right half of a flower has been drawn from memory. (d) Naming objects in a room: The subject was asked to name objects they could see around them – only items on the right side of space were identified. (e) Line bisection: Patients are asked to mark the middle of a horizontal line. This patient has marked a place that deviates to the right of centre. These tests together demonstrate several of the spatial deficits seen in neglect: failure to identify or copy objects in the left side of near (a and b) and far (d) space, problems reproducing the left half of items drawn from memory (c), failure to make eye (a and d) and hand (a and c) movements into the left side of space and a disordered sense of the midline (e). Most of these impairments may be exacerbated by non-spatial problems such as difficulty sustaining attention.

Figure 2  The anatomy of hemispatial neglect. A variety of cortical lesions can lead to the syndrome of neglect, tending to centre around the temporoparietal junction. ang, angular gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; ips, intraparietal sulcus; MFG, middle frontal gyrus; smg, supramarginal gyrus; STG, superior temporal gyrus.

disconnection of fronto-parietal circuits. Other studies have also suggested a role for lateral or medial temporal regions in the right hemisphere. Even within the typical inferior parietal and frontal regions associated with neglect, lesion extent varies considerably and because these regions have multiple functions, the exact combinations of deficits observed in patients is unlikely to be uniform. Improvements in our understanding of the functions and connectivity of these regions has influenced our idea of the range of cognitive processes which may be involved in the neglect syndrome.

Broadly speaking, the cognitive processes disrupted in neglect can be divided into spatial and non-spatial deficits (Table 1). Non-spatial processes have more recently been considered to be important in the manifestation of neglect and can interact with spatial impairments to exacerbate the severity of the syndrome in a given patient. Because the syndrome of neglect consists of several dissociable and/or interacting cognitive deficits, a full neuropsychological (as well as physical)
examination would ideally be required in all stroke patients, particularly those with right hemisphere lesions. No single test provides an adequate screening tool. Instead, a battery of standardized measures (such as from the Behavioural Inattention Test; Figure 1), examination for visual and somatosensory extinction and an assessment of functional activities (for example the Barthel Index or Functional Independence Measure) are needed to fully evaluate the syndrome in an individual patient. This information, along with an appreciation of the underlying lesion anatomy, could be used to guide attempts at effective rehabilitation.

Techniques used to rehabilitate neglect

Although research on the cognitive deficits underlying neglect has guided the development of treatment strategies for the disorder, few of these techniques have been associated with consistent functional recovery. This may be due to lack of randomized controlled trials and, as discussed above, heterogeneity of the syndrome in question. Clearly, in patients with different combinations of deficit, a technique which is effective for one may not be so for another. A related concern is that for a treatment to be effective it may rely on a particular brain region being intact. For example, learning a new strategy may depend on the integrity of particular frontal regions, so that patients with lesions encompassing these areas may not be responsive to such therapies. Mapping the lesions of patients who take part in treatment trials may therefore be particularly important in understanding variation in response to treatment.

Treatments used to rehabilitate neglect can be divided into three broad categories:

- purely behavioural strategies;
- techniques employing devices or specialized equipment; and
- pharmacological manipulations.

Behavioural strategies

Behavioural techniques have focused on the development of strategies to facilitate the orientation of attention into the contralesional, neglected side of space. Visual scanning or visuospatial training involves cueing right-hemisphere patients to make leftward eye or head movements and is the most common method used by therapists on stroke and rehabilitation units. It involves the use of explicit instructions to the patient encouraging these behaviours, for example asking the subject to locate the left hand margin of the page before reading the next line. The margin may also be marked by, for example, a thick red line, to make this more salient. Although this technique is used frequently in clinical practice, there have been relatively few randomized controlled trials assessing its efficacy and where improvements have been shown, these have been confined to pen-and-paper tests, rather than functional measures, or there has been no follow-up to demonstrate long-term benefits. In fact, some studies

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<th>Table 1</th>
<th>Spatial and non-spatial cognitive deficits contributing to neglect</th>
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<td>Spatial deficits</td>
<td>- A bias in the gradient of spatial attention towards the ipsilesional (towards the right in patients with right hemisphere lesions) side of space;</td>
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<td>- Difficulty disengaging attention from ipsilesional (right-sided) and shifting it to contral-</td>
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<td>- A pathological spatial bias, in which contralesional (left-sided) items lose in the competition for attention to ipsilesional (right-sided) stimuli;</td>
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<td>- Directional motor deficits, in which patients have difficulty directing movements into the contralesional (left side) of space;</td>
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<td>- Problems with spatial working memory, i.e. keeping track of spatial locations over time;</td>
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<td>- A disordered egocentric representation of space;</td>
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<td>Non-spatial deficits</td>
<td>- Difficulties in sustaining attention over time, even when items are presented at a central location;</td>
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<td>- Impairments in selective attention, which may occur in both left and right sides of space and at central locations. Neglect patients can demonstrate bilateral attentional impairments, even though the most obvious abnormality is a bias towards ipsilesional (usually right-sided) space.</td>
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suggest that there is little generalization to everyday behaviour.\footnote{3}

Another strategy has been employed by Robertson and colleagues to try to address some of the non-spatial deficits in neglect. In their investigation patients were required to perform tasks that required sustained attention, for example the sorting of objects such as coins. The experimenter would intermittently verbally prompt patients to attend during the task. Patients were made aware of their spatial deficit, as well as their difficulty in sustaining attention, and gradually were trained to prompt themselves subvocally. With an understanding of the importance of this self-alerting process, the eight patients who participated were able to demonstrate considerable improvements 24 hours after training on tests of neglect and sustained attention.\footnote{33} However, the degree to which individuals with neglect are able to appreciate their deficits, as well as the situations in which they may need to use the procedure, limits the general applicability of this technique.

**Limb activation therapy** is based on the idea that for people with left-sided neglect, making leftward movements with the left arm can activate poorly attended areas in extrapersonal space and thereby improve neglect. There is evidence to suggest that such ‘spatiomotor cueing’ may be effective even if the patient is unable to see the moving limb.\footnote{34} Obviously, this technique is constrained by the fact that some control over the often hemiparetic arm is required. However, it has been shown that even passive movements if large enough (i.e. at the elbow rather than the wrist) can lead to some improvement of neglect.\footnote{35} One randomized controlled trial has examined the efficacy of this intervention and found that it is associated with reduced inpatient stay; but although there was a trend towards improvement on standard tests of neglect, this did not reach significance on conventional statistical tests.\footnote{36}

In summary, behavioural interventions encourage the development of strategies by the patient to attempt to compensate for their functional impairment. This is achieved through training sessions with a therapist, tailored to the individual needs of the patient. Although some of these methods are long established, further trials are needed in order to demonstrate their functional efficacy over time.

## Therapies that use specialized devices

The development of a neglect alerting device (NAD) progressed from studies on limb activation. The neglect alerting device consists of a light box which emits a loud buzzing noise if its switch is not pressed (by the left hand in left neglect) within a predetermined but variable time limit. A single-blind randomized controlled trial of 32 patients followed up for six months demonstrated a significant improvement in left-sided motor function, but not in activities of daily living or tests assessing the severity of neglect.\footnote{37} It would seem, therefore, that while limb activation training using a neglect alerting device is beneficial to neglect patients in terms of their ability to move their affected limbs, it is not clear that this is paralleled by a more general amelioration of their neglect symptoms.

Because some active movement of the frequently hemiparetic limb is required for these methods of limb activation – limiting its general applicability – some studies have examined passive movements of the arm using functional electrical stimulation (FES). Functional electrical stimulation can be used to enhance or generate a muscle contraction in a paretic limb, by electrically stimulating peripheral motor nerves in a coordinated manner to produce movement. One such open investigation\footnote{38} examined the effect of functional electrical stimulation-induced passive movement on target detection in a visual scanning task compared with no movement and active movement conditions. They found that a subgroup of patients benefited from functional electrical stimulation in terms of performance on the visual scanning task, with these patients tending to have frontal and subcortical lesion locations. Further randomized controlled trials are needed to follow up on this finding.

A series of investigations have been conducted using computerized training tasks for alertness, vigilance, selective and divided attention. Such training led to significant improvements on tests assessing these attentional processes and was paralleled by an increase in brain activity – as measured by functional magnetic resonance imaging (fMRI) – in intact right fronto-parietal regions (areas associated with alerting and visuospatial functions). However, four weeks later, this
improvement had deteriorated – with a commensurate reduction in neural activity on fMRI. Rotation of the head or trunk towards the neglected side has been considered an alternative way to improve space exploration by reorienting the egocentric frame of reference. However, the devices used are often cumbersome and one recent study documented no improvement on neglect measures or functional performance. Neck muscle vibration (NMV) is also thought to effect a recentring of the egocentric frame of reference, by an illusory modification of the afferent information regarding the orientation of the head in space. Neck muscle vibration is delivered by transcutaneous stimulation of the posterior left neck muscles. In isolation, this method has also produced inconsistent results. However, in combination with visual scanning training there is evidence for a significant improvement in neglect and functional outcome measures, which were stable at two months follow-up.

Optokinetic stimulation, produced by a background of moving dots or lines, is also thought to alter the egocentric frame of reference. Recent studies suggest that this technique may lead to improvement in reading and writing, as well as on standard tests of neglect and that this effect can persist for at least two weeks. Further investigations, preferably randomized controlled trials, are required to investigate this method further.

Much interest has been generated in prism adaptation, following the demonstration in 1998 that an amelioration of left-sided neglect could follow the use of lenses producing a rightward optical deviation. Note that the positive effect of prisms occurs after wearing them, not while they are being worn (Figure 3). When subjects put on right deviating prisms, visual targets appear displaced to the right, so that when they perform pointing movements to such targets they miss and receive visual feedback that they have reached too far rightwards. With successive pointing movements, visual feedback leads to motor correction towards the left – a process called visuomotor adaptation or error reduction. When the prisms are removed and visual feedback regarding limb position is not available, or the subject makes rapid ballistic movements, they usually show a consistent deviation to the left, when pointing to visual targets. This is termed the prism after-effect. The process of adapting to right deviating prisms seems to lead to an improvement in left-sided neglect. The underlying mechanism by which this occurs is, however, controversial.

The effects of prism adaptation on measures of neglect, including some functional tasks, have been shown to be relatively long-lasting. For example, one study gave a group of seven patients twice-daily training sessions with prisms for two weeks and compared them with six control patients matched in terms of neglect severity. All but one of the experimental patients performed significantly better than the control patients on all tests used – with this improvement being maintained five weeks after the end of treatment. The duration of improvement in neglect was found to correlate with the length of the after-effect in this study. This has been explained in terms of an effect of prism adaptation on two levels: (1) low-order functions (i.e. sensorimotor coordination) and (2) higher order spatial representations. The authors postulated that the effects of prism adaptation on low-order functions were short-lasting, whereas those on spatial representations were longer lasting.

Studies have now demonstrated that prism adaptation can affect various aspects of neglect behaviour. For example, somatosensory extinction, visuo-verbal measures, postural control and even wheelchair navigation have all been shown to be improved. However, not all studies have shown a consistent benefit. Lack of effect of prism adaptation has been shown to be associated with large frontal lesions – perhaps as a result of the role the right frontal lobe plays in vigilance and the ability to sustain attention – as well as damage to the right intraparietal sulcus – perhaps because lesions of this region render it impossible for plastic changes of spatial representations to occur. Prism adaptation does, however, appear to produce remarkably positive effects in some patients with neglect. Future research needs to focus on defining those patient populations in which it is most likely to produce a benefit.

Repetitive transcranial magnetic stimulation (rTMS) is a recent technique which aims to restore balance between the two cerebral hemispheres following unilateral brain damage. rTMS transiently administered over the contralesional parietal lobe (causing short-lasting inhibition)
has been found to improve the performance of patients on a wide range of tasks assessing neglect, including some activities of daily living. In fact, some of these effects were found to persist for up to six weeks. Larger controlled studies are now needed to further evaluate this technique.

In summary, several specialized devices have been investigated for their potential use in the rehabilitation of neglect. These have been aimed at correcting a disordered egocentric representation of space, altering higher order spatial representations or restoring interhemispheric balance. Some of
these methods provide promise for future treatments. However, the mechanisms by which they improve aspects of neglect need to be further elucidated, so that future trials can target appropriate subgroups of patients if necessary.

**Pharmacological therapies**

Two different classes of drug have been investigated for their potential utility in rehabilitating neglect – the rationale for these strategies coming from animal studies. Both target catecholaminergic systems, either dopaminergic or noradrenergic.

**Dopaminergic drugs** have been found to ameliorate some of the signs of neglect in patients. Bromocriptine given daily for 3–4 weeks has been found to effect an improvement in measures of neglect in two individuals.\(^{57}\) Two further studies – one using levodopa\(^{58}\) and the other apomorphine\(^{59}\) – have also demonstrated improvement on standard tests of neglect, although these too were in small groups of patients. However, some reports have failed to demonstrate any benefit. In fact one study found that visual exploration of the left hemifield on a computerized search task actually deteriorated after bromocriptine in all but one of seven patients, although target detection remained unaltered.\(^{60}\) Lesion anatomy and extent, as well as the integrity of certain brain regions, may be one important factor in accounting for this variability in response.

**Noradrenergic compounds** have been studied even less. In monkeys the \(\alpha_2\)-noradrenergic agonist guanfacine has been found to improve performance on spatial delayed response tasks by modulating dorsolateral prefrontal cortex.\(^{61}\) Guanfacine also improves planning and working memory performance in healthy human participants.\(^{62}\) A small proof-of-principle, double-blind cross-over trial in neglect patients demonstrated an improvement in two of three patients on standard tests of neglect, as well as a computerized search task.\(^{63}\) Both of these patients were also able to sustain attention for longer periods of time on the visual exploration task following guanfacine. The patient who did not benefit had a lesion involving the right dorsolateral prefrontal region, making it possible that guanfacine had no effect due to lack of intact substrate. Larger trials are now needed in neglect patients (selected on the basis of lesion anatomy) to further investigate the potential of this drug.

**Summary of treatment approaches to neglect**

Several techniques aimed at rehabilitating neglect have been developed over the years. However, the syndrome remains difficult to treat effectively for several reasons. First, neglect is heterogeneous. It is caused by deficits in a variety of cognitive processes, which can dissociate from one another, so that one type of treatment may not be suitable for all patients. Second, the right hemisphere is critically responsible for sustaining attention, as well as maintaining spatiomotor representations. If a patient is unable to sustain their attention, they will have difficulty in participating in and benefiting from any form of therapy. Third, lesions of the right hemisphere are often accompanied by depression and anosognosia. If a patient is not motivated to participate in therapy, or does not believe they need any because there is nothing wrong with them, their engagement in such treatments will obviously be poor. Finally, neglect is frequently associated with extensive lesions of the right hemisphere, involving cortical and subcortical structures as well as white matter tracts. The larger the area of damage, the less potential there may be for plastic changes and functional reorganization of neural networks which may lead to recovery.

Despite these limitations, it has to be borne in mind that the systematic treatment of neglect is still in its infancy. A recent Cochrane review\(^{64}\) was unable to find sufficient evidence to support – or refute – the routine use of any of the treatment strategies described here. Few properly controlled trials have been performed that have used functional measures and followed patients up long term. In addition, we would argue there are often inconsistencies in outcome for individual treatment strategies. Despite this variability, there are reasons for optimism. Recent advances in the understanding of the various cognitive deficits underlying neglect and of the processes subserved by regions commonly lesioned in neglect, we hope will lead to improvements in the design of future trials. Furthermore, the combination of interventions in certain individuals may provide greater benefits than one technique alone.
Clinical implications

Currently there is insufficient evidence to recommend the general use of any of the treatment strategies outlined here. Neuropsychological evaluation of patients with right hemisphere stroke will, however, provide greater insight into the cognitive deficits contributing to neglect in particular individuals, as well as enhancing the detection rate of neglect. As we have seen, there is no single test that can be used to assess for the presence or absence of this syndrome. Instead, a battery of measures is essential to understand its manifestation in each patient. In this way the rehabilitative needs of individuals can begin to be addressed. We believe that well-designed trials, which take into account the heterogeneity of the syndrome, as well as lesion anatomy – with consideration to brain regions that are spared – will lead to effective treatment strategies in the future.

Clinical messages

- Hemispatial neglect is a heterogeneous syndrome composed of dissociable cognitive deficits.
- A battery of tests is essential to evaluate the precise deficits manifest in individual patients.
- Lesion anatomy is important in predicting the pattern of impairments likely in patients, as well as informing the choice of rehabilitative strategy.
- Although effective treatment of neglect is still in its infancy and better trials are needed, there are some promising techniques. It is possible to group these as behavioural strategies, specialized devices or pharmacological manipulations. Combinations of these methods may produce the best outcomes in the future.

Recommended reading


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