Published in final edited form as:
Nat Rev Neurol. 2012 October ; 8(10): 567–577. doi:10.1038/nrneurol.2012.170.

Prism adaptation for spatial neglect after stroke: translational practice gaps

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Abstract

Spatial neglect increases hospital morbidity and costs in around 50% of the 795,000 people per year in the USA who survive stroke, and an urgent need exists to reduce the care burden of this condition. However, effective acute treatment for neglect has been elusive. In this article, we review 48 studies of a treatment of intense neuroscience interest: prism adaptation training. Due to its effects on spatial motor 'aiming', prism adaptation training may act to reduce neglect-related disability. However, research failed, first, to suggest methods to identify the 50–75% of patients who respond to treatment; second, to measure short-term and long-term outcomes in both mechanism-specific and functionally valid ways; third, to confirm treatment utility during the critical first 8 weeks poststroke; and last, to base treatment protocols on systematic dose–response data. Thus, considerable investment in prism adaptation research has not yet touched the fundamentals needed for clinical implementation. We suggest improved standards and better spatial motor models for further research, so as to clarify when, how and for whom prism adaptation should be applied.

Introduction

Spatial neglect—a failure to report, respond to or orientate to contralesional stimuli, accompanied by functional disability[1–11]—affects about half of all survivors of acute stroke.[5] The presence of spatial neglect predicts poor motor recovery[6] and is, in fact, a stronger predictor of poststroke dependence than are paralysis or communication disability.[12] This striking behavioural disorder might be produced by impairment in brain–behaviour networks that continuously compute the relationships between our bodies and the world around us during daily activities.[13,14] Neglect symptoms vary, probably because brain injury can primarily affect different spatial brain systems, specifically disrupting one or more dissociable, sequential stages of spatial information processing, from perceptual–attentional input, to internal representation, to motor-intentional output processing.[1,15,16]

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Author contributions
A. M. Barrett and J. C. Basso researched data for the article. All three authors contributed to writing the article. A. M. Barrett and K. M. Goedert made substantial contributions to discussion of the content, and reviewed and edited the manuscript before submission.

Supplementary Information
Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol.

Competing interests
The authors declare no competing interests.

Distinct symptoms can result from dysfunction at each information-processing stage, so, like aphasia or memory disorder, spatial neglect maybe viewed as a cognitive mental disorder.[17]

Millions of people might benefit from the reductions in stroke morbidity, costs and burden that would result from more-effective spatial neglect treatment.[18] However, existing treatment approaches focus heavily on abnormal visual perceptual processing, meaning that survivors with deficits primarily affecting other spatial cognitive processing stages may not be optimally identified or treated. In this article, we focus on a different approach, prism adaptation training, which, our research indicates, may target impairments in spatial motor 'aiming' function.

The objective of this Review is to motivate more-rigorous translational research to address the knowledge gap presently blocking inpatient implementation of prism adaptation for spatial neglect (see Supplementary Box 1 online for further information on spatial cognitive neuroscience and prism adaptation for spatial neglect). We need neuroscience-based patient classification, allowing us to stratify spatial 'where' and spatial 'aiming' deficits at treatment initiation, because they are likely to predict different stroke recovery and treatment response trajectories; short-term and long-term studies supporting targeted treatment pathways, including acute stroke outcomes at three levels: mechanistic phenomena, clinical impairment, and activity limitation; and dose–response studies to optimize clinical practice guidelines. In addition to working to move prism adaptation beyond its current proof-of-concept stage toward demonstration of clinical utility, a theoretical paradigm shift may be needed. When we can regard neglect as a spatial—and not solely visual–perceptual—disorder, and when we can target prism adaptation to stroke survivors with dysfunction in neuroanatomical–behavioural networks supporting spatial motor-intentional 'aiming' improvement,[19] we may progress rapidly toward making prism adaptation a widely available in-hospital treatment.

Current therapeutic approaches

Therapeutic approaches for spatial neglect usually attempt to train visual perception through verbally mediated strategies that stroke survivors must consciously implement. One commonly used approach, visual scanning training,[20,21] forms the basis of interventions used in numerous US inpatient and outpatient settings (for example, urging the patient to scan leftward to a coloured line or edge in reading each line on a page). Exclusive use of visual scanning rehabilitation in hospital settings may be inappropriate for both practical and theoretical reasons. These approaches are extremely time-consuming: in initial trials demonstrating visual scanning benefit, patients spent 1 h daily on this training alone, for four consecutive weeks. This represents one-third of the current US inpatient rehabilitation time available (around three therapy hours on weekdays) to address all of a patient's cognitive, hand-and-arm-related, ambulation-related, social and self-care problems (speech pathology, occupational and physical therapy). The time devoted to US inpatient stroke rehabilitation continues, on average, for a 2–4-week hospitalization. Thus, a visual scanning training protocol is radically shortened in session duration and number of sessions when used in the US inpatient rehabilitation environment. Brief administration of visual scanning may result in reduced treatment benefit. Other spatial neglect treatment approaches are available and used in the USA, but most of these also utilize top-down (goal-driven) strategies to enrich visual perception and monitoring, and are intended for self-implementation. These strategies include training of visual awareness,[22] therapist-coached use of mental imagery (the 'lighthouse strategy'[23]), and review with a therapist of videotaped feedback of task performance.[24]

Currently, at least three problems are experienced with assessment and treatment of spatial neglect in US inpatient care. First, some patients with spatial neglect have relatively intact ability to perceive, attend and represent the external spatial environment (spatial 'where' functions[25]), but still make spatially biased, motor output, 'aiming' errors.[26–29] These patients are specifically challenged to generate an accurate movement trajectory, at the right time, to the right spatial location (for example, bed–chair transfers, wheelchair mobility), and may not be identified as having spatial neglect. Moreover, even if these patients are identified and receive treatment, training of visual perception may not resolve their neglect symptoms. Second, training that emphasizes conscious strategies may be ineffective for spatial motor-intentional 'aiming': even people without impairments have little conscious awareness of movement planning, and have limited ability, in some circumstances, to modify learned motor behaviours deliberately.[30] Last, the lumping together of spatial neglect symptoms may affect the results of randomized studies. When researchers looking for benefits of training visual perception compare the results of treatment with control therapies, their studies may yield negative results[31] if they unknowingly include large numbers of patients with primarily spatial 'aiming' symptoms.

Identifying spatial deficits

'Aiming' versus 'where' deficits

Basic research in animals and humans suggests that spatial responses are abnormal in spatial neglect, and that motor-intentional output processing errors are an important source of spatial dysfunction. Spatial neglect in rodents, cats, dogs and monkeys manifests with asymmetric movements (for example, rotatory behaviours), and unilaterally deviated head posture and eye position, induced by subcortical dopamine depletion or by collicular inhibition.[32–36] These results suggest that dysfunction of certain spatial brain networks may primarily affect spatial 'aiming' output. Thus, even if awareness of external events is improved after visual training treatments, a limited capacity for processing of automatic spatial action might still block biological, functional recovery. Of course, deductive reasoning based on animal models should proceed judiciously to human treatment, as many differences exist between animal and human cognition.

In summary, stroke can induce both classic visual–perceptual, 'where' spatial neglect and spatial motor-intentional 'aiming' deficits. Spatial 'aiming' deficits may not improve when stroke survivors are taught visual perceptual strategies intended for conscious self-implementation. Undetected spatial motor 'aiming' bias may be expensive for society, and harmful to the individual if not detected and treated. We witnessed the impact of undetected spatial bias when a stroke survivor systematically veered, while driving, toward people and objects in far space opposite her brain lesion. Her deficit was neither suspected nor treated as part of her routine clinical care.[37]

Screening different spatial systems

Previous authors have recommended bedside techniques to distinguish spatial 'where' from spatial 'aiming' deficits in stroke survivors,[1,38,39] Clinicians can assess spatial perceptual–attentional 'where' function by assessing visual extinction to double simultaneous stimulation—a failure to detect stimuli in the neglected body space when stimulated simultaneously on the left and right sides; distinguished from a visual field deficit by the patient's ability to detect single stimuli in the neglected body space reliably.[40] Other bedside tasks that may be primarily perceptual–attentional include a visual search task with verbal response (the examiner could, for example, group many people around the patient's bed, then ask the patient to "count all the people who are here") or a visual search task to identify a missing article, or an incongruity (the examiner might surreptitiously take an arm out of

the jacket sleeve appearing on the patient's left side, and then ask "is there anything wrong with the way I am dressed?").

Stroke survivors may also have spatial 'where' problems affecting internal representations, maps or mental images. These might affect the ability to inspect a mental map ("if you were going to drive to St. Louis, Missouri, from New York City, which way would you go?") or identify locations on a mental number line ("tell me what number is halfway between 13 and 31"). Patients may have spatial 'where' representational bias to the mental right-hand side ('east' for the map; '26' for the number line).

Assessment of spatial motor-intentional 'aiming' can take several forms.[41] Asymmetries of body posture and movement include ipsilesional head and eye deviation at rest, a skewed asymmetry of body posture in bed, and failure to activate the contralesional side of the body spontaneously, even in the absence of hemiparesis. Spatial 'aiming' neglect can be separated from a pure motor deficit; rather than weakness, survivors could manifest motor extinction, defined as an abnormality of contralesional limb or body movement that is present while the ipsilesional limb or body is being simultaneously mobilized, but absent when the contralesional limb or body is activated in isolation. Hemispatial hypometria[42] is another form of 'aiming' neglect; movements may be slower, or of a lesser extent, in contralesional space. Hemispatial hypometria can be tested by asking the patient to click a golf counter with the ipsilesional hand in both left and right body space repeatedly (in several separate trial sets). Consistently slower clicking in contralesional space is consistent with spatial 'aiming' neglect. A third form of 'aiming' neglect is directional hypokinesia; that is, disinclination to move in a contralesional direction. Directional hypokinesia can affect movement of the eyes, either hand, or the whole body; for example, a patient may repeatedly turn right when wheelchair ambulating, resulting in circling movements.

The relationship between bedside screening methods and activity in dissociable spatial systems is still based primarily on '$n = 1$' studies, case series and expert opinion, rather than on empirical confirmation over large groups or populations of patients. However, Goedert and colleagues[40] evaluated whether standardized bedside administration of spatial neglect assessment was able to identify dissociable 'where' and 'aiming' spatial functions. Stroke survivors with spatial neglect performed 'where' and 'aiming' laboratory tasks and bedside clinical neglect procedures, and also completed standardized neglect inventories. The results were consistent with separable stages of spatial processing: different items on a neglect inventory (the Catherine Bergego Scale, or CBS[43]) potentially sampled distinct perceptual–attentional 'where' versus motor-exploratory errors. Visual extinction, for example, strongly correlated with examiner-observed performance on "finding belongings" or "attending to noise or people" on the left. However, potential motor-exploratory CBS items ("collides with people or objects" on the left) were highly correlated with one another, forming a distinct subcomponent of the scale. Importantly, motor-exploratory performance items accounted for a unique 9.2% of the variance in stroke-related disability, over and above that predicted by traditional paper-and-pencil or visual–perceptual assessment.

Prism adaptation treatment

An NIH-sponsored workgroup[2] concluded that translation of basic science knowledge of spatial deficits might dramatically improve rehabilitation efficacy and functional impact after stroke. Among other approaches, this group recommended increased research on prism adaptation treatment (see below and Box 1),[44] which has attracted exponentially growing interest in the cognitive neuroscience literature since 2001.[45] In this treatment, stroke survivors are trained to make repeated visually guided movements while wearing prisms that

laterally displace viewed objects rightward. Survivors undergo brief, intensive one-to-one training over a period of days to weeks.

Box 1

Prism adaptation and spatial neglect

Prism adaptation therapy requires the stroke survivor to wear wedge prism lenses during intensive motor training.

- Unlike prism treatment for diplopia, both lenses should induce the same degree and direction of perceived displacement (rightward)
- Although no dose–response studies support a specific degree of prismatic displacement, the usual prisms are 20-diopter, 12.4°
- Survivors repeatedly point to targets, or perform continuous manual tasks
- Survivors' ability to view their own arm movements is usually partially blocked[86]
- Initially, participants err in the direction of optical displacement (rightward) but, after more than 50 trials, many point accurately
- With the lenses removed, participants typically demonstrate a training after-effect, erring in the opposite direction (leftward)
- Few adverse effects are reported in the literature; clinicians anecdotally report occasional instances of discomfort or dizziness
- Training sessions are brief (15–30 min); prisms are worn only during training, not during other activities or rehabilitation

Compared with treatment approaches like visual scanning training, prism adaptation may be much simpler, and more amenable to standardization for in-hospital use. Stroke survivors sit at a table (or even sit up in bed) and make repeated pointing movements, or other repetitive actions, while wearing wedge prisms that shift the external world about 12° rightward.[46] Most studies use a visual barrier (a shelf or cloth) to prevent the patients from continuously monitoring their own arm movements as they train; the tail end of the movement, as the hand approaches a target, may be all that the patient is able to see. However, not all studies blocked arm self-monitoring.[47,48] Standard training sessions last 15–20 min; individuals receive one—or at most two—training sessions daily on weekdays for 2 weeks (10 days total). Stroke survivors undergoing this treatment thus wear prisms for only a short period of time. For the rest of the day, patients are free to take part in other therapies, or diagnostic or medical procedures. The brief, structured nature of prism sessions means that they could be administered by therapists, or even by other trained and supervised rehabilitation personnel.

Prism adaptation might induce a change in the way that spatial information is transformed from retina-based perceptual coordinates for representing object locations to body-based motor coordinates for representing object locations.[45] Neglect patients wearing prisms that displace visual information rightward must make reaching movements to the left of where an object 'appears', to reach its actual location. In patients with neglect, this increase in leftward movement persists after the prism adaptation period, and can generalize to daily life tasks.[46,49] Importantly, prism adaptation is experience-dependent or activity-dependent, rather than strategic; it is a procedure, rather than a set of verbal instructions or conscious goals to be remembered, and it provides multiple opportunities for learning and direct experience of error. The neuroanatomical–neuropharmacological systems supporting prism

adaptation effects in neglect are not completely clear, but they may operate on the same principles that support implicit motor learning,[50] and might, therefore, constitute an optimal approach to support spatial motor 'aiming' recovery.

Emerging research suggests that prism adaptation treatment primarily and specifically ameliorates spatial motor-intentional—and not perceptual–attentional— deficits. Studies independently examining spatial perceptual awareness and spatial motor 'aiming' supported the possibility that 'where' visual perception does not improve after prism adaptation therapy; rather, more-accurate spatial motor 'aiming' may primarily drive prism adaptation treatment effects.[19,51] Thus, as in visual training tasks, the effects of prism adaptation might be task-specific in spatial neglect, and a task primarily assessing visual awareness may be relatively unaffected by prism adaptation compared with a task assessing accurate spatial motor movements.

We wished to understand whether task specificity of prism adaptation—its primary effect being on spatial motor 'aiming'—might explain the failure of some large-sample studies using controlled group assignment to reproduce large beneficial effects, despite reported improvements in real-life functions.[46,49] We decided to systematically review the literature when we realized that only two of five published Class II randomized, systematic trials[52,53] (plus yes, OK one reported in preliminary form[54]) demonstrated definite benefit compared with control conditions, and 25–50% of treated individuals in these studies still did not attain a spatial function score consistent with daily life independence. Two published randomized trials of prism adaptation,[55,56] and one reported in preliminary form,[54] reported no long-lasting benefit of prism adaptation over placebo; one[56] reported short-term improvement only, as compared with control treatment. The differences in findings between the studies may have been related to differences in equipment and training protocol used (discussed further below). Although smaller-scale studies strongly pointed to a primary and specific effect of prism treatment on spatial motor 'aiming',[19,51] larger-scale studies did not specifically assess this aspect of spatial function, or stratify patients by their degree of spatial 'aiming' deficit before treatment.

Of course, very restricted, specific and primary effects of prism adaptation (beneficially affecting performance in some patients, and on some tasks, while not affecting others) are not equivalent to null treatment effects. However, clinical outcomes of spatial neglect treatment trials are currently evaluated with generic, composite outcome measures. Thus, a non-generalized effect may resemble a smaller-magnitude, incomplete or even null effect on such a composite scale. Perhaps partly because the results of randomized studies using composite outcomes confused the clinical community, we find, 13 years after the introduction of prism adaptation treatment, that only a small number of inpatient centers utilize this approach, mainly within research protocols.[57]

Prism adaptation studies

Our review of the literature unearthed 48 reports for studies examining the effects of prism training on post-stroke spatial neglect.[19,44,46–49,51–53,55,56,59–94] The 48 articles included four randomized controlled trials with single blinding, nine other studies employing control conditions, two observational studies, 24 case series and within-individual designs, and nine case study evaluations (Table 1)

In Table 2, we present a summary of the studies reviewed, as a function of whether treated patients demonstrated improvement, lasting improvement, or no improvement. Our review confirmed that patients undergoing prism adaptation training did not consistently improve—a finding that demands explanation. As we discuss in the sections that follow, classification of the patients' spatial deficits, assessment at all three outcome levels (phenomena,

impairment and disability), and dose–response studies in patients with acute stroke could resolve conflicting research results constructively.

Need for neuroscience-based classification

As discussed above, prism adaptation may specifically affect spatial cognition at 'aiming' output-processing stages. If prism adaptation treatment specifically improves spatial cognitive output-processing capacity, it may not affect earlier perceptual or representational spatial processing, which could explain the lack of long-term treatment benefits.[55,56,59–64] Failure to stratify individuals included in randomized studies by their degree of spatial 'aiming' deficit (and potential for improvement), or failure to choose outcome measures that are sensitive to improvement in spatial motor function,[40] could explain otherwise confusing differences between studies in prism adaptation effects. Neglect-related impairments in left-sided visual search and reading, as well as left-sided perceptual size distortion and difficulty in discrimination of facial emotional expression, may depend relatively heavily on spatial attention or awareness; thus, a lack of improvement in these impairments after prism adaptation may not be surprising.[61,63,65–67] Similarly, prism adaptation might be expected primarily to improve manual motor response-related impairments like scene copying,[44,64,67] line bisection[44,67] and line cancellation,[44,67] and might actually stimulate and increase neglect-related abnormal movements (for example, neglect-related perseveration).[68]

Need for translational assessment

A striking result of our review of existing research is a dissociation between improvements on functional measures of daily activities (on the few occasions when those measures were employed; Table 3) and phenomenon-level or impairment-level spatial neglect measures. Of the 48 studies, only 22 employed quantitative self-care or activity-level-dependent variables, and many studied only one task (Table 2). Only four, including a single-patient report, examined ambulation,[49,53,69,70] only five used validated functional outcome measures,[19,46–48,53] and only two[19,48] explicitly examined whether changes in laboratory neglect phenomena or clinical impairment predicted daily life functional improvement. Most studies did not attempt to combine an investigation of laboratory phenomena with investigation of clinical impairment (performance on paper-and-pencil neglect tasks), and investigation of daily activities using functional-level assessments (Box 2). Because many studies that failed to obtain treatment improvements in impairments and function did not assess mechanistic phenomena, it is difficult to know why prism treatment was ineffective.

Box 2

Assessment in translational neurorehabilitation

A disabling syndrome can be assessed in the cognitive laboratory, at the hospital bedside, or in the rehabilitation clinic. The WHO provides a framework by which we can separate the measurement methods used in these three contexts. Laboratory phenomena are defined as distinct, replicable, definable behavioural or neurophysiological phenomena, assessed by a basic scientist, without definite clinical correlates. These phenomena may be distinct from clinical impairments (problems of body structure and function or disease signs, assessed by a cognitive neurologist or neuropsychologist), or limits imposed on functional activities (disability, assessed by a rehabilitationist in the home, workplace or other functional setting). Separation of these levels of assessment is essential to evaluation of translational outcomes that are relevant to spatial neglect. Analysis of treatment outcomes might require simultaneous assessment in more than one setting: a failure to improve function could result from a treatment's failure to act on the brain, a treatment's failure to reduce impairment despite a decent brain effect, or an insensitive

functional outcome measure that fails to demonstrate improvement despite reduction in clinical impairment.[102]

Phenomenon-level outcomes

- Contralesional 'where' unawareness of left-sided stimuli
- Degraded internal contralesional 'where' maps or representations
- Ipsilesional 'aiming' exploratory preference

Impairment-level outcomes

- Extinction to double simultaneous stimulation (visual, tactile, auditory)
- Ipsllesional bias on line bisection or cancellation task[103]
- Directional and hemispatial hypokinesia[42]

Disability-level outcomes

- Lost independence, prolonged hospitalization
- Falls, wheelchair accidents, medication self-administration errors
- Increased caregiver burden
- Increased risk of placement in skilled nursing facility rather than returning home

Future studies that include outcomes at both the mechanistic and functional levels should clarify whether lack of response resulted from dissociated effects among patient subgroups (for example, did non-responsive patients have deficits primarily affecting 'where' rather than 'aiming' systems?) or failure to engage brain systems due to dosage, protocol or administration differences. In the latter case, we would expect decreased or absent mechanistic engagement of 'aiming' or other spatial systems across individuals.

Need to assess long-term treatment benefit

Only 16 of 48 studies assessed long-term treatment response (up to 6 months); most observed at least some persistent improvement (Table 2), but with some discrepant results. A randomized controlled trial in acute stroke reported that treatment accelerated spatial neglect recovery, but did not provide long-term benefit, relative to controls.[56] Although three small-group or case studies reported only short-lived benefit,[65,71,73] two studies reported that participants continued to improve after training ended.[53,64] The studies again reveal dissociations between outcome measures. In one study, for example, 8-week improvement in laboratory phenomena occurred without associated functional improvement,[47] and in another study post-treatment functional improvement occurred without significant lessening of clinical impairment.[53]

Need for dose–response information

Dose–response questions include the degree of lateral prismatic shift used, the degree to which the arm movement is visible, and the optimal frequency and duration of prism adaptation training. A randomized controlled trial in 34 individuals[55] detected no benefit of prism adaptation over control treatment on two ecological performance measures, but the prisms in this study induced a 6° optical shift—a lesser degree of lateral displacement than that used in other studies (typically about 12° of shift).[44] We lack evidence that changes in neglect phenomena occurred, and we also lack dose–response studies demonstrating that 6° prisms exert potent influence at the level of mechanistic phenomena. Evidence exists that the degree to which stroke survivors can self-monitor arm movements may affect the

outcome of prism adaptation training;[83] unfortunately, this training parameter is not reported in many studies.

Studies support multiple treatment sessions,[47,49] but we found no specific dose–response studies that identified an ideal treatment frequency or duration. Most studies employed a 2-week (10-weekday) training protocol, so dose-finding studies may need to start in the US inpatient acute stroke setting, where patients reliably receive this frequency of care over a similar treatment period.

With respect to the phase of poststroke recovery in which participants were enrolled (Table 1), only three studies included mainly stroke survivors in true acute stroke recovery stages (less than 2 weeks after stroke[56,70,94]). Only 10 of 48 studies examined prism adaptation therapy exclusively in acute stroke survivors comparable to US inpatients (less than 2 months post-event).[19,46,53,56,63,69–71,73,74] Commencement of prism adaptation therapy during the acute poststroke period may be critical for post-injury relearning. Studies comparing gains in acute versus later administration are, therefore, very important to identify an optimal recovery period for treatment response. Early rehabilitation enrolment (less than 2 weeks poststroke), which is understudied at present, might help to maximize rehabilitation care delivery, and could also optimize behavioural management during a critical recovery period.

Reframing neglect as a spatial motor problem

Striemer and Danckert[51] suggested that prism adaptation may primarily affect the dorsal visual processing stream. However, this idea is not completely consistent with reported changes in mechanistic phenomena in neglect. For example, auditory perception (not a dorsal visual function) improves with prism adaptation.[75] In addition, laboratory assessment demonstrated that dorsal visual ‘where’ perceptual–attentional bias could be dissociated from improved spatial motor ‘aiming’ accuracy after prism adaptation.[19]

Specific identification of spatial motor ‘aiming’ deficits in patients undergoing treatment might better explain the observed pattern of response to prism adaptation. Other authors identified primary and secondary biases in neglect—primarily ‘aiming’, motor-intentional components of spatial neglect may respond best to prism adaptation, and other associated changes might represent a secondary impact of this intervention (Box 3).[16,95–97]

Box 3

Motoric aspects of spatial neglect

The characteristics of spatial motor neglect are as follows:

- Distinct from spatial perceptual neglect and neglect affecting internal images, maps or representations—these may be sequential cognitive processing stages
- Consistent with neglect demonstrated in animal models across the mammalian class, dissociable from spatial attention and perception[104,105]
- Asymmetric posture, exploratory movements, or ineffective activation of contralesional body parts can occur without perceptual deficits[106]
- Uniquely impairs ecological activities and complex environmental interaction[40]
- Is distinct from other forms of motor learning impairment, such as that supporting speech output

Most neglect treatments implemented in therapy settings train vision, perception or attention.[20–24] However, prism adaptation training requires intensive, controlled movement practice.[44] This treatment method may primarily emphasize patient-generated, active, rapid movements, as well as implicit learning. Distinct from pure motor learning, spatial motor learning may require an egocentric (body-mapped) reference frame, along with multimodal, accurate spatial perceptual input.[76]

This paradigm might explain why studies report that only 50–75% of patients benefit from prism adaptation treatment. Visual-feedback-dependent 'where' systems may not be strongly influenced by prism adaptation;[19] thus, patients with large-magnitude visual 'where' perceptual errors might not experience optimal benefit. These differences in patient characteristics could have a neuroanatomical basis. Although Serino and colleagues[65,76] reported that patients with occipital lobe lesions might not benefit from prism adaptation training, their findings were examined in only 17 patients, and damage to subcortical and frontal regions also, tended to predict reduced benefit. Another study confirmed an association between hemianopia and reduced benefit of prism adaptation,[58] but we suggest that these findings need to be re-examined once larger studies attempting neuroanatomical patient classification by brain regions[97] and spatial motor 'where' versus 'aiming' behaviours have been performed.

In addition to cortical structures, subcortical structures may support the brain–behaviour spatial 'aiming' system that is primarily responsive to prism adaptation therapy. Neuroscience students are familiar with the role of the superior colliculus in visual input processing, especially in detecting novel perceptual stimuli. However, the intermediate and deeper, motor superior colliculus seems to have a critical role in primate eye–hand coordination, and cells in this region,[98] overlapping with the mesencephalic reticular formation, may map both gaze-dependent and gaze-independent hand movements yes, OK. In animals[34–36] and humans,[99,100] damage to the motor (deep) superior colliculus induced asymmetric spatial behaviour and spatial neglect, indicating that this structure could be a critical node in the spatial motor network.[1,3,15,41,101] Whether this region participates in modulation of interhemispheric balance of eye–hand movement bias during prism adaptation, or whether it might map frontal–subcortical spatial 'aiming', requires further research.

Future prospects and recommendations

Prism adaptation training, with brief training sessions and inexpensive (less than US$50) equipment, is highly feasible. However, stroke survivors cannot receive prism adaptation in the clinical setting until treatment candidacy is well-defined, until we confirm that treatment is successful for in-hospital, acute stroke care, until we can translationally measure short-term and long-term outcomes, and until we understand optimal treatment dosing. As this treatment development is pending, we strongly suggest that prism adaptation, however fascinating from a cognitive neuroscience perspective, is not yet ready for broad administration in stroke rehabilitation. Although the treatment carries a low risk, the time invested for prism adaptation training is lost therapy time to treat and manage other symptoms during post-acute care, which is already a cost burden on families and society.

Prism adaptation training for spatial neglect may represent spatial motor cognitive remediation, primarily improving motor-intentional 'aiming'.[19,51] We might need to stratify patients for this treatment on the basis of their spatial cognitive profile; research seeking associations across laboratory, clinic and rehabilitation settings suggests that we might eventually use bedside tests.[40] Patients with spatial neglect have diverse brain lesions, neuropsychological profiles and demographic characteristics. Identification of the

neuroanatomical networks that, when damaged, predict treatment benefit might mean that we need to routinely use procedures to diagnose spatial motor 'aiming' neglect.[40,97] We should also explore whether prism adaptation response is functional-task-specific.

The idea that a spatial motor 'aiming' system primarily supports benefit from prism adaptation training suggests pragmatic considerations in its potential clinical application. During prism adaptation training, spatial motor 'aiming' requires reliable perceptual input. Therapists using the treatment should ensure that the patient can see pointing targets, consider using brief, predictable sessions to increase training intensity, and avoid extensive verbal explanations or strategic coaching. Spatial motor learning may be characteristically implicit, rather than top-down, goal-directed and conscious. Also, although we suggest that patients with spatial motor 'aiming' deficits should be good candidates for prism adaptation therapy, a severe 'aiming' deficit could, theoretically, block all leftward limb movements, even in the right-hand body space (severe directional akinesia[41]). Patients with this degree of deficit are rarely identified, as clinical assessment does not typically assess spatial movement separately from strength. In these severely affected patients, the spatial motor system may not be capable of responding, even to a targeted 'aiming' treatment.

Conclusions

In this Review, we stress that the functional disability caused by spatial neglect after stroke can result from perceptual–attentional, 'where' spatial unawareness, as is traditionally emphasized. However, functional disability caused by this syndrome can also be the result of a primary abnormality in spatial 'aiming', a motor-intentional disorder of asymmetric action. Given that spatial neglect in patients with primarily spatial motor 'aiming' bias may relate to a different right-brain neuroanatomical–behavioural network, and may respond more powerfully to the new approach to spatial neglect treatment, prism adaptation training, clinical practice may need to turn specifically to screening for spatial 'aiming' deficits in order to identify optimal treatment candidates. A specific effect of prism adaptation on spatial motor 'aiming' may also explain why studies including mixed groups showed variability in patient response, why results have been highly task-specific, and why translational research examining short-term and long-term outcomes in the acute stroke period at the level of laboratory phenomena, clinic-assessed impairments and population-level disability are critical to make the treatment ready for broad clinical application.

Bowen and Lincoln emphasized the need to include functional outcomes when researching spatial neglect treatment.[7] New translational measures to assess performance improvement during spatial neglect rehabilitation, but also sensitive to spatial motor 'aiming' recovery,[40] are also needed. Such measures may affect the results of studies examining many spatial neglect treatments, as well as other acute stroke treatments. Because spatial neglect affects a large proportion of acute stroke survivors, and exerts a substantial influence on motor recovery and functional independence, assessment of 'where' versus 'aiming' spatial neglect symptoms may identify major recovery and response subgroups when studying diverse treatments, from biological agents to emerging motor-behavioural training techniques.

Acknowledgments

The authors thank medical student Rong (Tina) Chen, University of Medicine & Dentistry of New Jersey, New Jersey Medical School (references, organizational assistance), the Kessler Foundation and NIH/National Institute of Neurological Disorders and Stroke (manuscript support; K02 NS 047099, R01 NS 055808, K24HD062647, Principal Investigator A. M. Barrett), and Jenny R. Masmela (Ideas central to the manuscript discussion). The authors are also grateful for the helpful suggestions of three anonymous reviewers, who read the manuscript in previous draft form.

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Review criteria

Our review of the literature included comprehensive, systematic surveys of three databases—Ovld PsychInfo, Ovld MEDLINE and Web of Science—for articles published from 1998–2011. We used the following search terms in all possible combinations, to identify all articles using a prism adaptation training protocol and enrolling stroke survivors with spatial neglect: “prism”, “adaptation”, “stroke”, and “neglect.” From the resulting list of over 2,000 articles, we eliminated all review articles, studies only enrolling healthy control individuals, studies not using optical prisms or prism adaptation training, and abstracts. We additionally examined the references of all the 48 data-driven reports identified, and of key review articles.

Key points

- Spatial neglect is a major predictor of stroke disability; survivors with this condition are at high risk of adverse outcomes during acute stroke care
- Stroke survivors with spatial neglect can demonstrate different symptoms: some have primarily ‘where’ spatial perceptual unawareness, whereas others have primarily ‘aiming’ spatial motor-exploratory dysfunction
- Prism adaptation treatment is a potentially efficient and hospital-feasible therapy approach, with strong basic science support
- We may need to target survivors with spatial ‘aiming’ neglect for prism adaptation training, as these individuals may demonstrate the best treatment response
- Before we can use prism adaptation in the clinical setting, we need to define treatment candidacy, demonstrate in-hospital efficacy and short-term and long-term benefits, and optimize treatment procedures and dosing

Table 1

Types of prism adaptation studies and time of enrolment poststroke

Studies	Number of patients with neglect	Time of enrolment poststroke	
		Mean	Range
Randomized controlled trials of prism adaptation efficacy versus control treatment			
Mizuno *et al.* (2011)[53]	38	65.8 days	43–85 days
Nys *et al.* (2008)[56]	16	9.7 days	2–23 days
Serino *et al.* (2009)[52]	20	7.3 months	1–60 months
Turton *et al.* (2010)[55]	37	46 days	8–86 days
Other studies using neglect control groups			
Angeli *et al.* (2004)[81]	13 (14 healthy controls)	12 months	1–72 months
Frassinetti *et al.* (2002)[64]	13	9.4 months	3–27 months
Jacquin-Courtois *et al.* (2010)[75]	12 (10 healthy controls)	152.7 days	41–566 days
Keller *et al.* (2009)[84]	10	3.2 months	2–5 months
Ládavas *et al.* (2011)[83]	30	16.9 months	2–30 months
Rossetti *et al.* (1998)[44]	16 (5 healthy controls)	9 weeks	3–14 weeks
Rossi *et al.* (1990)[88]	39	4.6 weeks	Not reported
Saevarsson *et al.* (2010)[72]	12	23.4 months	3–57 months
Tilikete *et al.* (2001)[93]	15	2.5 months	1–3 months
Observational studies			
Serino *et al.* (2006)[65]	24	13.2 months	3–96 months
Serino *et al.* (2007)[76]	21	14.9 months	3–96 months
Case series, or other studies with patient-based or within-individual control conditions			
Angeli *et al.* (2004)[58]	14	6.8 months	1–14 months
Berberovic *et al.* (2004)[77]	5 (32 healthy controls)	Not reported	Not reported
Bultitude *et al.* (2009)[82]	5 (10 healthy controls)	124.4 weeks	31–252 weeks
Dijkerman *et al.* (2003)[60]	3	162.3 days	40–360 days
Farne *et al.* (2002)[67]	6	3.7 months	2–8 months
Fortis *et al.* (2010)[48]	10	3.4 months	1–10 months
Fortis *et al.* (2011)[19]	5	3.2 weeks	2–5 weeks
Keane *et al.* (2006)[46]	4	Not reported	<60 days
Maravita *et al.* (2003)[85]	4	Not reported	4–24 months
Morris *et al.* (2004)[62]	4 (32 healthy controls)	3.5 months	1–6 months
Nijboer *et al.* (2007)[86]	2 (8 healthy controls)	46 months	22 and 70 months
Pisella *et al.* (2002)[63]	2	5.5 weeks	3–8 weeks
Rode *et al.* (2001)[71]	2 (2 healthy controls)	1 month	1 month
Rossetti *et al.* (2004)[87]	2 (4 healthy controls)	>2 months	>2 months
Rousseaux *et al.* (2006)[59]	10 (8 healthy controls)	54.3 days	17–102 days
Sarri *et al.* (2006)[66]	3	12 months	3–20 months
Sarri *et al.* (2008)[89]	13	20.3 months	1–174 months

Studies	Number of patients with neglect	Time of enrolment poststroke	
		Mean	Range
Sarri *et al.* (2011)[90]	11	22.1 months	1–175 months
Schindler *et al.* (2009)[91]	10 (10 stroke controls, 12 healthy controls)	14.7 months	2–36 months
Shiraishi *et al.* (2008)[47]	7	33.3 months	12–84 months
Striemer & Danckert (2007)[92]	4 (26 healthy controls)	13.3 months	8–22 months
Striemer & Danckert (2010)[51]	3 (8 healthy controls)	Not reported	Not reported
Watanabe & Amimoto (2010)[70]	10	15.1 days	5–38 days
Vallar *et al.* (2006)[94]	9	12.8 days	2–36 days
Case studies			
Bultitude & Rafal (2010)[78]	1 (8 healthy controls)	3 months	Not applicable
Jacquin-Courtois *et al.* (2008)[69]	1	3 months	Not applicable
Dijkerman *et al.* (2004)[79]	1	3 months	Not applicable
Ferber *et al.* (2003)[61]	1	12 months	Not applicable
Humphreys *et al.* (2006)[49]	1	11 years	Not applicable
McIntosh *et al.* (2002)[80]	1	9 months	Not applicable
Rode *et al.* (1998)[73]	1 (2 healthy controls)	1 month	Not applicable
Rode *et al.* (2006)[74]	1	1 month	Not applicable
Nys *et al.* (2008)[68]	1	11 months	Not applicable

Table 2

Published improvement ≥24 h following prism adaptation training

Study	Latest post-training interval assessed	Results
No improvement		
Farne *et al.* (2002)[67]	1 week	No improvement on visuomanual and visuoverbal tasks
Humphreys *et al.* (2006)[49]	1 week	No improvement in line-bisection task or reading
Rode *et al.* (2001)[71]	1 day	No improvement in map naming
Nys *et al.* (2008)[56] *	1 month	Prism adaptation showed short-term superiority only, compared with control treatment on BIT
Nys *et al.* (2008)[68]	4 days	Over 4 days' training, percentage of perseverative errors increased and shifted contralesionally
Turton *et al.* (2010)[55] *	Not specified	No improvement on CBS or BIT-conventional
Improvement		
Bultitude & Rafal (2010)[78]	18 days	Leftward-shifting prisms produced improvement on line-bisection task
Dijkerman *et al.* (2004)[79]	1 and 3 weeks	Improvement in finger position sense
Farne *et al.* (2002)[67]	1 day	Improvement on visuomanual and visuoverbal tasks, which deteriorated at 1 week
Frassinetti *et al.* (2002)[64]	2 days; 1 and 5 weeks	Improvement on reading and ecological tests
Humphreys *et al.* (2006)[49]	1 week	Improvement on star cancellation, line-bisection errors, grasping and letter cancellation; no improvement seen in line-bisection omission or reading
Ladavas *et al.* (2011)[83]	1 week	Improvement on BIT-behavioural and BIT-conventional
McIntosh *et al.* (2002)[80]	1 week	Possible improvement over repeated sessions
Pisella *et al.* (2002)[63]	4 days	Improvements on line bisection and straight-ahead pointing
Rode *et al.* (2001)[71]	1 day	Improvements on daisy drawing and map naming
Rode *et al.* (1998)[73]	1 day	Improvement on daisy drawing; no improvement in city naming on map
Rode *et al.* (2006)[74]	2 days	Improvement on writing tasks
Serino *et al.* (2006)[65]	1 week; 1 and 3 months	Improvement on BIT-behavioural and BIT-conventional
Serino *et al.* (2007)[76]	1 week; 1, 3 and 6 months	Improvement on BIT-behavioural and BIT-conventional, cancellation tasks, room description, fluff test, reading, tactile extinction, first saccade amplitude and space exploration
Serino *et al.* (2009)[52] *	1 month	Improvement on BIT-behavioural and BIT-conventional, cancellation task and reading
Shiraishi *et al.* (2008)[47]	1 and 3 days; 1, 2, 3, 4, 5 and 6 weeks	Improvement in degrees of eye movement on the neglected side during a search and continuous attention task; leftward shift of center of gravity
Lasting improvement		
Fortis *et al.* (2010)[48]	1, 2 and 3 months	Improvement on FIM
Frassinetti *et al.* (2002)[64]	2 days; 1 and 5 weeks	Improvement on BIT-behavioural and BIT-conventional
Mizuno *et al.* (2011)[53] *	14 days (T1); mean 95.5 ± 41.2 days (T2)	Improvement on BIT (conventional only) and FIM (mild neglect patients only)

* Randomized controlled trial.

Abbreviations: BIT, Behavioural Inattention Test; CBS, Catherine Bergego Scale; FIM, Functional Independence Measure; T1, first assessment; T2, second assessment.

Table 3

Prism adaptation studies including 'functional outcomes'*

Nature of task or outcome measure	Studies	Specific outcome measures
Tasks imitating life or including a fragment of a function		
Reading	Angeli *et al.* (2004),[58,81] Farne *et al.* (2002),[67] Keller *et al.* (2009),[84] Rossetti *et al.* (1998),[44] Rousseaux *et al.* (2006)[59]	Single words
	Frassinetti *et al.* (2002)[64]	Menu, article
	McIntosh *et al.* (2002)[80]	Poem
	Serino *et al.* (2006, 2007)[65,76]	Menu, article, additional reading task assessed through eye movements
	Humphreys *et al.* (2006)[49]	Ability to detect spelling errors, problems with mathematics
	Rode *et al.* (2006)[74]	Assessment of handwriting
Motor	Tilikete *et al.* (2001)[93]	Postural imbalance
	Keane *et al.* (2006)[46]	Upper-body dressing, walking, sit-to-stand transfers
	Jacquin-Courtois *et al.* (2008),[69] Watanabe & Amimoto (2010)[70]	Wheelchair driving
Visual–verbal, mental imagery	Frassinetti *et al.* (2002),[64] Serino *et al.* (2006, 2007)[65,76]	Picture scanning, telling time
	Rode *et al.* (1998, 2001)[71,73]	City naming on a map
Studies employing validated measures		
Validated functional performance measures	Fortis *et al.* (2010),[48] Mizuno *et al.* (2011)[53]	Functional Independence Measure: eating, grooming, bathing, toileting, dressing, walking, transfers
	Fortis *et al.* (2011)[19]	Catherine Bergego Scale: left body dressing, grooming
	Shiraishi *et al.* (2008)[47]	Barthel Scale: dressing, grooming, toileting, bathing transfers, walking
Validated impairment measures associated with functional ability	Frassinetti *et al.* (2002),[64] Ládavas *et al.* (2011),[83] Serino *et al.* (2006, 2007)[65,76]	Behavioural Inattention Test: telephone dialling, setting time, coin sorting, address and sentence copying, map navigation, card sorting

* Few studies directly assessed daily function.