Published in final edited form as:
Handb Clin Neurol. 2013 ; 110: 347–355. doi:10.1016/B978-0-444-52901-5.00029-0.

Rehabilitation of spatial neglect

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DEFINITIONS AND SCOPE OF THE HEALTH PROBLEM

Spatial neglect is defined as a failure to report, respond, or orient to stimuli in contralesional space after brain injury that is not explained by primary sensory or motor deficits (Heilman, 1979). Conservative estimates in the US population reveal that spatial neglect is present in at least 30% of stroke survivors leading to an estimated total annual incidence of 239 000 people with neglect in the acute phase. At least 10% of patients with acute neglect will experience symptoms in the chronic phase (Barrett et al., 2006); thus a conservative estimate of chronic neglect is about 3% of US stroke survivors, or 195 000 people. These numbers are comparable with the prevalence of spinal cord injury of 259 000 cases (National Spinal Cord Injury Statistical Center, 2009) and brain and central nervous system cancer of 111 000 cases in the USA. (National Cancer Institute, Surveillance Epidemiology and End Results, 2009). Neglect occurs in approximately 50% of right hemisphere stroke survivors (Buxbaumet al., 2004) and up to 75% of patients may persist with some symptoms in the chronic phase (Farne et al., 2004). Neglect can also occur after left hemisphere injury, but it is less common and persistent than when it occurs from right-sided lesions (Beis et al., 2004).

The estimated direct and indirect cost of stroke in the USA for 2009 is 68.9 billion dollars (American Heart Association, 2009). The number of stroke survivors may increase with the aging population, as aging is associated with increased stroke risk (Hier et al., 1983; Dooneief and Mayeux, 1989; Ringman et al., 2004). Disability associated with spatial neglect may be overlooked, and those most at risk, i.e., those with right hemispheric stroke, may be less likely to receive acute medical attention than those with a left hemisphere injury (Gainotti, 1972; Ringman et al., 2004; Fink, 2005; Foerch et al., 2005). Spatial neglect is associated with longer average length of hospital stay (Katz et al., 1999; Gillen et al., 2005), increased family burden (Buxbaum et al., 2004), and higher requirements for assistance and skilled nursing placement (Rundek et al., 2000). Spatial neglect rehabilitation thus

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represents a unique opportunity for promoting recovery and preserving precious economic resources.

CLINICAL CHARACTERISTICS OF SPATIAL NEGLECT

Spatial neglect, unlike many other cognitive disorders, is demonstrated in different species of mammals (Payne and Rushmore, 2004). In humans, recognition of the right hemisphere dominance for spatial attention is fundamental to understanding this disorder (Heilman and Van Den Abell, 1979, 1980). Accordingly, the right hemisphere, unlike the left, attends to both hemispaces and plays a critical role generating spatial-based perceptual-attention to external stimuli, producing and maintaining internal spatial representations and directing motor-intentional responses. Since the right hemispace is represented by both hemispheres while the left hemispace is only represented by the right, injury of the right hemisphere may disproportionately affect perceptual-attention, representation, and motor-intention functions related to the left side.

Cognitive neuroscience basis

Successful rehabilitation of a patient with spatial neglect requires understanding the neuropsychological mechanisms underlying its behavioral manifestations. Contrasting a subject's behavior between tasks with different demands allows the dissociation of a variety of functional processes involved in spatial attention, perception, and its related motor functions. The behavioral and neurophysiologic study of patients and animals with focal brain lesions and of normal individuals has provided the main methodology for the recognition of spatial neglect as a distinct entity and for the localization of the brain regions most commonly associated with its clinical characteristics. Functional neuroimaging allows the visualization of regions of increased activity during the execution of a task. Sometimes functional imaging studies reveal brain activation in more extensive or distant areas than might be expected from lesion studies. The findings of these different methodologies are consistent with the brain's organization as a functional network where, depending on their connectivity, some areas of the network are more critical in the processing of information than others. Therefore, lesion studies identify the critical areas of a network while functional imaging identifies the participating components of the network without necessarily demonstrating which of these components are crucial (Mesulam, 2000). An extensive analysis of the neuroscientific foundations of spatial neglect is not the focus of this chapter and has been reviewed elsewhere (Adair and Barrett, 2008). Here we summarize some of the essential concepts that are relevant for the application of neuroscience knowledge to theoretically based models of rehabilitation.

Two broadly defined stages of neuropsychological processing have been dissociated in spatial neglect: a perceptual-attentional component, necessary for spatial operations or "where" constructs, and a premotor-intentional component necessary for "aiming" or directing movements in three-dimensional, and especially contralesional, space. Posterior brain regions of dorsal and lateral parieto-temporal polymodal association cortex and their subcortical connections, including associated white matter tracts, are thought to be involved in the perceptual-attentional component (Mort et al., 2003; Hillis et al., 2005). This component includes a variety of "downstream" operations, from the detection of a stimulus to its representation and manipulation. It may also affect tactile, visual, and auditory sensory modalities. The phenomenon of extinction, in which the patient fails to perceive a contralesional stimulus only when it is presented simultaneously with a stimulus on the ipsilesional side, may be best explained by limited capacity of perceptual-attentional resources (Heilman, 1979) since the “extinguished” stimulus is actually processed through sensory systems (Marzi et al., 2001; Beversdorf et al., 2008) and its perception may vary depending on modality (Hillis et al., 2006) or specific task demands (Riestra et al., 2001, 2002). Anterior brain regions of prefrontal and premotor cortex and their subcortical basal ganglia connections are thought to critically support an “aiming” premotor-intentional component. This component is often referred to as directional hypokinesia but it is better conceptualized as a disorder of intentional movement directed toward or performed in the contralesional hemispace, or involving the contralesional hemibody (Coslett et al., 1990; Heilman, 2004; Nys et al., 2006; Sapir et al., 2007). Of note, some patients with dorsal, parietal cortical lesions who lack putamenal or frontal subcortical injury may also demonstrate prominent “aiming” dysfunction (Triggs et al., 1994; Na et al., 1999; Barrett and Burkholder, 2006). Therefore, the critical brain substrate of “where” versus “aiming” spatial bias is still underspecified. Finally, ascending regulation from the reticular activation system and long dopaminergic pathways is crucial to maintain the level of arousal and motor activation related to spatial tasks.

Clinical behavioral abnormalities associated with spatial dysfunction

In addition to the level of arousal/activation and stage of processing, other factors influence behavior in spatial neglect. A subject may engage different frames of reference in the performance of a task: an egocentric frame in which the subject uses his own body and midline as a reference for spatial computations and an allocentric frame in which the subject performs these computations based on the object’s spatial features regardless of its location relative to the subject’s body (Hillis et al., 1998; Bartolomeo and Chokron, 1999). Stimulus distance location also plays an important role depending on whether the subject operates in personal space related to bodily surface, peripersonal space related to near, reaching distance, or far extrapersonal space (Mennemeier et al., 1992; Halligan et al., 2003; Committeri et al., 2007). Other manifestations of right hemisphere injury including mood disorders and disorders of emotional communication (Gainotti, 1972; Starkstein et al., 1989), unawareness of deficit (anosognosia) (Bisiach et al., 1986), changes in body schema (Coslett, 1998), and primary sensory and motor deficits (Bottini et al., 1995, 2005; Vallar et al., 1995) are important for planning rehabilitation strategies, as they impact the therapeutic outcome.

Clinical impact of neglect-associated abnormalities

Specific spatial neglect-related problems, such as those described above, can be observed to affect patients not only in the laboratory, but also in their daily activities. Deficits in orienting to or exploring stimuli in contralesional space related to abnormal “where” input, internal imagery or representation, and “aiming” motor-intentional output appear to the careful observer to be distinctly manifest in natural performance errors. For example, “where” errors may occur when the patient does not notice family or clinicians approaching in the neglected space; imagery errors may occur when patients attempt to direct a helper in fetching personal effects from the room or navigating the hospital; "aiming" errors may affect posture or transfers. Behavior may also vary depending on whether the subject is expected to bathe, shave or dress (personal space), read or explore a food tray (peripersonal space), or walk to the bathroom or a therapy room down the hall (extrapersonal space). Rehabilitation interventions may have specific effects on "where," imagery, or "aiming" processing and depend on frame of reference or operational space. Therefore, an incomplete understanding of the patient's symptomatology and assigning all spatial neglect patients to a single rehabilitation approach or outcome measure may present a major problem with validity, as it would be expected to produce disparate or incongruent results across studies.

TREATMENT THEORY AND TREATMENT FOR SPATIAL NEGLECT

Approaches to the spatial neglect syndrome

The different personnel who make up the interdisciplinary rehabilitation team may actually employ different treatment approaches. A restorative or restitutive approach attempts to reinstate premorbid capacity of injured brain-behavior systems via visual, tactile or auditory stimulation cuing, which is gradually reduced and then eliminated, and with integration of engaging activities. A vicariative strategy activates a system closely related to or sharing key components with spatial cognitive systems in order to increase spatial activation. For example, patients might be asked to walk and encouraged to advance the hemiparetic left leg, while they are simultaneously instructed to monitor their body spatial position or take note of physical details of their surroundings. A compensatory approach may involve counseling the family about safety issues, and arranging for the patient's immediate environment to be visually simplified. Physician prescription of medication treatment to increase arousal or attention may be viewed as either restitutive or compensatory. It is not clear what combination of restitutive, vicariative, and compensatory approaches is ideal to improve spatial neglect symptoms, and at present we prefer to use restitutive and vicariative approaches, with compensation limited to environmental management for physical safety.

Evidence-based medicine approach to spatial neglect treatment

Different treatment and rehabilitation approaches for spatial neglect have been described (see Pierce and Buxbaum, 2002; Proto et al., 2009 for reviews). We believe that using these different treatments to selectively target "where" and "aiming" components might greatly improve rehabilitation. Current literature, however, does not reflect attempts to examine this aim directly and few studies discuss how patient characteristics influence treatment candidacy. There is not a definite answer to whether there are any spatial neglect treatments generally applicable to improve functional behavior and recent reviews emphasized that few studies employ functional-based outcomes (Bowen et al., 2002; Lincoln and Bowen, 2006; Bowen and Lincoln, 2007). We reviewed these three articles and seven other evidence-based published resources (Cicerone et al., 2000, 2005; Bowen et al., 2002; Jutai et al., 2003; Cappa et al., 2005; Luauté et al., 2006; Teasell et al., 2008; Menon et al., 2009) and concluded that evidence-based reviews unfortunately do not provide either direct clinical or scientific guidance in spatial neglect treatment because they are internally inconsistent in several ways. Not all the reviews support a treatment or treatments as potentially effective nor do they agree on the level of evidence supporting these treatments. Only some of the above papers acknowledged that efficacy might differ by intervention, or considered efficacy of different types of treatment separately. The evidence-based reviews also do not consider the reasons for failure to obtain treatment effect in reviewed studies. Whether failed treatments were potentially effective, but inappropriately targeted, or how subject characteristics influenced treatment efficacy at the level of impairment, behavior, or function was not considered and may be critically important.

Pathways and protocols of interest—As we stated, there is disagreement among the evidence-based sources, and the information they present cannot be regarded as definitive. However, based on our best assessment of the available information we favour three treatment approaches which received Level 1a or “strong” support in evidence-based reviews and that may be used for research treatment studies and for standardizing clinical patient care. These approaches are: visual scanning treatment (Weinberg et al., 1977, 1979), limb activation therapy (Robertson and North, 1993; see also Kalra et al., 1997; Eskes et al., 2003), and “general treatment” (Jutai et al., 2003), which we interpret as similar to “perceptual training” (Teasell et al., 2008). Prism adaptation training (Rossi et al., 1990; Rossetti et al., 1998) is an emerging therapy for which there is positive supportive evidence (see review of studies in Menon et al., 2009), at this point; however, we are reluctant to recommend it as standard because the critical determinants of treatment effect, the functional abilities likely to improve, and characteristics of patients most likely to benefit are still not established.

We recognize that therapists may be enthusiastic about treatments with which they have personal, hands-on successful experience and that have been reported to be useful and therefore we believe it is reasonable for a team to develop rehabilitation programs that combine evidence-based and empirically supported approaches. Unfortunately, manualized treatments of definite functional benefit for a variety of patients with spatial neglect and different symptom complexes are not currently available. Clinical teams should develop standardized approaches of assessment and treatment based on good quality clinical reasoning. We recommend taking treatment procedures directly from research sources in which treatment efficacy was reported. Commonly, research procedures are too time-consuming, difficult to understand, and hard to administer reliably. It is often helpful to involve a colleague experienced in clinical research to help with this stage. Such a colleague can recommend methods of shortening treatment procedures, can translate research terminology into treatment terms, and can assist with hands-on instruction of the therapy team. A number of proposed “where” interventions and “aiming” interventions are listed in Table 29.1.

We would also recommend that instead of having one set of practitioners targeting one task (for example, reading), while another set of practitioners work on another set of behaviors (for example, toileting), the rehabilitation team leader train the therapy team in identifying two or three behaviors or functions that the team agrees are priorities for interdisciplinary care. If the entire team can prioritize one set of behaviors, for example, toileting, appropriate targets for treatments for other modalities can be derived, for example, reliable identification of visual-spatial cues to locate the bathroom from different perspectives, or thematic language exercises focused on grooming and hygiene. The assessment pathway may then include deciding upon which targeted behaviors involve either "where" or "aiming" deficits or a combination of both. The team may also designate strategies for a coexistent major cognitive deficit (memory loss, communication disorders, and executive dysfunction) whose contribution may imply that a prioritized task will need to be treated slightly differently. For those prioritized target behaviors that the team agrees are primarily either "where" or "aiming" behaviors, it is then appropriate to implement a treatment that primarily addresses either the "where" or "aiming" system. Therapists should be provided with the choice of at least two behavioral treatments in each modality as can be seen in Table 29.1. As we have stated, one of the shortcomings of the treatment evidence information available is that outcomes of different rehabilitation approaches have not been related to underlying neglect mechanisms. The information included in the table is based on "proof of principle" evidence (Vallar et al., 1996; Barrett et al., 1999, 2001; Barrett and Burkholder, 2006; Fortis et al., 2009) and it is intended to suggest a structure for future systematic clinical research and clinical trials that include patient stratification according to both the type and level of deficit.

Recording outcomes and periodic self-audit—Responsible use of behavioral spatial neglect treatment protocols or pathways requires periodically examining the treatment outcomes and picking measures appropriately close to the proposed mechanism of the treatment rather than generic functional measures, which may be more distant from direct treatment effect. Recording severity of spatial neglect as measured by a standard instrument such as the Catherine Bergego Scale (Azouvi et al., 2003) and Functional Independence Measure (FIM) score at treatment initiation is necessary. In many settings the FIM score (Uniform Data System for Medical Rehabilitation, 1997) is the only periodic reassessment tool utilized, but we find that recording neglect-specific scores are much more accurate, as many factors which do not pertain to visual-spatial function can affect the FIM. Key staff members identified as having knowledge and interest in directing the spatial neglect program should review outcomes for each of the protocols being implemented at the institution to see which appear most promising for further development. Staff can also be instructed to utilize a treatment that emerges as clearly most feasible or superior.

PHARMACOLOGICALTREATMENT OF SPATIAL NEGLECT

Dopaminergic modulation

Theoretically, several pharmacological agents could be useful for the treatment of neglect; however, there are few controlled studies addressing specifically the effect of drug therapy in this condition. Among the pharmacological approaches, the best documented are those directed to monoamines, particularly the dopaminergic system. In animal models dopamine pharmacotherapy restores contralesional spatial attention and orienting (see Schwarting and Huston, 1996, for a review). Dopaminergic pharmacotherapy may improve spatial neglect in humans (Fleet et al., 1987;Mukand et al., 2001) and neglect symptoms sensitive to dopaminergic supplementation may be identified with intentional premotor exploratory function (Bisiach et al., 1990; Coslett et al., 1990; Tegnér and Levander, 1991; Barrett et al., 1999; Mapstone et al., 2003; Heilman, 2004). However, the influence of these agents may be selective to certain symptoms or may even worsen neglect in some patients, particularly those with basal ganglia lesions affecting ipsilesional postsynaptic dopaminergic transmission (Geminiani et al., 1998; Grujic et al., 1998; Barrett et al., 1999).

Combined dopaminergic and adrenergic modulation

Other agents with aminergic properties have been tried with varied success. Amantadine, a medication with dopaminergic activity (but that also has anticholinergic and antiglutamatergic effects) was ineffective for improving several neglect measures in a double-blind placebo controlled study involving four patients with neglect (Buxbaum et al., 2007). Methylphenidate, which affects both norepinephrine and dopamine, had favorable results in a case report but its effects were inferior and shorter acting than those of bromocriptine (Hurford et al., 1998). Malhotra et al. (2006) found that guanfecine, a noradrenergic agonist, improved leftward exploration in two patients with temporo-parietal lesions but not in another patient with a frontal lesion, suggesting that increasing dorsolateral prefrontal cortex-mediated vigilance may improve neglect symptoms even in patients with posterior injuries. Woods et al. (2006) reported improvement in magnitude estimation using modafinil, a psychostimulant with probable dopaminergic effects (Volkow et al., 2009) in a patient with neglect symptoms associated with a left hemisphere lesion. In a study of healthy volunteers, modafinil, but not methylphenidate, decreased the rightward bias in a perceptual task apparently mediated by an increase in right hemisphere mediated alertness (Dodds et al., 2009).

Serotonergic modulation

Right hemisphere lesions are associated with negative affective symptoms and depression (Starkstein et al., 1989) thus patients with neglect may often be treated with antidepressants. These drugs may have overall positive effects in affective symptoms, but how they affect neglect has not been investigated. Physicians treating neglect patients should consider that serotonin reuptake inhibitors have multiple mechanisms of action involving different monoamines and, in some cases, anticholinergic effects. Serotonin may modulate dopaminergic activity by means of multiple mechanisms (see Alex and Pehek, 2007 for review) and produce extrapyramidal and behavioral symptoms including parkinsonism and apathy (Leo, 1996; Lane, 1998; Barnhart et al., 2004; Wongpakaran et al., 2007). Hypokinesia and apathy are likely to be overlooked as part of the depressive symptomatology or right hemisphere injury, therefore, physicians should be observant of possible “paradoxical” effects of these substances and consider the differences in pharmacodynamic profiles, favoring more activating agents with noradrenergic and dopaminergic properties.

Cholinergic modulation

Experiments using nicotine have shown that cholinergic activity plays an important role in a fronto-parietal-thalamic network that regulates arousal, motor activation, and visual attention in humans (Lawrence et al., 2002; Nelson et al., 2005). Nicotine modulates reorienting of visuospatial attention through regulation of neural activity in human parietal cortex (Thiel et al., 2005; Vossel et al., 2008). One study found that nicotine improved performance in a visual location task in chronic neglect subjects, provided that the lesions spared right parietal and temporal cortex (Vossel et al., 2009).

The studies reviewed above suggest that a variety of drugs with dopaminergic, noradrenergic, and cholinergic activity may have beneficial effects in some manifestations of neglect, however these effects may vary depending on lesion location, individual patient susceptibility, and the pharmacodynamic profiles and doses of specific agents.

“Accidental” treatment effects

In many care settings, treatments that may be offered for other related medical or neurological conditions may impair recovery of spatial neglect. For example, a compression glove to decrease dependent edema may interfere with tactile input from one limb increasing stimulation asymmetry. Therefore, it is the authors’ opinion that stimulus-depriving interventions should be carried out symmetrically as much as possible. The use of splints or orthoses when these are not orthopedically indicated in order to “increase attention” to the neglected side or limb, also increases tactile sensory inhibition directly decreasing motor awareness in that body region and must be avoided. Physicians also must be aware of the different mechanisms of action of medication being prescribed. Drugs with anticholinergic, GABAergic, anti-dopaminergic, or sedative effect should be avoided whenever possible. These definitely include benzodiazepines, which in some patients may cause exacerbation or re-emergence of previously recovered spatial neglect or aphasia (Lazar et al., 2002). The reported paradoxical effect of zolpidem increasing alertness in patients with vegetative state (Cohen and Duong, 2008; Shames and Ring, 2008) does not justify its routine use in spatial neglect, as we feel adverse effects on arousal and attention of this medication are much more likely than is paradoxical improvement. Unnecessary antiepileptic medication, standing narcotic analgesics, and medications commonly used for gastrointestinal conditions, which may induce delirium and impair attention, should be avoided as well.

CONCLUSIONS AND FUTURE DIRECTIONS

An enormous amount of research dating back to the mid 20th century has advanced our knowledge of the brain mechanisms involved in spatial attention and behavior and has revealed how failure of these mechanisms may result in the clinical picture of spatial neglect. In order to achieve the goal of applying neuroscience theory to patient care in spatial neglect it is necessary to integrate essential physiologic subcomponents of attentional-perceptual and motor-intentional mechanisms within a comprehensive model that defines specific targets for therapeutic intervention. The lack of consensus regarding the most effective therapy for neglect illustrates the high complexity of the clinical problem and suggests that it is unlikely that a single form of intervention will prevail as the sole rehabilitative treatment. Future challenges thus also involve developing outcome measures with appropriate construct and external validity that effectively measure clinically significant change due to treatment as well as the interaction of recovery components with specific treatment effects. This will allow us to evaluate the effectiveness of theoretically supported rehabilitation treatments and choose the best combination of these treatments for the individual patient. Success in identifying dysfunctional brain-behavior mechanisms, predicting their effects on spatial neglect associated behavior, validly assessing for symptoms, and developing appropriate treatments will result in high benefits to both society and the individual stroke survivor.

Acknowledgments

The support of the Kessler Foundation and the NIH (K24 HD062647 and NS055808) is acknowledged.

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Table 29.1

Translational classification of spatial neglect treatments

"Where" interventions	**"Aiming" interventions**
Devices, medications increasing arousal • "Phasic alerting" self-cuing • Transdermal electrical nerve stimulation (TENS) Induced asymmetry/selective sensory deprivation • Scanning training • Environmental manipulation • Monocular patching/right visual field occlusion Internal or external illusions • Optikinetic stimulation • Exposure to right-shifting optical prisms • Galvanic stimulation/neck vibration • Mirror therapy • Caloric stimulation Medication?	Adaptation to right-shifting prisms Limb activation therapy Constraint induced movement therapy Tool use movement therapy Scanning training, if administered as motor habit training Physical therapy/mobilization of the neglected body or both sides of the body (e.g., standing) Medication?

Theoretically proposed mechanisms of action of rehabilitative treatments (framework for future research). "Where" interventions may affect perceptual/attentional input, or internal sensory representations or spatial imagery. "Aiming" interventions may affect motorintentional output or premotor imagery.